

MULTIPLE PRIMARY CANCERS IN SURVIVORS OF ADOLESCENT AND YOUNG  
ADULT CANCERS IN THE UNITED STATES, SEER 1973-2012

DISSERTATION

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Despite improvements in cancer survival rates, cancer survivors have an increased risk for a number of health issues including the development of multiple primary cancers (MPCs). MPCs have been well-studied in childhood and adult cancer survivors, but the risk of developing MPCs is not well-characterized in survivors of adolescent and young adult (AYA) cancers. Additionally, the role of survival from MPCs in AYA cancers has not yet been examined. The present study utilized data from the Surveillance, Epidemiology, and End Results (SEER) registries (1973-2012) to assess the risk for MPCs and survival after a second primary cancer (SPC) in survivors of AYA cancers. Individuals diagnosed with a first primary cancer between the ages of 15 and 39 were included in this study. Overall and site-specific standardized incidence ratios (SIR) and excess absolute risks (EAR) were assessed, and multivariable Poisson regression models were used to assess the risk for MPCs over time. Kaplan-Meier and Cox proportional hazards modeling were utilized to assess survival after a SPC. Out of 227,569 AYA survivors, 15,069 (6.6%) developed a MPC two or more months after the first primary cancer. Survivors of AYA cancers had a nearly 2-fold increased risk of developing an MPC (SIR=1.86, 95% CI 1.84-1.89). The most common MPCs in AYAs were breast cancer, digestive system cancers, and skin cancers. Age at first cancer diagnosis, gender, race, radiation treatment, type of first primary cancer, and latency were significantly associated with the development of a MPC. We observed females

had a reduced risk for death compared to males (HR=0.73, 95% CI 0.68-0.78) after a SPC, and Blacks had an increased risk for death after a SPC compared to Whites (HR=1.23, 95% CI 1.18-1.38). Our findings indicate that AYA cancer survivors are at higher risk for multiple primary cancers and provide new knowledge of the survival from second primary cancers in the AYA population. We observed that males and Blacks have a worse prognosis after the development of a subsequent cancer. This may have direct implications on the clinical management and prevention strategies for AYA cancer survivors.

## CHAPTER I

### INTRODUCTION

#### **Statement of the Problem**

Improvements in the early detection and treatment of cancer have led to increases in survival over the past several decades. Currently, there are nearly 14.5 million cancer survivors in the United States and this number is expected to increase to 19 million by the year 2024 (DeSantis et al., 2014). Cancer survivors may face a myriad of health issues including increased risk for obesity, cardiovascular disease, pulmonary dysfunction, endocrine disorders, infertility, psychosocial distress, and multiple primary cancers (MPCs) (Hudson et al, 2013; Valdivieso et al., 2012). Accordingly, more research is now focused on the late effects of cancer including the development of subsequent cancers (Hudson et al, 2013; Valdivieso et al., 2012). The incidence of multiple primary cancers, defined as second and/or more primary cancers, has doubled over the past three decades and MPCs now comprise about 18% of incident cancers in the United States (Morton et al., 2014b; Morton et al., 2014a; Travis et al., 2013). Research shows MPCs are a leading cause of morbidity and mortality in both childhood and adult cancer survivors and are one of the National Cancer Institute's Provocative Questions (Choi et al., 2014; Morton et al., 2014b; NCI, 2013). Different groups of survivors bear an unequal burden of subsequent cancers (Morton et al., 2014b). Therefore, understanding who is at greater risk for MPCs is of both clinical and public health importance.

Although numerous studies have assessed the development of subsequent primary cancers in childhood and adult cancer survivors, the risk of developing MPCs is not well-characterized in survivors of adolescent and young adult (AYA) cancers (Soliman & Agresta, 2008). The most recent estimate reported there are about 614,000 AYA cancer survivors in the United States (Guy et al., 2014). AYAs are defined as persons between the ages of 15 and 39 (AYAOPRG, 2006). AYAs with cancer are a special population with unique characteristics and challenges. This population, poised between childhood and older adulthood, undergoes distinct physical and emotional changes. The types and patterns of malignancies that develop in this population are different than those that develop during childhood or older adulthood (Bleyer, 2002). AYA needs along the cancer continuum, from diagnosis into survivorship, are different than that of children and older adults. Only recently has this population been considered a distinct age-group in oncology (Bleyer, 2002). AYA cancer research is limited because cancer risk and adverse cancer outcomes have been under-recognized in this population, mainly due to physicians and researchers poor understanding of the patient and tumor biology. Little is known about the biologic, epidemiologic, therapeutic, & psychosocial factors that affect cancer incidence, disease outcomes, and quality of life in AYAs (AYAOPRG, 2006). Further research needs to be conducted to better understand the unique survivorship needs of this population, including the risk for subsequent cancers, in order to provide adequate care and monitoring for AYAs.

Previous studies of MPCs among AYA cancer survivors have been limited by the inclusion of age categories with children and older adults in observational studies. Only a few international studies have estimated the risk of second and subsequent primary

cancers specifically in AYAs, but are limited by a small number of subsequent primary cancer cases, shorter follow-up periods, and diverse age inclusion criteria. (Aben et al., 2012; Hammal et al., 2005; van Gaal et al., 2009; Zhang et al., 2012). Further exploration in a large cohort, with a longer period of follow-up, and a formal age inclusion definition is needed. To date, no study has assessed the risk of MPCs specifically among survivors of AYA cancers in the United States or the effect of subsequent primary cancers on survival of AYA cancer survivors. This study is one of the first U.S. population-based studies to provide an overview of the development and survival of subsequent malignancies specifically in survivors of adolescent and young adult cancers.

## **Purpose**

The main objective of this study is to assess risk for the development of MPCs in survivors of AYA cancers compared to the general U.S. population, and to evaluate the effect subsequent cancers have on survival of patients in this population. This population-based retrospective study will utilize cancer data from 9 population-based registries in the Surveillance Epidemiology and End Results (SEER) program, collected between 1973 and 2012. The results of this study may facilitate better understanding of the risk of subsequent cancers in survivors of AYA cancers in order to optimize follow-up care, enhance screening and prevention efforts for MPCs, and ultimately improve survival outcomes in this population.

## Significance

A critical barrier to improving outcomes in adolescents and young adults (AYAs) with cancer is the limited research, in general, in this population. Additionally, much of the research on risk of MPCs in cancer survivors has focused on survivors of childhood cancers (up to ages 18-20 at diagnosis of first cancer) (Friedman et al., 2010; Inskip & Curtis, 2007; Meadows et al., 2009; Olsen et al., 2009), whereas few studies to date have focused on MPCs specifically in survivors of AYA cancers. This study addresses this barrier by assessing both the overall and tumor-site specific risk for the development of MPCs in survivors of AYA cancers in the United States, by site of first primary cancer, gender, race/ethnicity, age group, year of diagnosis, years after diagnosis, and treatment type. This will provide an overview of the risk for MPCs in AYA cancer survivors in the United States.

Many previous studies have assessed demographic, disease-related, and treatment-related factors individually to determine their association with the risk for a subsequent primary cancer, but few studies have utilized a multivariable approach to determine the simultaneous effect of these factors on risk for subsequent cancers (Friedman et al., 2010; Jégu et al., 2014; Reulen et al., 2008). It is probable that many of these patient, disease, and treatment characteristics are not independent of each other and confounding is likely to obscure results. This study incorporates a multivariable analysis to enhance the validity of the risk estimates. This information can be used by physicians to better adapt screening and surveillance guidelines based on patient risk factors.

To our knowledge, this is the first study to explore second primary cancers' effect on survival specifically among survivors of AYA cancers. Research shows that subsequent cancers are the leading cause of treatment-related death in survivors of childhood cancers (Armstrong et al., 2008). Quantifying the effect of SPCs on survival in AYA cancer survivors may have important implications for guiding therapeutic and surveillance strategies to improve survival in this population.

### **Specific Aims**

**Aim 1:** To estimate the overall and tumor site-specific standard incidence ratios (SIR) and the excess absolute risk (EAR) of multiple primary cancers following adolescent and young adult cancer by site of first primary cancer, gender, race/ethnicity, age group, year of diagnosis, years after diagnosis of first primary cancer, and treatment type for first primary cancer.

**Aim 2:** To determine whether demographic, treatment, and disease-related factors have an effect on the risk of developing multiple primary cancers among survivors of AYA cancers, using a multivariable approach.

**Aim 3:** To estimate the survival rates of AYA cancer survivors after diagnosis of a second primary cancer by site of second primary cancer, gender, and race/ethnicity; and, assess the effect of patient characteristics on survival rates of AYA cancer survivors after diagnosis of a second primary cancer.

## CHAPTER II

### REVIEW OF THE LITERATURE

#### **Multiple Primary Cancers**

**Definition.** Multiple primary cancers are defined as two or more histologically distinct primary cancers that are not an extension, recurrence, or metastasis of the first primary cancer (ACS, 2009; Soerjomatarum & Coebergh, 2009). MPCs may occur in the same tissue or organ as the first primary cancer, or they can occur at different locations in the body (Soerjomatarum & Coebergh, 2009). There is a distinction between subsequent primary cancers and metastatic cancer. With regards to metastatic cancer, cells within a tumor have developed the ability to invade into surrounding tissues and move to different sites within the body. The cells of the new tumors that appear in surrounding tissues or in other sites are biologically identical to the original tumor. In contrast, a subsequent primary cancer is the occurrence of a new cancer that is biologically distinct from the original primary cancer. These cancers display a different microscopic composition of cells and/or tissue (ACS, 2009; Begg, 1999).

MPCs are characterized as either synchronous or metachronous (Koubkova et al., 2014). Synchronous tumors are subsequent malignancies occurring at the same time or within a defined time period from the first primary cancer. Metachronous tumors occur after the first primary cancer, depending on the time definition applied (ACS, 2009; Koubkova et al., 2014; Soerjomatarum & Coebergh, 2009). The time frame to distinguish synchronous tumors from metachronous tumors varies worldwide. In the

United States, the SEER program identifies metachronous multiple primary cancers as occurring more than 2 months following the first primary cancer (Curtis et al., 2006). The International Agency on Research for Cancer (IARC) uses a more strict time criteria of 6 months to distinguish synchronous and metachronous tumors (Soerjomatarum & Coebergh, 2009).

It sometimes can be difficult to distinguish a new primary cancer from a cancer recurrence or metastasis, especially in regards to cancers in paired organs and cancers in organs with the same morphology (ACS, 2009; Soerjomatarum & Coebergh, 2009). This distinction is important for staging procedures, prognosis, and treatment. Usually, pathological and clinical information indicates histological differences between the cancers. In questionable cases, DNA analysis can be used to determine if cells from the first primary cancer and the new primary cancer share the same origin (ACS, 2009). To count multiple primary cancers, cancer registries rely on coding rules that take into account the histology, behavior, laterality of paired organs, and the cancer site of origin (ACS, 2009; SEER, 2007).

**Epidemiology.** The incidence of multiple primary cancers across all ages has nearly doubled in the past three decades. Subsequent primary cancers compromised 9% of cancer diagnoses in 1975-1979 and now comprise over 18% of new cancer diagnoses (Morton et al., 2014b; Travis et al., 2013). According to the most recent SEER estimate, cancer survivors of all ages have a 14% increased risk of developing an MPC compared to the general U.S. population (Curtis et al., 2006). Numerous epidemiological studies have assessed the risk of development of MPCs in both

childhood and adult cancer survivors. Recent studies assessing the risk for subsequent primary malignancies across all ages are highlighted in Appendix Table 1.

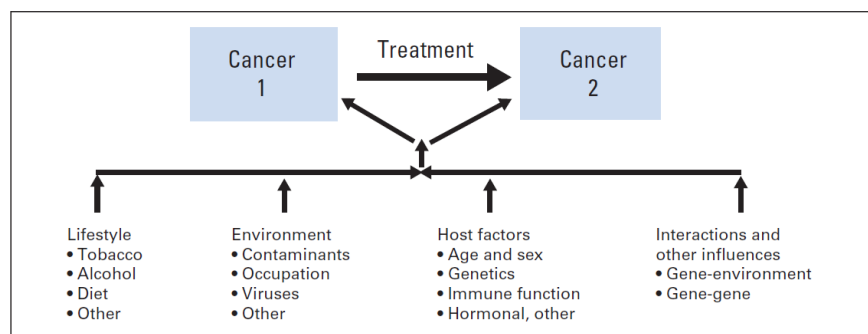
Research indicates the risk of subsequent cancers is often disproportionate by age, gender, and race (Curtis et al., 2006; Morton et al., 2014b; Ng et al., 2010). The proportion of MPCs is greatest among the elderly, with the highest number of MPCs observed among those 70–79 years (Soerjomatarum & Coebergh, 2009). However, the risk of a MPC is greatest among those diagnosed with a first cancer at a younger age and declines with increasing age. Previous studies have found that those diagnosed with a first cancer during childhood have more than a six-fold increased risk for a second cancer (Neglia et al., 2001). The SEER monograph on new malignancies among cancer survivors, from 1973-2000, assessed the risk for MPCs in over 2 million cancer survivors and for 50 sites of a first primary cancer (Curtis et al., 2006). Results of this monograph showed a six-fold increased risk for MPC for those diagnosed with a first cancer during childhood (ages 0-17), a 2-to-3-fold increased risk in those diagnosed during young adulthood (ages 18-39), and a 1.4-to-1.6-fold increased risk among those diagnosed between the ages 40 and 59 (Curtis et al., 2006). The SEER researchers also observed a slightly statistically significant higher relative risk for a MPC among females (O/E=1.17) compared to males (O/E=1.11) for all multiple primary cancers combined (Curtis et al., 2006). However, the risk for a MPC was higher among males for survivors diagnosed with a first cancer before the age of 60 (Curtis et al., 2006). Furthermore, blacks had an overall higher risk for a MPC compared to Whites (O/E=1.31, EAR=46 vs. O/E=1.13, EAR=20, respectively), and this racial difference was also observed when analyses were stratified by gender and age (Curtis et al., 2006).

The risk for multiple primary cancers has also been shown to differ by site of first primary cancer. MPCs have been observed more frequently among survivors of breast cancer, testicular cancer, and Hodgkin lymphoma, which are common cancers diagnosed during young adulthood (Morton et al., 2014b). Among males who developed an MPC, the 10 most common types of first primary cancers included prostate, colon and rectum, urinary bladder, melanoma, kidney and renal pelvis, oral cavity and pharynx, lung and bronchus, non-Hodgkin lymphoma, leukemia, and thyroid (ACS, 2009). Breast, colon and rectum, uterine corpus, melanoma, lung and bronchus, thyroid, ovary, urinary bladder, non-Hodgkin lymphoma, and uterine cervix were the 10 most common first primary cancers among female survivors who developed a MPC (ACS, 2009).

Certain types of multiple primary cancers are more commonly associated with specific first primary cancers. Females with a first primary breast cancer have a higher risk of developing another breast cancer, lung, uterine corpus, ovary, and acute non-lymphocytic leukemia (ACS, 2009; Curtis et al., 2006). Women diagnosed with breast cancer at an earlier age (age < 40) have a higher risk of another cancer, compared to women diagnosed at a later age (ACS, 2009; Curtis et al., 2006). The MPCs most observed after a first primary colorectal cancer is another cancer of the colon or rectum (ACS, 2009). Furthermore, individuals diagnosed with a tobacco-related first primary cancer have an increased risk of developing another tobacco-related cancer (ACS, 2009).

**Etiology.** The etiology of subsequent primary cancers is multifactorial and risk factors include host factors such as age and sex, type of treatment for the first cancer, genetic susceptibility, environmental exposures, lifestyle factors (diet, smoking, and alcohol), or combinations of any of these factors (Curtis et al., 2006; Koubkova et al., 2014; Morton et al., 2014b; Travis et al., 2013; Wood et al., 2012). The figure below depicts the different risk factors for multiple primary cancers (Wood et al., 2012).

Figure 1. Multiple Primary Cancers Etiologic Factors



Research indicates treatment for the first primary cancer and genetic susceptibility are likely the main contributors to MPCs in survivors of childhood cancer (Morton et al., 2014b; Travis et al., 2013). It is estimated that 1-2% of all cancers are associated hereditary cancer disorders (ACS, 2009). It is well established that individuals with certain hereditary disorders (Fanconi anemia, Cowden disease, BRCA1- and/or BRCA2-related breast and/or ovarian cancer, and Li Fraumeni syndrome) are at increased risk for cancer and subsequent cancers (Travis et al., 2006), and individuals with ataxia telangiectasia have increased sensitivity to the carcinogenic effects of radiation (Travis et al., 2006). There is little data on the molecular mechanisms for the genetic susceptibility for subsequent cancers (Travis et al., 2006). Many of the hereditary cancer disorders are autosomal dominant, meaning a

child who inherits the abnormal gene from only 1 parent may develop the disorder (ACS, 2009). Individuals with an inherited disorder must acquire additional mutations to develop a cancer (ACS, 2009).

Research from the Childhood Cancer Survivor Study (CCSS), a cohort of over 14,000 survivors of childhood cancers, has provided much of the evidence linking cancer treatment with the development of subsequent cancers (Morton et al., 2014b). More specifically, the CCSS found that survivors of childhood cancers have a greater risk for the development of a subsequent cancer if they received radiation or chemotherapy for treatment of the first primary cancer. Subsequent cancers associated with radiation treatment, observed among childhood cancer survivors, include: leukemias, breast, thyroid, lung, brain and central nervous system, non-melanoma skin, bone, and soft tissue cancers (ACS, 2009; Inskip & Curtis, 2007). Chemotherapy is primarily associated with the development of leukemia (ACS, 2009). Risk of another cancer after treatment with radiation or chemotherapy is usually higher at young ages when exposed tissues are still developing. However, the dose of therapy and patient characteristics play a role in treatment-related subsequent cancers (ACS, 2009).

Cancer treatment may account for only a small percentage of MPCs in survivors of adult-onset first cancers (Travis et al., 2013). A recent study, utilizing data from the Surveillance Epidemiology and End Results program, found that only about 8% of second cancers after adult-onset cancer are likely related to radiotherapy treatment for the first cancer (de Gonzalez et al., 2011). Lifestyle factors, such as tobacco, alcohol, diet, and environmental exposures that can accumulate over many years are likely the main risk factors for subsequent cancers in adults (de Gonzalez et al., 2011; Morgan et

al., 2014a). Research has shown that individuals with tobacco and alcohol-related first cancers have a high risk of developing another tobacco or alcohol-related cancer such as respiratory, oral cavity and pharynx, breast, colorectal, liver, kidney, esophageal, and pancreatic cancers (ACS, 2009; CDC, 2015; Curtis et al., 2006).

Immunodeficiency syndromes and some infections have also been shown to increase the risk for certain types of primary cancers and multiple primary cancers. Immunosuppression weakens the body's ability to destroy cancer cells or fight infections that can cause cancer (NCI, 2015a). Persons with either an inherited or acquired immunodeficiency syndrome have an increased risk for non-Hodgkin lymphoma (ACS, 2009). Patients with the human immunodeficiency virus (HIV) are shown to have increased risk for non-Hodgkin lymphoma, Kaposi sarcoma, lung, and cervical and anal cancers (ACS, 2009; NCI, 2015a). The Human Papillomavirus (HPV) is the cause of nearly all cervical cancers, and also causes some anal, vaginal, penile, and oropharyngeal cancers (ACS, 2009; NCI, 2015b). Hepatitis B and C have been linked to liver cancer, and infection with *Helicobacter pylori* (*H. pylori*) bacteria has been shown to cause stomach cancer (NCI, 2015b).

Hormonal factors have also been shown to increase the risk for certain types of primary and multiple primary cancers. Estrogen, and in some cases progesterone, are known carcinogens for breast cancer and some other female reproductive cancers (ACS, 2009; NCI, 2015c). Studies of multiple primary cancers have shown increased risk for breast, ovarian, uterine, and prostate cancers that may be due to hormonal factors (ACS, 2009; Curtis et al., 2006)

**Survival.** Few studies have investigated multiple primary cancers' effect on patient survival. It is difficult to determine, based on the mixed results from the existing literature, as to whether multiple primary cancers have a favorable or unfavorable impact on survival. Some studies have reported no differences in survival in patients with one primary cancer compared to those with multiple primary cancers (Kollias et al., 2001; Wong et al., 2007). Others have reported both decreased survival in those with multiple primary cancers (Rosso et al., 2009; Soerjomataram et al., 2005) and increased survival in those with more than one cancer (Amer, 2014; Sankila & Hakulinen, 1998). One retrospective study, among patients 15 years and older from 22 European countries, was conducted to explore the effect of including multiple primary cancers in survival estimates. Traditionally, survival estimates include only first primary cancers. This study found that including multiple primary cancers in survival estimates lowered the age-standardized relative survival estimates in 44 out of 45 cancers, with the greatest survival differences seen in cancers of the larynx, oropharynx, and penis (Rosso et al., 2009). Another U.S. study, conducted among patients of all ages at a regional cancer center, assessed multiple primary cancers' impact on survival. The findings indicate that the five-year survival rates were higher for metachronous cancers (95%) than for synchronous cancers (59%) and single primary cancers (59%) (Amer, 2014). Differences in the study populations' distribution of types of multiple primary cancers and stages of cancer may account for some of the discrepancies found in past research. The literature does indicate that patients with a first cancer diagnosis tend to receive more check-ups and screening tests for another cancer (Sankila & Hakulinen,

1998). Many second cancers are caught at an earlier stage which may improve the prognosis of MPCs (Soerjomataram et al., 2009).

## **Cancer in Adolescents and Young Adults**

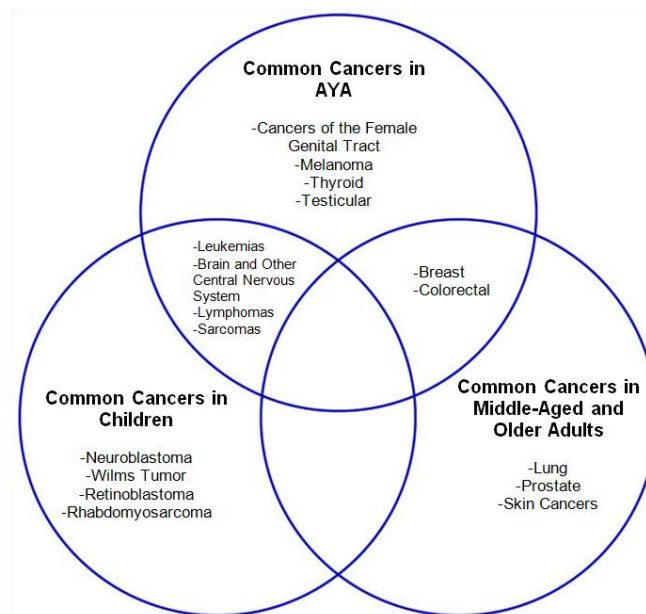
While much research has been devoted to improving cancer outcomes in children and older adults, relatively little attention has been given to cancer in adolescents and young adults - defined as those 15 to 39 years of age at the time of initial cancer diagnosis (Bleyer & Barr, 2009; Wu et al., 2005). This population, poised between childhood and older adulthood, undergoes distinct physical and emotional changes. Only until recently have AYAs been considered a distinct age-group in oncology, and cancer research in this group is limited (Bleyer, 2002; Thomas et al., 2010). Little is known about the biologic, epidemiologic, genetic, and psychosocial factors that affect cancer outcomes and quality of life in this population (AYAOPRG, 2006). Often termed a “lost tribe”, AYAs are a special population with unique characteristics and challenges (AYAOPRG, 2006; Stevens, 2006).

**Epidemiology.** Approximately 70,000 AYAs are diagnosed with cancer each year in the United States and cancer is the leading cause of non-accidental death in this population (AYAOPRG, 2006; Coccia et al., 2014). More than six times the number of cancer cases are diagnosed in AYAs as compared to children 0 to 14 years of age (NCI, 2014A).

There is a distinctive compilation of cancer types that develop among AYAs compared to those that develop during childhood or older adulthood (Bleyer, 2002; Bleyer 2008). The most common types of cancers that account for nearly 90% of

cancer diagnoses in this population include breast cancer, lymphomas, melanoma, female genital tract tumors, thyroid cancer, sarcomas, testicular cancer, colorectal cancer, leukemias, and brain tumors (AYAOPRG, 2006; Bleyer et al., 2008). In comparison, the main types of cancers that develop in children are mostly embryonal-type tumors (e.g. neuroblastoma, retinoblastoma, and Wilms tumor) and the main types seen in middle-aged and older adults are predominately epithelial cancers (lung, colorectal, breast, and prostate cancers) (Bleyer et al., 2008; Burke, Albritton, & Marina, 2007). Some types of cancers reach a peak incidence in AYAs compared to children and older adults. These include Hodgkin lymphoma, testicular cancer, bone sarcomas, and Kaposi sarcoma (Bleyer, 2008). The following figure displays the most common types of primary cancers diagnosed during childhood, adolescence and young adulthood, and middle and older adulthood.

Figure 2. Common Types of Primary Cancers in Children, AYA, and Middle-Aged and Older Adults



The distribution of certain types of cancer in AYAs differs by age. Lymphomas, followed by leukemias, sarcomas and brain tumors are the most common cancer types among

15-19 years-olds. Lymphomas, melanoma, thyroid cancer and testicular cancer are more predominant in 20-29 year-olds, and breast and colorectal carcinomas begin to occur in this age group (Bleyer, 2008). There is a transition to more epithelial type cancers in AYAs 30 years of age and older. A greater proportion is observed in females who tend to develop more epithelial cancers about 15 years earlier than males (Patterson et al., 2015; Wu et al., 2005).

There is evidence that a large fraction of the cancers in AYAs have a different biology and probably etiology, than that of what appears to be the same cancer in children or older adults (Bleyer & Barr, 2009). Genetic differences have been observed in AYA cancers compared to the same cancers in younger and older patients including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), breast cancer, colorectal cancer, and sarcomas (Bleyer, 2009). Some cancers, such as AML, ovarian cancer, and non-Kaposi soft tissue sarcomas reach a peak in incidence in AYAs and sharply rise in incidence again during later adulthood. This may suggest different biological types of cancer with the same histology occurring in different age groups (Bleyer, 2008). Due to these biological differences, the diagnosis, treatment, and follow-up care needs of AYAs are different than that of their younger and older counterparts (Bleyer & Barr, 2009).

While the 5-year survival rate in the U.S. for AYAs is 70-80%, this population has experienced little to no improvement in survival compared to children and older adults (AYAOPRG, 2006; Bleyer, 2005). A number of cancers in AYAs have a worse survival than the same cancers in children and older adults including breast cancer, colorectal cancer, soft-tissue sarcomas, non-Hodgkin lymphomas, and leukemias (Bleyer, 2008).

Several factors may account for the stagnant improvement in survival for AYAs. AYAs typically receive treatments designed for children or older adults, which may not be as effective in this age group (Bleyer, 2008). Access to care may be limited in this population due to the high uninsured rate in this age group. Also, AYAs may delay seeking medical care which can lead to a delay in diagnosis (AYAOPRG, 2006). Other factors that may contribute include physicians' lack of awareness of cancer in this population; low participation in clinical trials and lack of available clinical trials; differences in tumor biology; treatment compliance; inconsistencies in treatment and follow-up care; and lack of psychosocial support and education programs for AYAs (AYAOPRG, 2006; Ramphal et al., 2011).

**Definition of AYAs.** There is considerable variability in the literature regarding the age range used to define AYAs. The most common age ranges seen in previous studies include 15-24, 15-29, and 15-39 (Geiger & Castellino, 2011). These differences may have important consequences for AYA clinical care and cancer research, especially regarding cancer statistics and the different types of cancers observed among AYAs (Patterson et al., 2015). The National Cancer Institute (NCI) and the Adolescent and Young Adult Oncology Progress Review Group (AYAOPRG) define AYAs as persons diagnosed with cancer between the ages 15-39 (AYAOPRG, 2006). The rationale for utilizing this wider age range is that this age range continues to experience a relative lack of improvement in cancer survival (AYAOPRG, 2006). The AYAOPRG acknowledges that there is biological, emotional, and social heterogeneity within such a wide age range. However, individuals in this age group are unified based

on their unique differences in both medical and psychosocial needs along the cancer trajectory when compared to other age groups (AYAOPRG, 2006).

**Medical Care.** In terms of medical care, AYAs are typically split between either pediatric or adult oncology specialists, depending on the decision made by the referring physician (Bleyer, 2007; Ramphal et al., 2011). There is a lack of education and focus on AYAs in most pediatric or adult oncology training programs, which likely reduces an oncologist's ability to understand AYA issues (Ramphal et al., 2011). This often leads to unmet physical, psychosocial, emotional, and treatment needs. AYAs may see a variety of practitioners, internists, general practitioners, pediatricians, emergency room physicians, and other specialists during the initial cancer diagnosis period (AYAOPRG, 2006; Bleyer, 2007). The majority of AYAs are treated in the community rather than in cancer centers (AYAOPRG, 2006). Cancer treatments and follow-up care are inconsistent, which in turn has hampered the development of treatment and monitoring guidelines for AYAs (AYAOPRG, 2006; LSYAA, 2006). Some data indicate that AYAs treated by pediatric oncologists for certain types of cancer have better outcomes than those treated by adult oncologists (Albritton et al., 2007; Ramphal et al., 2011). However, contact with AYAs is often lost following the completion of treatment, making it difficult to gather data on late effects and cancer outcomes (AYAOPRG, 2006). These discrepancies highlight the need for oncology programs specifically tailored to adolescents and young adults.

**AYA Cancer Survivors.** The most recent estimate reported there are about 614,000 AYA cancer survivors in the United States (Guy et al., 2014). AYA cancer survivors are at risk for a number of health-related quality of life issues and increased

health care costs. One of the main concerns AYA survivors face are late effects of cancer treatment including infertility, cardiac and pulmonary conditions, and subsequent primary malignancies (Bleyer, 2007; Woodward et al., 2011). AYA survivors may also experience poor psychosocial and social well-being effects. AYAs may have difficulties forming new relationships, have problems with family relationships, misuse alcohol and other addictive substances, develop depression or have a negative outlook on life, and have difficulties achieving educational and employment goals (Woodward et al., 2011). One study examined the self-reported health status of AYA cancer survivors using data from the Behavioral Risk Factor Surveillance System (BRFSS) (Tai et al., 2012). This study found that AYA cancer survivors, compared to respondents with no history of cancer, reported a significantly higher prevalence of current smoking, obesity, cardiovascular disease, hypertension, asthma, disability, poor mental and physical health, and not receiving medical care because of the costs (Tai et al., 2012). Increased health care expenditures are another issue plaguing AYA cancer survivors. Another study measured the economic burden of cancer among those diagnosed as AYAs using Medical Expenditure Panel Survey data (Guy et al., 2014). This study found that AYA cancer survivors spent \$7,417 per person per year on medical costs. This amounted to excess annual medical expenditures of \$3,170 per person and excess annual productivity losses of \$2,250 per person, both of which are higher than costs for older survivors (Guy et al., 2014). Furthermore, AYA survivors were less likely to be employed and more likely to report disability, work limitations, and complete inability to perform work activities (Guy et al., 2014).

Due to the distinctive nature of AYA cancer, specific prevention and control strategies need to be created to target this underserved population (Wu et al., 2005). In order to meet the distinct needs of AYA cancer patients and survivors, the AYAOPRG have made specific recommendations to improve cancer outcomes and awareness for this population (AYAOPRG, 2006). Two recommendations provided by the AYAOPRG include more research to better understand the tumor and host factors that contribute to AYAs' susceptibility to cancer and to ensure excellence in care across the cancer continuum (i.e. prevention, screening, diagnosis, treatment, survivorship, and end of life) (AYAOPRG, 2006). Further research needs to be conducted to better understand the unique survivorship needs of this population, including the risk for subsequent cancers, in order to provide adequate care and monitoring for AYAs.

### **Subsequent Primary Cancers in Adolescents and Young Adults**

Although AYAs have been included in assessing the risk of subsequent primary cancers in previous research, they have often been grouped into age categories with children and older adults. The SEER monograph on new malignancies among cancer survivors estimated a nearly 3-fold greater overall risk for a MPC for those diagnosed with a first cancer between the ages 18-29 and nearly 2.4 times greater overall risk for those diagnosed with a first cancer between the ages 30-39 (Curtis et al., 2006). However, when evaluating subsequent cancer risk by first primary cancer site, AYAs were often included in age categories with older adults (e.g. those >50 or >60) in this study. Age category cut points did differ by type of first primary cancer. Reasoning for this strategy was not provided, but may have been chosen by the nature of the first cancer or small numbers for rare cancers.

To date, only a few studies have evaluated the risk of second and subsequent primary cancers specifically among AYA cancer survivors. These studies are limited by smaller number of cases, shorter periods of follow-up time, and diverse age inclusion criteria. One of the first studies was conducted among patients diagnosed with a first cancer at the ages 0 to 25 in the North of England, between 1968 and 1999. Out of 4,072 individuals between the 0 and 25 with a first primary cancer, 68 second primary cancer cases were found in this study. The results indicated that children and young adults had 4 times the risk of a second primary malignancy compared to the general population, and the risk of a second primary malignancy was non-significantly higher in those diagnosed with a first cancer during young adulthood (15-24 years of age) rather than during childhood (0-14 years of age) (RR=1.2, 95% CI 0.7, 2.0) (Hammal et al., 2005). Two studies have been conducted among AYA cancer survivors in the Netherlands. The first was conducted among patients diagnosed with a first cancer at the ages 12 to 24 in the northern part of the Netherlands between 1989 and 2003. In this study, 1118 patients were diagnosed with a first primary cancer and 26 of these patients developed a second primary cancer. Results of this study show that the SIR for a second cancer is 30.55 (95% CI 19.96, 44.76) among AYA cancer survivors compared to the general population (van Gaal et al., 2009). This study was limited by the small number of second primary cancers observed in the cohort and a median follow-up time of only 5.5 years. The second study was among a cohort of patients (n=23,161) with a first cancer diagnosis at the ages of 15 to 29 in the Netherlands between 1989 and 2009. In this study, 884 developed a second cancer. The results indicate that male AYA cancer survivors have about 6 times the risk (SIR=6.2, 95% CI

5.6-6.9) of developing a second cancer and female AYA cancer survivors have nearly 5 times the risk (SIR=4.8, 95% CI 4.4-5.2) of developing a second cancer (Aben et al., 2012). Also, the most frequently diagnosed second cancers in males were hematological malignancies, gastrointestinal cancers, and gonadal germ cell tumors. Those most frequent in females included breast cancers, melanoma, and hematological malignancies (Aben et al., 2012). While this was the largest study to date, it was limited by a small follow-up period (median 7 years) and results could under-represent the true risk of developing a second cancer. A more recent study was conducted among young adults in British Columbia (ages 20-24) diagnosed with a first cancer from 1970-1995, and followed until 2007. Only 62 second primary cancers were observed in this cohort (n=1248) during the follow-up period. The results showed a three-fold increased risk (SIR=3.0, 95% CI, 2.3-3.8) of second primary cancer in survivors of cancers diagnosed during young adulthood. Breast cancer was the most frequently diagnosed second cancer among females, while cancer of the digestive system was the most frequent second cancer among males (Zhang et al., 2012). Differences in the size, time period, and age composition of study cohorts most likely account for the differences in risk of subsequent cancers observed in these previous studies. These studies also did not explore some of the risk factors (e.g. race, latency, age at first cancer diagnosis) that have been shown to increase the risk for MPCs. Further exploration of the risk and survival of subsequent cancers is needed in this growing body of research in order to identify high-risk groups, enhance screening and prevention, and improve the survival in the AYA population.

## CHAPTER III

### METHODOLOGY

#### **Study Design and Data Source**

This population-based retrospective study utilized data from 9 population-based registries in the Surveillance, Epidemiology, and End Results (SEER) database, collected between January 1, 1973 and December 31, 2012. The 9 SEER registries include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. These nine registries comprise about 10% of the U.S. population, capture nearly 100% of incident cancer cases, and allow for up to 39 years of follow-up time for multiple cancer occurrence (Park et al., 2012).

The SEER Program is the most authoritative and comprehensive source of cancer data in the United States. It was established in 1973 by the National Cancer Institute (NCI) to collect high-quality, population-based data on cancer incidence, treatment, and survival in the U.S. (Park et al., 2012). The population of the SEER database is comparable to the U.S. population with regard to measures of poverty and education, but patients in SEER are slightly more likely to be foreign-born and reside in urban areas (NCI, 2014b). Additionally, the SEER program intentionally over-represents racial and ethnic minorities (Park et al., 2012). Despite these minor discrepancies, SEER data is considered an accurate representation of the U.S. population (Park et al., 2012). SEER has a high-quality assurance program and maintains a high level of incident cancer case ascertainment by searching hospital, radiotherapy, diagnostic

laboratory, and treatment center records (Curtis et al., 2006). All cancers occurring among residents of the defined SEER regions are reportable to the program (Curtis et al., 2006). Patient demographics (sex, race/ethnicity, age, marital status, county of residence), date of cancer diagnosis, primary cancer site and morphology, diagnosis confirmation, stage of disease, first course of cancer treatment, vital status, and cause of death for those who have died are collected by SEER (Park et al., 2012).

### **Study Population**

A cohort of adolescent and young adult individuals diagnosed with a first primary cancer at ages 15 to 39, between January 1, 1973 and December 31, 2012 was assembled using data from 9 registries in the SEER database. The age range of 15-39 used to define adolescents and young adults in this study is based on the definition provided by the National Cancer Institute (NCI) and the Adolescent and Young Adult Oncology Progress Review Group (AYAOPRG). This is an inclusive age range that continues to experience a relative lack of improvement in cancer survival and has unique differences in both medical and psychosocial needs along the cancer trajectory when compared to other age groups (AYAOPRG, 2006).

### **Outcome Assessment**

The first outcome of interest in this study was the incidence of multiple primary cancers ( $\geq 2$  primary cancers) among AYA cancer survivors during follow-up period. The SEER\*STAT 8.1.5 MP-SIR session was used to search the 9 SEER registry incidence files for multiple primary cancers that developed at least 2 months after the patient's first primary cancer diagnosis and before the study cutoff date (i.e. December 31, 2012). A person was counted more than once if diagnosed with 3 or more primary

cancers. SEER uses a combination of clinical diagnosis, pathology, and laboratory reports to determine whether a cancer meets the new primary cancer criteria (NCI, 2012). SEER has specific rules for classifying multiple primary cancers depending on the cancer site of origin, date of the cancer diagnosis, histology, tumor behavior (in situ versus invasive), and laterality of paired organs (NCI, 2012). Generally, SEER considers all metachronous cancers, occurring 2 or more months after the initial cancer diagnosis, as separate primary cancers unless the medical record states that the cancer is recurrent or metastatic (Curtis et al., 2006). Non-melanoma skin cancers, including basal cell and squamous cell skin cancer, were excluded from second and subsequent cancer calculations because most of these cancers are not reportable to the SEER Program (Curtis et al., 2006). Additionally, death certificate only and autopsy only cases were excluded. Although collected by SEER, death certificate and autopsy information often contain ambiguous terminology that makes it difficult to conclusively identify a new primary cancer (NCI, 2012). Therefore, it was beneficial to exclude cases only identified by death certificate or autopsy to reduce error in new primary cancer diagnosis.

The second outcome of interest was survival after a second primary cancer. Survival time was measured from the date of diagnosis of the second primary cancer until the date of death, date of loss to follow-up, or end of the follow-up period. SEER collects information on vital status, date of death, and date of last follow-up. There is more than a 97% rate of follow-up for vital status because SEER actively traces all living patients, including those who have migrated out of the SEER regions, and links with state and national death registries (Curtis et al., 2006). To assess survival, the study population was restricted to all AYA cancer survivors who had only a second primary

cancer. AYA cancer survivors who had a 3<sup>rd</sup> or more primary cancer were excluded because these survivors also previously had a second primary cancer (or other higher order cancer), which could bias the survival estimate. It is reasonable to assume that survivors with a 3<sup>rd</sup> or more primary cancer will have decreased survival time due to the effects of the second cancer (e.g. a weakened immune system).

### **Confounding Variables**

The risk for development of multiple primary cancers, as well as survival after a second primary cancer, vary by a number of demographic, disease-related, and treatment factors (Curtis et al., 2006; Morton et al., 2014b; Milano et al., 2012; Ng et al., 2010; Rosso et al., 2009; Travis et al., 2013). Therefore, these factors were considered as potential confounding variables in the analyses. Selection of the following potential confounding variables was based on *a priori* knowledge. The demographic variables that were considered as potential confounders included age at diagnosis of first primary cancer, attained age (defined as age at second or subsequent cancer diagnosis), sex, and race.

The disease-related variables that were considered as potential confounders were site of first primary cancer, year of diagnosis of first primary cancer, and years after diagnosis of first primary cancer until diagnosis of second primary cancer. First primary tumors were classified into the 10 broad categories provided by the AYA tumor classification scheme which is provided in SEER. This classification scheme is based on the scheme proposed by Barr et al. (2006) and it was developed to better define the major cancer sites that affect AYAs between the ages of 15-39. The categories include: leukemias, lymphomas, CNS and other intracranial and intraspinal neoplasms (all

behaviors), osseous and chondromatous neoplasms, soft tissue sarcomas, germ cell and trophoblastic neoplasms, melanoma and skin carcinomas, carcinomas, miscellaneous specified neoplasms, and unspecified malignant neoplasms. The SEER AYA site variable uses the 3<sup>rd</sup> edition of the International Classification of Diseases for Oncology (ICD-O-3) definitions for cancer morphology and topography. Radiation treatment was the only treatment related variable considered as a potential confounding variable.

Additionally, age at second cancer diagnosis and type of second cancer diagnosis were considered as covariates in the survival analyses (Aim 3). The SEER Site Recode ICD-O-3/WHO 2008 Definition was used to help define the major groupings of second cancer types. The 19 categories include: Oral Cavity and Pharynx; Digestive System; Respiratory System; Bones and Joints; Soft Tissue (including heart); Skin (excluding Basal and Squamous); Breast; Female Genital System; Male Genital System; Brain and Other Nervous System; Eye and Orbit; Urinary System; Endocrine System; Lymphoma; Leukemia; Kaposi Sarcoma; Myeloma; and Miscellaneous. The following table displays the covariates used in the analyses (Appendix Table 2)

| Table 1. Potential Confounding Variables |                                                      |                                                                                                                                          |
|------------------------------------------|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Variable                                 | Variable Type                                        | Variable Categories                                                                                                                      |
| Age at first primary cancer diagnosis    | Categorical                                          | 15-19<br>20-24<br>25-29<br>30-34<br>35-39                                                                                                |
| Sex                                      | Categorical                                          | Male<br>Female                                                                                                                           |
| Race                                     | Categorical                                          | White<br>Black<br>Other (American Indian/AK native,<br>Asian/Pacific Islander)<br>Unknown                                                |
| Type of first primary cancer             | Categorical<br>(AYA site recode ICD-O-3/WHO<br>2008) | Leukemias<br>Lymphomas<br>CNS and other intracranial and intraspinal<br>neoplasms (all behaviors)<br>Osseous and chondromatous neoplasms |

|                                                                          |             |                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                          |             | Soft tissue sarcomas<br>Germ cell and trophoblastic neoplasms<br>Melanoma and skin carcinomas<br>Carcinomas<br>Miscellaneous specified neoplasms<br>Unspecified malignant neoplasms                                                                                                                                                                                                            |
| Years since diagnosis of first cancer until development of second cancer | Categorical | <1 year<br>1-4 years<br>5-9 years<br>≥10 years                                                                                                                                                                                                                                                                                                                                                 |
| Treatment                                                                | Categorical | Radiation<br>No Radiation<br>Unknown                                                                                                                                                                                                                                                                                                                                                           |
| Age at 2 <sup>nd</sup> Cancer diagnosis                                  | Categorical | 15-19<br>20-29<br>30-39<br>40-49<br>50-59<br>60-69<br>70-79<br>80+                                                                                                                                                                                                                                                                                                                             |
| Type of 2 <sup>nd</sup> Cancer                                           | Categorical | Oral Cavity and Pharynx<br>Digestive System<br>Respiratory System<br>Bones and Joints<br>Soft Tissue (including heart)<br>Skin (excluding Basal and Squamous)<br>Breast<br>Female Genital System<br>Male Genital System<br>Central Nervous System<br>Eye and Orbit<br>Urinary System<br>Endocrine System<br>Lymphoma<br>Leukemia<br>Kaposi Sarcoma<br>Myeloma<br>Mesothelioma<br>Miscellaneous |

## Statistical Analyses

**Aim 1.** We estimated the overall and tumor site-specific standard incidence ratios (SIR) of multiple primary cancers following adolescent and young adult cancer. The SIR is the ratio of observed to the expected number of subsequent cancers (O/E). The SIR can be interpreted as the relative risk of MPCs among persons with a first primary cancer compared to the general U.S. population without cancer (Curtis et al., 2006). It was calculated by dividing the *observed* number of subsequent cancers in survivors of AYA cancers by the number of new cancers *expected* if patients in this cohort

experienced the same cancer rates as persons in the general reference population (i.e. the U.S. population). All subsequent cancers, diagnosed 2 or more months following the initial cancer diagnosis, were included in the observed numbers of cases in order to be comparable with the expected number of second and subsequent cancers. A person was counted more than once in the observed calculation if they have been diagnosed with 3 or more primary cancers. The expected number was derived from baseline SEER incidence rates and included all multiple cancers in this age group. Person years-at-risk (PYR) were counted from 2 months after the initial cancer diagnosis until the diagnosis of a MPC, death, or end of the study. The expected number of MPCs is calculated by multiplying the accumulated (PYR) by cancer incidence rates for the US population standardized by age, race, and calendar-year. Since the observed number of multiple cancers is a count of an event in a specified time period, it was assumed that the observed number of multiple cancers followed a Poisson distribution. The Poisson distribution is often used when a number of events are counted across time. Byar's accurate approximation to the exact Poisson distribution was used to calculate 95% confidence intervals for the O/E ratios (Breslow & Day, 1987). The SIRs were stratified by site of first primary cancer, sex, race, age group, year of diagnosis, years after diagnosis of first primary cancer, and radiation therapy (categories as listed in table above).

We also estimated the excess absolute risk (EAR) of multiple primary cancers following adolescent and young adult cancer. The EAR is the difference between the observed subsequent cancer rate in adolescents and young adults with a first primary cancer and the expected subsequent cancer rate in the general U.S. population. The

EAR can be interpreted as the overall burden of multiple cancers in adolescents and young adults with a prior first primary cancer (Curtis et al., 2006). It was calculated using the following equation:  $[(\text{observed} - \text{expected})/\text{PYR}] \times 10,000$ . EARs were also stratified by site of first primary cancer, sex, race, age group, year of diagnosis, years after diagnosis of first primary cancer, and radiation therapy.

The SEER\*STAT 8.1.5 MP-SIR session was used to calculate SIRs, EARs, and 95% confidence intervals.

**Aim 2.** Multivariable Poisson regression models were utilized to assess the simultaneous effect of demographic, disease-related, and treatment factors on the risk of developing multiple primary cancers among survivors of AYA cancers. Poisson regression models, described by Breslow and Day (1987), have recently been used in subsequent primary cancer research (de Gonzalez et al., 2011; Friedman et al., 2010; Jégu et al., 2014; Neglia et al., 2001; Reulen et al., 2008). As opposed to Cox regression, Poisson regression allows for the direct modeling of the SIRs and uses the age-specific incidence rates for the reference population to account for the natural increase in risk of cancer with age during the follow-up period which must be taken into account (Yasui et al., 2003).

A total of 4 models were utilized for this analysis: one model with all MPCs combined as the outcome, one model for breast cancer MPCs as the outcome, one model for leukemia MPCs as the outcome, and one for lymphoma MPCs as the outcome. The disease-specific models were used to assess the risk of developing some of the most common types of MPCs that develop in AYAs, which include breast cancer, lymphomas, and leukemias. There was also an elevated risk of developing these

specific MPCs, which was observed in the analyses in aim1. The incidence rate ratios (IRR) for developing a second cancer were estimated for each demographic, disease, and treatment factor included in the model(s). A backwards variable selection strategy was utilized to obtain the best model(s). Age at first cancer diagnosis, sex, race, type of first cancer, year of diagnosis of first primary cancer, years after diagnosis of first primary cancer until development of subsequent primary cancer, and radiation treatment for first cancer were considered as potential covariates. The expected number of subsequent cancers, calculated from age, race, and calendar-year standardized cancer incidence rates, were included as the offset in each model. The final models controlled for age at first cancer diagnosis, sex, race, type of first cancer, years after diagnosis of first primary cancer until development of subsequent primary cancer, and radiation treatment for first cancer. Type of first primary cancer was dichotomized into solid and non-solid cancers (leukemias and lymphomas) in order to obtain enough power for the models to estimate risks. All analyses for this aim were completed using SAS<sup>®</sup> 9.3 software.

**Aim 3.** Kaplan-Meier survival curves were utilized to determine the overall survival rates of AYA cancer survivors after diagnosis of a second primary cancer by age at first cancer diagnosis, sex, race, type of first cancer, year of diagnosis of first primary cancer, years after diagnosis of first primary cancer until development of subsequent primary cancer, and radiation treatment for first cancer. The log-rank test was used to compare survival in these different groups (p-value < 0.05 indicated statistical significance).

Cox proportional hazards modeling was used to assess the effect of patient and disease characteristics on survival rates of AYA cancer survivors after diagnosis of a second primary cancer. Again, this analysis was restricted to all AYA cancer survivors who had only a second primary cancer, and those who had a 3<sup>rd</sup> or more primary cancer were excluded. The proportional hazards assumption was checked for every variable in the model using three different methods: graphically with log[-log S(t)] plots, interaction terms with time, and checking the deviance residuals. If the results from each method differed, the log[-log S(t)] plots were used to make a final determination. The hazard ratio (HR) for survival of a second cancer was estimated for each demographic, disease, and treatment factor included in the model. We considered age at first cancer diagnosis, age at second cancer diagnosis, sex, race, type of first cancer, type of second cancer, year of diagnosis of first primary cancer, years after diagnosis of first primary cancer until development of second primary cancer, and treatment for first cancer as potential covariates. A backwards variable selection strategy was used to obtain the best model. All covariates were included in the model. All analyses for this aim were completed using SAS<sup>®</sup> 9.3 software.

### **Methodological Considerations**

One of the main anticipated challenges of this study was whether there would be a sufficient number of multiple primary cancers to perform a stratified analysis by first primary tumor site. In order to obtain enough numbers, cancer sites were grouped into more broad categories. Our approach utilized the adapted classification scheme for tumors of adolescents and young adults. This classification scheme, available in SEER,

is based on the scheme proposed by Barr et al. (2006) and it was developed to better define the major cancer sites that affect AYAs between the ages of 15-39.

Another challenge was how to categorize types of MPCs since there were over 50 different types observed in this study. This was especially important when considering type of second primary cancer as a covariate in the survival analyses for aim 3. We wanted to create representative categories that reflect the types of second cancers occurring in AYAs while maintaining good statistical power of the model. The SEER Site Recode ICD-O-3/WHO 2008 Definition was used to define the major groupings of MPC types. A total of 19 major categories were used in the analyses. The SIR and EARs are also displayed for these 19 categories. However, if the SIR for a specific site was particularly high (i.e.  $SIR \geq 3$ ), it was also presented in the results.

## CHAPTER IV

### RESULTS

#### **Cohort Characteristics**

We conducted a population-based retrospective study to assess risk for the development of MPCs in survivors of AYA cancers compared to the general U.S. population, and to evaluate the effect subsequent cancers have on survival of patients in this population. A total of 227,569 individuals in 9 registries in the SEER program were diagnosed with a first primary cancer at the ages of 15 to 39 from 1973 to 2012. These individuals yielded 2,737,751 person-years at risk over the follow-up period.

Table 2 displays the frequency and percent of the cohort demographic, disease, and treatment characteristics. The majority of survivors of AYA cancers in this cohort were female and White (58% and 81%, respectively). The majority of first primary cancers in this cohort were carcinomas (solid tumors including digestive, respiratory, endocrine, breast, reproductive cancers etc.) (49%), followed by lymphomas (12.5%) and Melanoma and skin carcinomas (12%). Among all survivors, 15,069 individuals (6.6%) developed a MPC two or more months after the first primary cancer.

Approximately 46% of those with a MPC developed their first primary cancer between the ages of 35 and 39, compared to 38% of those without a MPC. The majority of those with a MPC developed the subsequent primary cancer 10 or more years after the first primary cancer (56%). Of those that developed a MPC, 13,421 (89.1%) developed only one subsequent primary cancer, 1,431 (9.5%) developed 2 subsequent primary cancers, and 217 (1.4%) developed 3 or more subsequent primary cancers. The mean

age at MPC diagnosis (includes all MPCs) was 46.9 years. About 35% of individuals with a MPC received any type of radiation as treatment for their first primary cancer, compared to nearly 32% of those without a MPC. Nearly 59% of survivors with a MPC were alive at the time of this analysis, compared to 68.5% of survivors without a MPC.

**TABLE 2 – Characteristics of Survivors of AYA Cancer Cohort (15-39 years of age), SEER 9 1973-2012**

|                                                                                          | Overall Cohort<br>n = 227,569 | Survivors without a Multiple<br>Primary Cancer<br>n = 212,500 | Survivors with a Multiple Primary<br>Cancer<br>n = 15,069 |
|------------------------------------------------------------------------------------------|-------------------------------|---------------------------------------------------------------|-----------------------------------------------------------|
| <b>Sex (%)</b>                                                                           |                               |                                                               |                                                           |
| Male                                                                                     | 94,958 (41.7)                 | 89,702 (42.2)                                                 | 5236 (34.7)                                               |
| Female                                                                                   | 132,631 (58.3)                | 122,798 (57.8)                                                | 9833 (65.3)                                               |
| <b>Race (%)</b>                                                                          |                               |                                                               |                                                           |
| White                                                                                    | 184,746 (81.2)                | 172,132 (81.0)                                                | 12,614 (83.7)                                             |
| Black                                                                                    | 22,743 (10.0)                 | 21,226 (10.0)                                                 | 1,517 (10.1)                                              |
| Other                                                                                    | 17,338 (7.6)                  | 16,412 (7.7)                                                  | 926 (6.1)                                                 |
| Unknown                                                                                  | 2,742 (1.2)                   | 2,730 (1.3)                                                   | 12 (0.1)                                                  |
| <b>Age at 1<sup>st</sup> Cancer Diagnosis (%)</b>                                        |                               |                                                               |                                                           |
| 15-19                                                                                    | 14,287 (6.3)                  | 13,761 (6.5)                                                  | 526 (3.5)                                                 |
| 20-24                                                                                    | 24,015 (10.6)                 | 22,936 (10.8)                                                 | 1,079 (7.2)                                               |
| 25-29                                                                                    | 40,233 (17.7)                 | 37,988 (17.9)                                                 | 2,245 (14.9)                                              |
| 30-34                                                                                    | 60,861 (26.7)                 | 56,625 (26.6)                                                 | 4,236 (28.1)                                              |
| 35-39                                                                                    | 88,173 (38.7)                 | 81,190 (38.2)                                                 | 6,983 (46.3)                                              |
| <b>Type of 1<sup>st</sup> Primary Cancer (%)</b>                                         |                               |                                                               |                                                           |
| Leukemias                                                                                | 8,952 (3.9)                   | 8,752 (4.1)                                                   | 200 (1.3)                                                 |
| Lymphomas                                                                                | 28,528 (12.5)                 | 26,540 (12.5)                                                 | 1,988 (13.2)                                              |
| CNS and Other                                                                            | 9,881 (4.3)                   | 9,567 (4.5)                                                   | 314 (2.1)                                                 |
| Intracranial & Intraspinal<br>Neoplasms                                                  |                               |                                                               |                                                           |
| Osseous & Chondromatous<br>Neoplasms                                                     | 3,166 (1.4)                   | 3,046 (1.4)                                                   | 120 (0.8)                                                 |
| Soft Tissue Sarcomas                                                                     | 15,709 (6.9)                  | 14,833 (7.0)                                                  | 876 (5.8)                                                 |
| Germ Cell & Trophoblastic<br>Neoplasms                                                   | 19,995 (8.8)                  | 18,809 (8.9)                                                  | 1,186 (7.9)                                               |
| Melanoma & Skin Carcinomas                                                               | 26,898 (11.8)                 | 24,972 (11.8)                                                 | 1,926 (12.8)                                              |
| Carcinomas*                                                                              | 110,793 (48.7)                | 102,513 (48.2)                                                | 8,280 (54.9)                                              |
| Miscellaneous Specified Neoplasms                                                        | 2,684 (1.2)                   | 2,567 (1.2)                                                   | 117 (0.8)                                                 |
| Unspecified Malignant Neoplasms                                                          | 962 (0.4)                     | 900 (0.4)                                                     | 62 (0.4)                                                  |
| <b>Year of 1<sup>st</sup> Cancer Diagnosis (%)</b>                                       |                               |                                                               |                                                           |
| 1973-1979                                                                                | 26,767 (11.8)                 | 23,396 (11.0)                                                 | 3,371 (22.4)                                              |
| 1980-1989                                                                                | 54,846 (24.1)                 | 49,406 (23.3)                                                 | 5,440 (36.1)                                              |
| 1990-1999                                                                                | 63,622 (28.0)                 | 59,525 (28.0)                                                 | 4,097 (27.2)                                              |
| 2000-2012                                                                                | 82,334 (36.1)                 | 80,173 (37.7)                                                 | 2,161 (14.3)                                              |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer (%)</b>                                 |                               |                                                               |                                                           |
| Any Radiation                                                                            | 72,670 (31.9)                 | 67,467 (31.7)                                                 | 5,203 (34.5)                                              |
| No Radiation                                                                             | 151,524 (66.6)                | 141,876 (66.8)                                                | 9,648 (64.0)                                              |
| Unknown                                                                                  | 3,375 (1.5)                   | 3,157 (1.5)                                                   | 218 (1.5)                                                 |
| <b>Vital Status (%)</b>                                                                  |                               |                                                               |                                                           |
| Alive                                                                                    | 154,389 (67.8)                | 145,554 (68.5)                                                | 8,835 (58.6)                                              |
| Dead                                                                                     | 73,180 (32.2)                 | 66,946 (31.5)                                                 | 6,234 (41.4)                                              |
| <b>Number of Subsequent Primary Cancers (%)</b>                                          |                               |                                                               |                                                           |
| 1 only                                                                                   | ---                           | ---                                                           | 13,421 (89.1)                                             |
| 2 only                                                                                   |                               |                                                               | 1,431 (9.5)                                               |
| 3 or more                                                                                |                               |                                                               | 217 (1.4)                                                 |
| <b>Time Since AYA 1<sup>st</sup> Cancer Diagnosis to Second Cancer<br/>Diagnosis (%)</b> |                               |                                                               |                                                           |
| 2-11 Months                                                                              | ---                           | ---                                                           | 1,011 (6.7)                                               |
| 1-4 Years                                                                                |                               |                                                               | 2,970 (19.7)                                              |
| 5-9 Years                                                                                |                               |                                                               | 2,719 (18.0)                                              |
| ≥10 Years                                                                                |                               |                                                               | 8,369 (55.6)                                              |

Mean Age at Subsequent Cancer Diagnosis (SD)

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46.9 (10.7)

\*Carcinomas include: thyroid carcinoma; nasopharyngeal carcinoma; other sites in lip, oral cavity, and pharynx; nasal cavity, mid-ear, sinus, larynx, ill-def head and neck; carcinoma of the trachea, bronchus, and lung; carcinoma of the breast; carcinoma of genitourinary tract; carcinoma of gastrointestinal tract; adrenocortical carcinoma; other and ill-def sites, NOS

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MPC defined as subsequent cancer developing 2+ months after first primary cancer

## Specific Aim 1

To estimate the overall and tumor site-specific standard incidence ratios (SIR) and the excess absolute risk (EAR) of multiple primary cancers following adolescent and young adult cancer by site of first primary cancer, gender, race/ethnicity, age at first primary cancer group, year of diagnosis, years after diagnosis of first primary cancer, and treatment type for first primary cancer.

**Overall Risk.** Table 3 displays the overall SIRs and EARs for MPCs in survivors of AYA cancer. A total of 17,001 multiple primary cancers were observed among 15,069 survivors of adolescent and young adult cancers from 1973 to 2012. Overall, survivors of AYA cancers had an 86% higher risk of developing a MPC (SIR=1.86, 95% CI 1.84-1.89) compared to the general U.S. population and the excess absolute risk was 28.78 excess MPC cases per 10,000 person-years.

More MPCs were observed among females than males, but the overall risk for a MPC was higher in males (SIR=1.99, 95% CI 1.94-2.04) compared to females (SIR=1.80, 95% CI 1.77-1.84). However, the EAR was higher in females (EAR=29.24) compared to males (EAR=28.02). Although there was a larger number of MPCs observed in Whites, both the SIRs and EARs were higher in Blacks ((SIR=2.45, 95% CI 2.34-2.57, EAR=47.36)) and Other race ((SIR=2.59, 95% CI 2.43-2.75, EAR=37.31)) compared to Whites ((SIR=1.80, 95% CI 1.77-1.83, EAR=27.24)).

The risk for an MPC decreased with increasing age at first primary cancer diagnosis. The SIR was highest in those diagnosed with a first primary cancer between the ages of 15 and 19 (SIR=3.03, 95% CI 2.79-3.29) and lowest in those diagnosed between the ages 35 and 39 (SIR=1.70, 95% CI 1.66-1.73). The opposite trend was observed for the EARs.

Individuals diagnosed with soft tissue sarcomas ((SIR=2.61, 95% CI 2.44-2.78), EAR=45.68) and lymphomas ((SIR=2.58, 95% CI 2.48-2.69), EAR=39.55) as the first primary cancer had the highest risk for the development of a subsequent cancer. The risk for MPC was also the highest 2-11 months after the time of first cancer diagnosis ((SIR=5.60, 95% CI 5.27-5.96), EAR=47.40)) and lowest for a time span of 10 or more years from first primary cancer diagnosis ((SIR=1.47, 95% CI 1.44-1.50), EAR=25.50). Additionally, individuals who received any type of radiation as treatment for their first primary cancer had a higher risk for an MPC ((SIR=2.44, 95% CI 2.38-2.51), EAR=44.00) compared to those who did not receive radiation treatment ((SIR=1.65, 95% CI 1.62-1.68), EAR=22.37).

**TABLE 3 – Overall Risk of MPC among 15,069 Survivors of Adolescent and Young Adult Cancer by Sex, Age, Race, 1<sup>st</sup> Primary Cancer, Latency, Year of 1<sup>st</sup> Cancer Diagnosis, and Radiation Treatment, SEER 9 1973-2012**

|                                               | Observed<br>(O) | Expected<br>(E) | SIR<br>(O/E) | 95% CI        | EAR<br>(O-E) |
|-----------------------------------------------|-----------------|-----------------|--------------|---------------|--------------|
| <b>Total MPCs</b>                             | 17,001          | 9,122.37        | 1.86*        | (1.84 – 1.89) | 28.78        |
| <b>Sex</b>                                    |                 |                 |              |               |              |
| Male                                          | 5,863           | 2,946.97        | 1.99*        | (1.94 – 2.04) | 28.02        |
| Female                                        | 11,138          | 6,175.40        | 1.80*        | (1.77 – 1.84) | 29.24        |
| <b>Race</b>                                   |                 |                 |              |               |              |
| White                                         | 14,250          | 7,926.65        | 1.80*        | (1.77 – 1.83) | 27.24        |
| Black                                         | 1,695           | 691.12          | 2.45*        | (2.34 – 2.57) | 47.36        |
| Other                                         | 1,043           | 403.07          | 2.59*        | (2.43 – 2.75) | 37.31        |
| Unknown                                       | 13              | 101.53          | 0.13*        | (0.07 – 0.22) | -27.03       |
| <b>Age at 1<sup>st</sup> Cancer Diagnosis</b> |                 |                 |              |               |              |
| 15-19                                         | 580             | 191.22          | 3.03*        | (2.79 – 3.29) | 20.94        |
| 20-24                                         | 1,212           | 510.86          | 2.37*        | (2.24 – 2.51) | 21.84        |
| 25-29                                         | 2,485           | 1,249.93        | 1.99*        | (1.91 – 2.07) | 23.62        |
| 30-34                                         | 4,817           | 2,510.47        | 1.92*        | (1.86 – 1.97) | 31.59        |

|                                                      |        |          |       |               |       |
|------------------------------------------------------|--------|----------|-------|---------------|-------|
| 35-39                                                | 7,907  | 4,659.89 | 1.70* | (1.66 – 1.73) | 33.20 |
| <b>Type of 1<sup>st</sup> Primary Cancer</b>         |        |          |       |               |       |
| Leukemias                                            | 220    | 121.96   | 1.80* | (1.57 – 2.06) | 16.48 |
| Lymphomas                                            | 2,240  | 866.84   | 2.58* | (2.48 – 2.69) | 39.55 |
| CNS and Other                                        | 335    | 174.4    | 1.92* | (1.72 – 2.14) | 18.53 |
| Intracranial & Intraspinal                           |        |          |       |               |       |
| Neoplasms                                            |        |          |       |               |       |
| Osseous & Chondromatous                              | 133    | 71.77    | 1.85* | (1.55 – 2.20) | 18.34 |
| Neoplasms                                            |        |          |       |               |       |
| Soft Tissue Sarcomas                                 | 940    | 360.84   | 2.61* | (2.44 – 2.78) | 45.68 |
| Germ Cell & Trophoblastic                            | 1,306  | 792.83   | 1.65* | (1.56 – 1.74) | 17.08 |
| Neoplasms                                            |        |          |       |               |       |
| Melanoma & Skin Carcinomas                           | 2,246  | 1,375.20 | 1.63* | (1.57 – 1.70) | 22.35 |
| Carcinomas**                                         | 9,382  | 5,240.67 | 1.79* | (1.75 – 1.83) | 30.53 |
| Miscellaneous Specified                              | 132    | 83.99    | 1.57* | (1.32 – 1.86) | 17.84 |
| Neoplasms                                            |        |          |       |               |       |
| Unspecified Malignant                                | 67     | 33.86    | 1.98* | (1.53 – 2.51) | 31.20 |
| Neoplasms                                            |        |          |       |               |       |
| <b>Time Since AYA 1<sup>st</sup> Cancer</b>          |        |          |       |               |       |
| <b>Diagnosis to Subsequent Cancer</b>                |        |          |       |               |       |
| <b>Diagnosis</b>                                     |        |          |       |               |       |
| 2-11 Months                                          | 1,026  | 183.10   | 5.60* | (5.27 – 5.96) | 47.4  |
| 1-4 Years                                            | 3,066  | 884.61   | 3.47* | (3.34 – 3.59) | 32.35 |
| 5-9 Years                                            | 2,919  | 1,252.14 | 2.33* | (2.25 – 2.42) | 26.43 |
| ≥10 Years                                            | 9,990  | 6,892.53 | 1.47* | (1.44 – 1.50) | 25.40 |
| <b>Year of 1<sup>st</sup> Cancer Diagnosis</b>       |        |          |       |               |       |
| 1973-1979                                            | 4,024  | 2,802.61 | 1.44* | (1.39 – 1.48) | 21.79 |
| 1980-1989                                            | 6,212  | 3,580.99 | 1.73* | (1.69 – 1.78) | 27.72 |
| 1990-1999                                            | 4,480  | 2,025.73 | 2.21* | (2.15 – 2.28) | 30.91 |
| 2000-2012                                            | 2,285  | 713.05   | 3.20* | (3.07 – 3.34) | 36.24 |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer</b> |        |          |       |               |       |
| Radiation                                            | 5,873  | 2,403.56 | 2.44* | (2.38 – 2.51) | 44.00 |
| No Radiation                                         | 10,889 | 6,608.51 | 1.65* | (1.62 – 1.68) | 22.37 |
| Unknown                                              | 239    | 110.3    | 2.17* | (1.90 – 2.46) | 36.32 |

\*p-value < 0.05

\*\*Carcinomas include: thyroid carcinoma; nasopharyngeal carcinoma; other sites in lip, oral cavity, and pharynx; nasal cavity, mid-ear, sinus, larynx, ill-def head and neck; carcinoma of the trachea, bronchus, and lung; carcinoma of the breast; carcinoma of genitourinary tract; carcinoma of gastrointestinal tract; adrenocortical carcinoma; other and ill-def sites, NOS

**Risk per Subsequent Cancer Site.** The standardized incidence ratios and excess absolute risks for each subsequent cancer site are presented in Table 4. Breast cancers, followed by cancers of the digestive system, and skin cancers (excluding Basal and Squamous cell cancers), respiratory system cancers, and genital system cancers were the most commonly diagnosed MPCs among survivors of AYA cancers. Survivors had the highest risk of developing a subsequent vaginal cancer (SIR=5.49, 95% CI 4.08-7.21), Acute Monocytic Leukemia (SIR=5.33, 95% CI 3.41-7.93), Acute Non-

Lymphocytic Leukemia (ANLL) (SIR=4.53, 95% CI 4.05-5.06), and Acute Myeloid Leukemia (SIR=4.39, 95% CI 3.89-4.95). The excess absolute risk was highest for breast cancer (EAR=8.15) and skin cancers (excluding Basal and Squamous) (EAR=3.64).

**TABLE 4 –Overall Risk of Multiple Primary Cancers by Site in Survivors of Adolescent and Young Adult Cancer, SEER 9 1973-2012**

| MPC Site                              | O      | E        | SIR   | 95% CI      | EAR   |
|---------------------------------------|--------|----------|-------|-------------|-------|
| All sites                             | 17,001 | 9,122.37 | 1.86* | 1.84 - 1.89 | 28.78 |
| All Solid Tumors                      | 14,960 | 8,228.04 | 1.82* | 1.79 - 1.85 | 24.59 |
| Oral Cavity and Pharynx               | 537    | 226.53   | 2.37* | 2.17 - 2.58 | 1.13  |
| Salivary Gland                        | 108    | 27.46    | 3.93* | 3.23 - 4.75 | 0.29  |
| Digestive System                      | 2,088  | 1,201.60 | 1.74* | 1.66 - 1.81 | 3.24  |
| Respiratory System                    | 1,398  | 847.67   | 1.65* | 1.56 - 1.74 | 2.01  |
| Bones and Joints                      | 74     | 21.15    | 3.50* | 2.75 - 4.39 | 0.19  |
| Soft Tissue including Heart           | 251    | 68.07    | 3.69* | 3.25 - 4.17 | 0.67  |
| Skin excluding Basal and Squamous     | 1,639  | 641.42   | 2.56* | 2.43 - 2.68 | 3.64  |
| Breast                                | 4,637  | 2,404.85 | 1.93* | 1.87 - 1.98 | 8.15  |
| Female Genital System                 | 1,258  | 902.93   | 1.39* | 1.32 - 1.47 | 1.3   |
| Vagina                                | 51     | 9.3      | 5.49* | 4.08 - 7.21 | 0.15  |
| Male Genital System                   | 1,063  | 787.32   | 1.35* | 1.27 - 1.43 | 1.01  |
| Testis                                | 387    | 101.8    | 3.80* | 3.43 - 4.2  | 1.04  |
| Urinary System                        | 868    | 479.43   | 1.81* | 1.69 - 1.94 | 1.42  |
| Eye and Orbit                         | 27     | 17.69    | 1.53* | 1.66 - 3.94 | 0.03  |
| Brain and Other Nervous System        | 309    | 154.26   | 2.00* | 1.01 - 2.22 | 0.57  |
| Endocrine System                      | 766    | 437.01   | 1.75* | 1.63 - 1.88 | 1.2   |
| Lymphoma                              | 1,142  | 470.28   | 2.43* | 2.29 - 2.57 | 2.45  |
| Hodgkin Lymphoma                      | 130    | 87.36    | 1.49* | 1.24 - 1.77 | 0.16  |
| Non-Hodgkin Lymphoma                  | 1,012  | 382.92   | 2.64* | 2.48 - 2.81 | 2.3   |
| Myeloma                               | 97     | 82.67    | 1.17  | 0.95 - 1.43 | 0.05  |
| Leukemia                              | 503    | 199.51   | 2.52* | 2.31 - 2.75 | 1.11  |
| Acute Lymphocytic Leukemia            | 35     | 16.77    | 2.09* | 1.45 - 2.9  | 0.07  |
| Non-Lymphocytic Leukemia              | 395    | 110.39   | 3.58* | 3.23 - 3.95 | 1.04  |
| Acute Non-Lymphocytic Leukemia (ANLL) | 317    | 69.91    | 4.53* | 4.05 - 5.06 | 0.9   |
| Myeloid and Monocytic Leukemia        | 366    | 102.45   | 3.57* | 3.22 - 3.96 | 0.96  |
| Acute Myeloid Leukemia                | 271    | 61.69    | 4.39* | 3.89 - 4.95 | 0.76  |
| Acute Monocytic Leukemia              | 24     | 4.5      | 5.33* | 3.41 - 7.93 | 0.07  |
| Chronic Myeloid Leukemia              | 58     | 33.82    | 1.71* | 1.30 - 2.22 | 0.09  |
| Mesothelioma                          | 16     | 9.8      | 1.63  | 0.93 - 2.65 | 0.02  |
| Kaposi Sarcoma                        | 119    | 64.02    | 1.86* | 1.54 - 2.22 | 0.2   |
| Miscellaneous                         | 209    | 106.18   | 1.97* | 1.71 - 2.25 | 0.38  |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

**MPC Risk by Sex.** The overall and site specific risks for MPCs in survivors of AYA cancer were stratified by sex (Table 5). Both males and females had high risks of developing subsequent ANLL, Acute Myeloid Leukemia, and Acute Monocytic Leukemia. Males also had higher risk for the development of a subsequent salivary

gland cancer (SIR=4.78, 95% CI 3.55-6.31), cancer of the bones and joints (SIR=4.48, 95% CI 3.22-6.08), and soft tissue cancers (SIR=3.96, 95% CI 3.27-4.75), while females had a high risk for the development of a subsequent vaginal cancer (SIR=5.49, 95% CI 4.08-7.21) and Kaposi Sarcoma (SIR=4.07, 95% CI 1.32-9.50). Among males, EARs were highest for Non-Hodgkin's lymphoma (EAR=4.81) and cancers of the digestive system (EAR=4.36), and EARs for a subsequent breast cancer (EAR=13.13) were highest in females.

**TABLE 5 – Overall and Site specific Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by Sex, SEER 9 1973-2012**

| MPC Site                              | Males |               |       | Females |               |       |
|---------------------------------------|-------|---------------|-------|---------|---------------|-------|
|                                       | SIR   | 95% CI        | EAR   | SIR     | 95% CI        | EAR   |
| All sites                             | 1.99* | (1.94 – 2.04) | 28.02 | 1.80*   | (1.77 – 1.84) | 29.24 |
| All Solid Tumors                      | 1.86* | (1.80 – 1.91) | 20.93 | 1.80*   | (1.77 – 1.84) | 26.84 |
| Oral Cavity and Pharynx               | 2.41* | (2.15 – 2.69) | 1.81  | 2.31*   | (2.02 – 2.65) | 0.72  |
| Salivary Gland                        | 4.78* | (3.55 – 6.31) | 0.38  | 3.41*   | (2.59 – 4.41) | 0.24  |
| Digestive System                      | 1.86* | (1.75 – 1.98) | 4.36  | 1.64*   | (1.54 – 1.74) | 2.55  |
| Respiratory System                    | 1.72* | (1.58 – 1.87) | 2.30  | 1.60*   | (1.50 – 1.72) | 1.83  |
| Bones and Joints                      | 4.48* | (3.22 – 6.08) | 0.31  | 2.75*   | (1.89 – 3.86) | 0.12  |
| Soft Tissue including Heart           | 3.96* | (3.27 – 4.75) | 0.83  | 3.49*   | (2.93 – 4.12) | 0.57  |
| Skin excluding Basal and Squamous     | 2.74* | (2.53 – 2.95) | 4.14  | 2.44*   | (2.29 – 2.60) | 3.34  |
| Breast                                | 1.79  | (0.89 – 3.20) | 0.05  | 1.93*   | (1.87 – 1.98) | 13.13 |
| Female Genital System                 | 0     | 0             | 0     | 1.39*   | (1.32 – 1.47) | 2.09  |
| Vagina                                | 0     | 0             | 0     | 5.49*   | (4.08 – 7.21) | 0.25  |
| Male Genital System                   | 1.35* | (1.27 – 1.43) | 2.65  | 0       | 0             | 0     |
| Testis                                | 3.80* | (3.43 – 4.20) | 2.74  | 0       | 0             | 0     |
| Urinary System                        | 1.89* | (1.73 – 2.06) | 2.31  | 1.71*   | (1.54 – 1.9)  | 0.87  |
| Eye and Orbit                         | 1.47  | (0.74 – 2.64) | 0.03  | 1.57    | (0.89 – 2.54) | 0.03  |
| Brain and Other Nervous System        | 2.33* | (1.99 – 2.72) | 0.9   | 1.73*   | (1.46 – 2.03) | 0.36  |
| Endocrine System                      | 2.43* | (2.09 – 2.82) | 0.99  | 1.62*   | (1.49 – 1.75) | 1.33  |
| Lymphoma                              | 3.46* | (3.22 – 3.72) | 5.19  | 1.52*   | (1.38 – 1.69) | 0.78  |
| Hodgkin Lymphoma                      | 1.95* | (1.55 – 2.43) | 0.37  | 1.08    | (0.8 – 1.42)  | 0.02  |
| Non-Hodgkin Lymphoma                  | 3.81* | (3.53 – 4.11) | 4.81  | 1.63*   | (1.46 – 1.81) | 0.76  |
| Myeloma                               | 1.51* | (1.13 – 1.98) | 0.17  | 0.93    | (0.68 – 1.25) | -0.02 |
| Leukemia                              | 2.39* | (2.08 – 2.73) | 1.21  | 2.63*   | (2.34 – 2.96) | 1.05  |
| Acute Lymphocytic Leukemia            | 1.98* | (1.11 – 3.26) | 0.07  | 2.18*   | (1.33 – 3.36) | 0.06  |
| Non-Lymphocytic Leukemia              | 3.66* | (3.12 – 4.26) | 1.17  | 3.52*   | (3.08 – 4.01) | 0.96  |
| Acute Non-Lymphocytic Leukemia (ANLL) | 4.80* | (4.01 – 5.69) | 1     | 4.36*   | (3.76 – 5.04) | 0.84  |
| Myeloid and Monocytic Leukemia        | 3.56* | (3.01 – 4.17) | 1.04  | 3.58*   | (3.12 – 4.10) | 0.91  |
| Acute Myeloid Leukemia                | 4.67* | (3.85 – 5.61) | 0.85  | 4.21*   | (3.58 – 4.92) | 0.71  |
| Acute Monocytic Leukemia              | 4.45* | (1.92 – 8.76) | 0.06  | 5.92*   | (3.38 – 9.61) | 0.08  |
| Chronic Myeloid Leukemia              | 1.67* | (1.09 – 2.45) | 0.10  | 1.75*   | (1.20 – 2.48) | 0.08  |
| Mesothelioma                          | 1.33  | (0.53 – 2.73) | 0.02  | 1.99    | (0.91 – 3.78) | 0.03  |
| Kaposi Sarcoma                        | 1.82* | (1.50 – 2.18) | 0.49  | 4.07*   | (1.32 – 9.50) | 0.02  |
| Miscellaneous                         | 1.64* | (1.28 – 2.07) | 0.27  | 2.19*   | (1.84 – 2.59) | 0.44  |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

**MPC Risk by Race.** The risk estimates for MPCs by race are shown in Table 6.

Overall, minority groups (blacks and other) were at greater risk of a subsequent cancer compared to whites. Site specific analysis demonstrated the only two exceptions were the salivary gland and acute monocytic leukemia. The risk of subsequent salivary gland cancer among whites (SIR = 4.03) notably exceeded blacks (SIR =1.92), but not other races (SIR = 5.76). Conversely, risk of subsequent acute monocytic leukemia was higher in whites (SIR = 5.28) compared with other races (SIR = 3.89), but not blacks (SIR = 9.08) Whites, Blacks and Other race were at greater than 4 times the risk for subsequent ANLL, Acute Myeloid Leukemia, vaginal cancer. Other race was also at a significantly higher risk for subsequent cancer of the bones and joints (SIR=16.92) and prostate cancer (SIR=7.48). EARs were elevated for breast cancer in Blacks and Other race (EAR=21.92 and EAR=11.62, respectively) compared to whites (EAR=6.86).

TABLE 6 – Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by Race, SEER 9 1973-2012

| MPC Site                              | White |           |       | Black |            |       | Other  |            |       | Unknown |         |       |
|---------------------------------------|-------|-----------|-------|-------|------------|-------|--------|------------|-------|---------|---------|-------|
|                                       | SIR   | 95% CI    | EAR   | SIR   | 95% CI     | EAR   | SIR    | 95% CI     | EAR   | SIR     | 95% CI  | EAR   |
| All sites                             | 1.80* |           | 27.24 | 2.45* |            | 47.36 | 2.59*  |            | 37.31 | 0.13*   | 0.0 -   | -     |
| All Solid Tumors                      | 1.75* | 1.7 - 1.8 | 23.24 | 2.41* | 2.3 - 2.5  | 40.96 | 2.48*  | 2.3 - 2.5  | 31.93 | 0.13*   | 0.2     | 27.03 |
| Oral Cavity and Pharynx               | 2.34* | 1.7 - 1.7 | 1.12  | 2.95* | 2.2 - 2.5  | 1.59  | 2.60*  | 2.2 - 2.5  | 1.08  | 0.13*   | 0.0 -   | -     |
| Salivary Gland                        | 4.03* | 2.1 - 2.5 | 0.3   | 1.92  | 2.2 - 3.8  | 0.09  | 5.76*  | 2.2 - 3.8  | 0.48  | 0       | 0.2     | 24.21 |
| Digestive System                      |       | 3.2 - 4.9 |       |       | 0.5 - 4.9  |       |        | 0.5 - 4.9  |       | 0       | 0 - 1.4 | -0.79 |
| Respiratory System                    | 1.68* | 1.6 - 1.7 | 2.91  | 1.89* | 1.6 - 2.1  | 5.08  | 2.60*  | 1.6 - 2.1  | 6.7   | 0       | 0 -     | -0.09 |
| Bones and Joints                      | 1.58* | 1.4 - 1.6 | 1.82  | 2.21* | 1.9 - 2.5  | 4.78  | 2.27*  | 1.9 - 2.5  | 37.31 | 0.08*   | 0 - 0.4 | -3.59 |
| Soft Tissue including Heart           | 3.04* |           | 0.16  | 2.98  |            | 0.13  | 16.92* |            | 0.71  | 0.00*   | 0 - 0.4 | -2.72 |
| Skin excluding Basal and Squamous     |       | 2.3 - 3.9 |       |       | 0.8 - 7.6  |       |        | 0.8 - 7.6  |       | 0       | 0 -     | -0.08 |
| Breast                                | 3.42* | 2.9 - 3.9 | 0.6   | 4.89* | 3.3 - 6.9  | 1.13  | 7.00*  | 3.3 - 6.9  | 1.15  | 0       | 14.0    | -0.24 |
| Female Genital System                 | 2.55* |           | 4.17  | 3.31* |            | 0.49  | 5.81*  |            | 1.16  | 0       | 0 - 4.6 | -0.24 |
| Vagina                                |       | 2.4 - 2.6 |       |       | 1.8 - 5.4  |       |        | 1.8 - 5.4  |       | 0.82    | 0.3 -   | -0.46 |
| Male Genital System                   | 1.78* | 1.7 - 1.8 | 6.86  | 3.30* | 3.0 - 3.5  | 21.92 | 2.51*  | 3.0 - 3.5  | 11.62 | 0.04*   | 1.6     | -0.46 |
| Testis                                | 1.35* |           | 1.17  | 1.73* |            | 2.31  | 1.73*  |            | 2.44  | 0.04*   | 0 - 0.2 | -7.27 |
| Urinary System                        |       | 1.2 - 1.4 |       |       | 1.4 - 2.0  |       |        | 1.4 - 2.0  |       | 0.21*   | 0.0 -   | -     |
| Eye and Orbit                         | 4.86* |           | 0.13  | 7.42* |            | 0.37  | 10.44* |            | 0.21  | 10.96   | 0.7     | -2.26 |
| Brain and Other Nervous System        |       | 3.4 - 6.7 |       |       | 3.4 - 14.0 |       |        | 3.4 - 14.0 |       | 0.00*   | 0.2 -   | 0.28  |
| Endocrine System                      | 1.37* | 1.2 - 1.4 | 1.12  | 1.07  | 0.8 - 1.3  | 0.19  | 2.54*  | 0.8 - 1.3  | 1.27  | 0.00*   | 61.0    | 0.28  |
| Lymphoma                              | 3.80* | 3.4 - 4.2 | 1.17  | 2.31  | 0.4 - 6.7  | 0.08  | 7.48*  | 0.4 - 6.7  | 0.81  | 0.00*   | 0 - 0.3 | -2.95 |
| Hodgkin Lymphoma                      | 1.77* | 1.6 - 1.9 | 1.42  | 2.39* | 1.8 - 3.0  | 1.95  | 2.72*  | 1.8 - 3.0  | 1.36  | 0       | 0 - 2.5 | -0.45 |
| Non-Hodgkin Lymphoma                  | 1.53  |           | 0.04  | 0     |            | -0.01 | 3.98   |            | 0.04  | 0.00*   | 0 - 0.6 | -1.71 |
| Myeloma                               |       | 1 - 2.2   |       |       | 0 - 17.1   |       |        | 0 - 17.1   |       | 0       | 0 -     | -0.07 |
| Leukemia                              | 1.95* |           | 0.58  | 2.16* |            | 0.35  | 4.09*  |            | 0.84  | 0       | 16.4    | -0.07 |
| Acute Lymphocytic Leukemia            |       | 1.7 - 2.2 |       |       | 1.1 - 3.6  |       |        | 1.1 - 3.6  |       | 0       | 0 - 1.9 | -0.58 |
| Non-Lymphocytic Leukemia              | 1.72* | 1.5 - 1.8 | 1.18  | 2.31* | 1.7 - 3.0  | 1.26  | 2.14*  | 1.7 - 3.0  | 1.89  | 0.19    | 0 - 1.0 | -1.34 |
| Acute Non-Lymphocytic Leukemia (ANLL) | 2.37* | 2.2 - 2.5 | 2.45  | 3.14* | 2.5 - 3.8  | 3.35  | 3.33*  | 2.5 - 3.8  | 2.16  | 0.18    | 0 - 1   | -1.39 |
| Myeloid and Monocytic Leukemia        | 1.42* |           | 0.14  | 1.99* |            | 0.31  | 3.05*  |            | 0.24  |         | 0.0 -   | -     |
| Acute Myeloid Leukemia                |       | 1.1 - 1.7 |       |       | 1.0 - 3.4  |       |        | 1.0 - 3.4  |       | 0.88    | 4.8     | -0.04 |
| Chronic Myeloid Leukemia              | 2.59* | 2.4 - 2.7 | 2.31  | 3.43* | 2.7 - 4.2  | 3.04  | 3.37*  | 2.7 - 4.2  | 1.93  | 0.00*   | 0 - 0.8 | -1.35 |
| Mesothelioma                          | 1.17  | 0.9 - 1.4 | 0.05  | 1.18  | 0.6 - 1.9  | 0.11  | 1.66   | 0.6 - 1.9  | 0.12  | 0       | 0 - 4.4 | -0.25 |
| Kaposi Sarcoma                        | 2.33* | 2.1 - 2.5 | 1.01  | 4.11* | 3.0 - 5.4  | 1.82  | 5.06*  | 3.0 - 5.4  | 1.87  | 0       | 0 - 1.5 | -0.71 |
| Miscellaneous                         | 1.57  |           | 0.04  | 8.34* |            | 0.33  | 3.98*  |            | 0.17  |         | 0 -     | -     |
| Acute Monocytic Leukemia              |       | 1 - 2.3   |       |       | 3.6 - 16.4 |       |        | 3.6 - 16.4 |       | 0       | 18.0    | -0.06 |
| Chronic Myeloid Leukemia              | 3.43* | 3.0 - 3.8 | 0.99  | 4.39* | 3.0 - 6.0  | 1.35  | 5.60*  | 3.0 - 6.0  | 1.58  | 0       | 0 - 2.9 | -0.39 |
| Acute Non-Lymphocytic Leukemia (ANLL) | 4.41* |           | 0.89  | 5.96* |            | 1.1   | 5.68*  |            | 1.1   |         | 0 -     | -     |
| Myeloid and Monocytic Leukemia        |       | 3.8 - 4.9 |       |       | 3.9 - 8.6  |       |        | 3.9 - 8.6  |       | 0       | 0 - 4.6 | -0.24 |
| Acute Myeloid Leukemia                | 3.41* |           | 0.92  | 4.52* |            | 1.25  | 5.64*  |            | 1.49  |         | 0 -     | -     |
| Chronic Myeloid Leukemia              |       | 3.0 - 3.8 |       |       | 3.1 - 6.3  |       |        | 3.1 - 6.3  |       | 0       | 0 - 3.1 | -0.36 |
| Mesothelioma                          | 4.25* | 3.7 - 4.8 | 0.74  | 5.65* | 3.6 - 8.4  | 0.93  | 5.84*  | 3.6 - 8.4  | 1.01  | 0       | 0 - 5.2 | -0.22 |
| Kaposi Sarcoma                        | 5.28* |           | 0.07  | 9.08* |            | 0.08  | 3.89   |            | 0.04  |         | 0 -     | -     |
| Miscellaneous                         |       | 3.2 - 8.0 |       |       | 1.1 - 32.7 |       |        | 1.1 - 32.7 |       | 0       | 70.2    | -0.02 |
| Acute Monocytic Leukemia              |       | 1.0 - 1.9 |       |       | 1.2 - 5.5  |       |        | 1.2 - 5.5  |       | 0       | 0 - 9.3 | -0.12 |
| Chronic Myeloid Leukemia              | 1.41* |           | 0.03  | 2.83* |            | 0.24  | 5.69*  |            | 0.43  |         | 0 -     | -     |
| Mesothelioma                          | 1.77* |           |       | 0     |            | -0.02 | 0      |            | -0.01 |         | 31.8    | -0.04 |
| Kaposi Sarcoma                        |       | 1.0 - 2.8 |       |       | 0 - 9.8    |       |        | 0 - 9.8    |       | 0       | 0 - 4.8 | -0.23 |
| Miscellaneous                         | 1.87* | 1.5 - 2.2 | 0.21  | 1.82  | 0.9 - 3.2  | 0.23  | 3.06   | 0.9 - 3.2  | 0.12  | 0       | 0 - 3.2 | -0.34 |
| Miscellaneous                         | 1.87* | 1.6 - 2.1 | 0.33  | 2.31* | 1.5 - 3.3  | 0.7   | 3.52*  | 1.5 - 3.3  | 0.67  | 0       |         |       |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

### MPC Risk by Time between First and Subsequent Cancer Diagnosis. We

stratified MPC risk estimates by time between first cancer diagnosis and subsequent cancer diagnosis (Table 7). Overall, the risk for MPCs was greatest 2 to 11 months from the time of first cancer diagnosis until the development of a MPC, and risk decreased as the period of time increased. Survivors of AYA cancers had the highest risk for the development of a subsequent vaginal cancer (SIR=27.41, 95% CI 8.90-63.96), kidney

cancer (SIR=25.29, 6.89-64.76), and Non-Hodgkin Lymphoma (SIR = 18.03) 2 to 11 months after the first cancer diagnosis. Risks for these cancers declined over time.

Conversely, data may suggest that subsequent bone cancer, brain cancer, and leukemias are more likely >1 year from initial diagnosis of primary cancer.

TABLE 7 – Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by Time Since First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                          | 2-11 Months |             |      | 1-4 Years |            |      | 5-9 Years |            |      | ≥10 Years |           |      |
|-----------------------------------|-------------|-------------|------|-----------|------------|------|-----------|------------|------|-----------|-----------|------|
|                                   | SIR         | 95% CI      | EAR  | SIR       | 95% CI     | EAR  | SIR       | 95% CI     | EAR  | SIR       | 95% CI    | EAR  |
| All sites                         | 5.6*        | 5.2 - 5.9   | 47.4 | 3.4*      | 3.3 - 3.5  | 32.3 | 2.3*      | 2.2 - 2.4  | 26.4 | 1.4*      | 1.4 - 1.5 | 25.4 |
| All Solid Tumors                  | 5.1*        | 4.7 - 5.4   | 36.3 | 3.2*      | 3.1 - 3.3  | 25.6 | 2.3*      | 2.2 - 2.4  | 23.2 | 1.4*      | 1.4 - 1.5 | 23.0 |
| Oral Cavity and Pharynx           | 6.0*        |             | 1.0  | 3.7*      |            | 0.7  | 3.4*      |            | 1.1  | 1.9*      |           | 1.3  |
| Salivary Gland                    | 4.3*        | 3.7 - 9.1   | 0.1  | 4.3*      | 2.8 - 4.7  | 0.1  | 4.3*      | 2.8 - 4.2  | 0.2  | 3.7*      | 1.7 - 2.1 | 0.3  |
| Digestive System                  | 5.0*        | 1.1 - 11.0  | 3.1  | 2.7*      | 2.5 - 6.9  | 1.9  | 2.0*      | 2.6 - 6.7  | 2.1  | 1.5*      | 2.8 - 4.7 | 4.5  |
| Esophagus                         | 9.1*        | 3.8 - 6.3   | 0.1  | 3.4*      | 2.3 - 3.1  | 0.0  | 2.4*      | 1.8 - 2.3  | 0.1  | 1.5*      | 1.5 - 1.6 | 0.2  |
| Stomach                           | 4.2*        | 1.8 - 26.7  | 0.3  | 2.4*      | 1.3 - 7.0  | 0.1  | 2.3*      | 1.2 - 4.3  | 0.2  | 2.0*      | 1.2 - 1.9 | 0.6  |
| Small Intestine                   | 5.9*        | 1.7 - 8.7   | 0.1  | 4.4*      | 1.4 - 3.7  | 0.1  | 2.2*      | 1.5 - 3.3  | 0.0  | 2.0*      | 1.7 - 2.3 | 0.2  |
| Colon and Rectum                  | 4.7*        | 1.2 - 17.4  | 1.7  | 2.6*      | 2.3 - 7.8  | 1.0  | 1.9*      | 1.0 - 4.1  | 1.0  | 1.4*      | 1.5 - 2.6 | 1.9  |
| Pancreas                          | 9.1*        | 3.3 - 6.5   | 0.5  | 1.9       | 2.1 - 3.1  | 0.0  | 1.6*      | 1.6 - 2.2  | 0.1  | 1.6*      | 1.3 - 1.5 | 0.6  |
| Respiratory System                | 4.3*        | 4.3 - 16.8  | 1.1  | 4.0*      | 0.9 - 3.3  | 1.6  | 2.3*      | 1.0 - 2.5  | 1.5  | 1.4*      | 1.3 - 1.8 | 2.6  |
| Bones and Joints                  | 2.4         | 2.8 - 6.3   | 0.1  | 5.6*      | 3.4 - 4.7  | 0.3  | 3.4*      | 2 - 2.7    | 0.1  | 2.7*      | 1.3 - 1.5 | 0.1  |
| Soft Tissue including Heart       | 4.5*        | 0.5 - 7.2   | 0.5  | 4.4*      | 3.6 - 8.2  | 0.5  | 4.1*      | 1.9 - 5.7  | 0.6  | 3.2*      | 1.8 - 3.9 | 0.7  |
| Skin excluding Basal and Squamous | 7.4*        | 2.3 - 7.9   | 7.9  | 3.8*      | 3.3 - 5.9  | 4.1  | 2.7*      | 3.1 - 5.4  | 3.2  | 1.9*      | 2.7 - 3.8 | 2.9  |
| Breast                            | 4.0*        | 6.3 - 8.7   | 7.2  | 3.8*      | 3.4 - 4.2  | 10.1 | 2.5*      | 2.4 - 3.0  | 9.7  | 1.4*      | 1.7 - 2.0 | 6.3  |
| Female Genital System             | 3.9*        | 3.4 - 4.6   | 3.6  | 1.9*      | 3.5 - 4.0  | 1.4  | 1.5*      | 2.4 - 2.7  | 1.2  | 1.1*      | 1.4 - 1.5 | 0.9  |
| Ovary                             | 7.5*        | 3.1 - 4.8   | 1.7  | 3.8*      | 1.6 - 2.1  | 0.9  | 2.1*      | 1.3 - 1.7  | 0.6  | 1.6*      | 1.1 - 1.2 | 0.7  |
| Vagina                            | 27.4*       | 5.2 - 10.4  | 0.2  | 11.2*     | 3.1 - 4.7  | 0.1  | 5.4*      | 1.6 - 2.6  | 0.0  | 4.1*      | 1.4 - 1.8 | 0.1  |
| Male Genital System               | 3.6*        | 8.9 - 63.9  | 1.3  | 4.0*      | 5.3 - 20.6 | 1.5  | 3.3*      | 2.2 - 11.2 | 1.7  | 1.0       | 2.8 - 6   | 0.2  |
| Prostate                          | 14.7*       | 2.4 - 5.1   | 0.2  | 2.1       | 3.3 - 4.7  | 0.0  | 1.8*      | 2.8 - 3.9  | 0.2  | 0.9       | 0.9 - 1.1 | -0.3 |
| Testis                            | 3.0*        | 4.7 - 34.3  | 0.9  | 4.2*      | 0.9 - 4.2  | 1.5  | 4.4*      | 1.2 - 2.6  | 1.4  | 3.0*      | 0.8 - 1.0 | 0.5  |
| Urinary System                    | 11.5*       | 2.0 - 4.5   | 3.2  | 3.6*      | 3.5 - 5.0  | 1.1  | 1.6*      | 3.6 - 5.2  | 0.5  | 1.5*      | 2.5 - 3.7 | 1.7  |
| Urinary Bladder                   | 7.2*        | 8.8 - 14.7  | 0.7  | 2.5*      | 3 - 4.4    | 0.2  | 1.6*      | 1.3 - 2.0  | 0.2  | 1.4*      | 1.4 - 1.6 | 0.6  |
| Kidney and Renal                  | 13.4*       | 4.1 - 11.7  | 2.2  | 4.0*      | 1.7 - 3.6  | 0.7  | 1.6*      | 1.1 - 2.3  | 0.2  | 1.5*      | 1.2 - 1.6 | 0.9  |
| Pelvis                            |             | 9.7 - 18.1  |      |           | 3.1 - 5.0  |      |           | 1.2 - 2.1  |      |           | 1.4 - 1.7 |      |
| Kidney                            | 25.2*       | 6.8 - 64.7  | 0.2  | 11.2*     | 5.1 - 21.2 | 0.1  | 3.7*      | 1.2 - 8.7  | 0.0  | 3.7*      | 2.7 - 4.8 | 0.3  |
| Renal Pelvis                      | 13.8*       | 10.0 - 18.6 | 2.2  | 4.0*      | 3.1 - 5.1  | 0.7  | 1.6*      | 1.1 - 2.1  | 0.2  | 1.5*      | 1.3 - 1.7 | 0.8  |
| Eye and Orbit                     | 0           | 0 - 45.0    | 0    | 2.2       | 0.0 - 12.7 | 0.0  | 2.7       | 0.3 - 9.9  | 0.0  | 2.6*      | 1.6 - 4.1 | 0.1  |
| Brain and Other Nervous System    | 0           |             | -0.0 | 1.9       |            | 0.0  | 1.8       |            | 0.0  | 1.4       |           | 0.0  |
| Endocrine System                  | 4.9*        | 0 - 8.3     | 4.0  | 1.9*      | 0.5 - 5.0  | 1.1  | 1.4*      | 0.6 - 4.3  | 0.6  | 1.5*      | 0.8 - 2.2 | 1.1  |
| Lymphoma                          | 11.3*       | 3.9 - 6.0   | 9.6  | 4.9*      | 1.6 - 2.2  | 4    | 2.0*      | 1.2 - 1.7  | 1.2  | 1.4*      | 1.4 - 1.7 | 1.2  |
| Hodgkin Lymphoma                  | 2.0*        | 9.7 - 13.0  | 0.4  | 1.6*      | 4.4 - 5.5  | 0.2  | 1.2       | 1.7 - 2.3  | 0.1  | 1.3       | 1.3 - 1.6 | 0.1  |
| Non-Hodgkin Lymphoma              | 18.0*       | 1.1 - 3.3   | 9.2  | 6.8*      | 1.2 - 2.2  | 3.7  | 2.2*      | 0.8 - 1.8  | 1.1  | 1.5*      | 1 - 1.8   | 1.1  |
| Myeloma                           | 6.0*        | 15.4 - 20.9 | 0.1  | 1.5       | 6.0 - 7.6  | 0.0  | 1.3       | 1.9 - 2.7  | 0.0  | 1.0       | 1.3 - 1.6 | 0.0  |
| Leukemia                          | 3.3*        | 1.6 - 15.4  | 0.7  | 7.7*      | 0.5 - 3.3  | 2.2  | 3.8*      | 0.6 - 2.4  | 1.2  | 1.4*      | 0.8 - 1.3 | 0.4  |
| Acute Lymphocytic Leukemia        | 5.0*        | 1.9 - 5.2   | 0.2  | 3.3*      | 6.6 - 8.9  | 0.1  | 2.4*      | 3.1 - 4.6  | 0.0  | 1.1       | 1.2 - 1.6 | 0.0  |
| Non-Lymphocytic Leukemia          | 3.3*        | 1.6 - 11.8  | 0.5  | 10.0*     | 1.7 - 5.8  | 2.1  | 5.0*      | 1.0 - 4.7  | 1.1  | 1.7*      | 0.5 - 2.0 | 0.4  |
|                                   |             | 1.7 - 5.7   |      |           | 8.6 - 11.7 |      |           | 4.0 - 6.1  |      |           | 1.4 - 2.1 |      |

|                                       |      |            |      |       |             |      |      |           |     |      |           |      |
|---------------------------------------|------|------------|------|-------|-------------|------|------|-----------|-----|------|-----------|------|
| Acute Non-Lymphocytic Leukemia (ANLL) | 4.5* |            | 0.4  | 14.0* |             | 1.9  | 6.5* |           | 0.9 | 2.0* |           | 0.3  |
| Myeloid and Monocytic Leukemia        | 3.3* | 2.2 - 8.1  | 0.4  | 9.8*  | 11.8 - 16.5 | 1.9  | 5.1* | 5.1 - 8.1 | 1.1 | 1.7* | 1.6 - 2.4 | 0.4  |
| Acute Myeloid Leukemia                | 4.7* | 1.7 - 5.8  | 0.4  | 13.0* | 8.3 - 11.5  | 1.5  | 6.8* | 4.1 - 6.3 | 0.9 | 1.9* | 1.4 - 2.1 | 0.3  |
| Acute Monocytic Leukemia              | 7.3  | 2.2 - 8.7  | 0.0  | 24.5* | 10.7 - 15.6 | 0.2  | 2.7  | 5.3 - 8.7 | 0.0 | 1.9  | 1.5 - 2.4 | 0.0  |
| Chronic Myeloid Leukemia              | 0    | 0.1 - 40.6 | -0.0 | 2.6*  | 13.7 - 40.4 | 0.1  | 2.8* | 0.3 - 9.9 | 0.1 | 1.2  | 0.7 - 4.3 | 0.0  |
| Mesothelioma                          | 0    | 0 - 2.9    | -0.0 | 0     | 1.4 - 4.4   | -0.0 | 2.9  | 1.6 - 4.4 | 0.0 | 1.6  | 0.8 - 1.8 | 0.0  |
| Kaposi Sarcoma                        | 9.2* | 0 - 26.5   | 2.4  | 2.1*  | 0 - 5.4     | 0.3  | 1.0  | 0.6 - 8.6 | 0.0 | 0.5* | 0.8 - 2.7 | -0.0 |
| Miscellaneous                         | 5.2* | 6.7 - 12.2 | 2.4  | 2.9*  | 1.5 - 2.8   | 0.2  | 2.5* | 0.6 - 1.6 | 0.3 | 1.7* | 0.2 - 0.9 | 0.4  |
| Miscellaneous                         | 5.2* | 2.4 - 9.9  | 0.4  | 2.9*  | 1.9 - 4.3   | 0.2  | 2.5* | 1.7 - 3.6 | 0.3 | 1.7* | 1.4 - 2.0 | 0.4  |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

**MPC Risk by Treatment for 1<sup>st</sup> Primary Cancer.** Risks for different types of MPCs varied by whether individuals received any radiation for treatment for their first primary cancer (Table 8). Those treated with radiation have an overall higher risk for a MPC compared to those treated without radiation. Specifically, AYAs treated with radiation were at highest risk for developing leukemia including Acute Monocytic Leukemia (SIR=8.99, 95% CI 4.49-16.09), ANLL (SIR=6.66, 95% CI 5.55-7.93), and Acute Myeloid Leukemia (SIR=6.23, 95% CI 5.09-7.54). AYAs who received radiation were also at high risk for male genital system cancers (SIR=10.42, 95% CI 6.7-15.5) salivary gland cancer (SIR=6.90, 95% CI 5.15-9.05), soft tissue cancer (SIR=5.99, 95% CI 4.20-8.29), and skin cancer (excluding Basal and Squamous) (SIR=5.87, 95% CI 4.83-7.07). EARs were elevated for female genital system cancers (EAR=16.88) among those who received radiation.

**TABLE 8 – Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by Radiation Treatment for First Cancer, SEER 9 1973-2012**

| MPC Site                | Any Radiation |           |       | No Radiation |           |       |
|-------------------------|---------------|-----------|-------|--------------|-----------|-------|
|                         | SIR           | 95% CI    | EAR   | SIR          | 95% CI    | EAR   |
| All sites               | 2.44*         | 2.3 - 2.5 | 44    | 1.65*        | 1.6 - 1.6 | 22.37 |
| All Solid Tumors        | 2.40*         | 2.3 - 2.4 | 38.42 | 1.60*        | 1.5 - 1.6 | 18.74 |
| Oral Cavity and Pharynx | 3.54*         | 3.0 - 4.0 | 2.01  | 1.95*        | 1.7 - 2.1 | 0.8   |
| Salivary Gland          | 6.90*         | 5.1 - 9.0 | 0.56  | 2.86*        | 2.1 - 3.7 | 0.19  |

|                                       |        |            |       |       |           |       |
|---------------------------------------|--------|------------|-------|-------|-----------|-------|
| Digestive System                      | 2.29*  | 2.1 - 2.4  | 5.2   | 1.53* | 1.4 - 1.6 | 2.39  |
| Respiratory System                    | 2.49*  | 2.0 - 3.0  | 0.71  | 1.41* | 1.1 - 1.6 | 0.23  |
| Bones and Joints                      | 2.66*  | 2.4 - 2.9  | 4.03  | 1.31* | 1.2 - 1.4 | 0.92  |
| Soft Tissue including Heart           | 5.99*  | 4.2 - 8.2  | 0.38  | 2.55* | 1.8 - 3.5 | 0.12  |
| Skin excluding Basal and Squamous     | 5.87*  | 4.8 - 7.0  | 1.17  | 2.75* | 2.3 - 3.2 | 0.44  |
| Breast                                | 1.21*  | 1.0 - 1.3  | 0.45  | 3.09* | 2.9 - 3.2 | 4.71  |
| Female Genital System                 | 3.18*  | 3.0 - 3.3  | 16.88 | 1.48* | 1.4 - 1.5 | 4.4   |
| Vagina                                | 2.31*  | 1.9 - 2.7  | 0.92  | 1.97* | 1.7 - 2.2 | 0.83  |
| Male Genital System                   | 10.42* | 6.6 - 15.5 | 0.28  | 3.92* | 2.5 - 5.7 | 0.11  |
| Testis                                | 1      | 0.8 - 1.1  | -0.01 | 0.96  | 0.8 - 1.0 | -0.11 |
| Urinary System                        | 3.42   | 0.9 - 8.7  | 0.04  | 1.05  | 0.2 - 3.0 | 0     |
| Eye and Orbit                         | 2.26   | 0.7 - 5.2  | 0.04  | 2.79* | 1.6 - 4.4 | 0.06  |
| Brain and Other Nervous System        | 1.06   | 0.3 - 2.4  | 0     | 1.65* | 1.0 - 2.5 | 0.04  |
| Endocrine System                      | 2.11*  | 1.8 - 2.3  | 1.75  | 1.62* | 1.4 - 1.7 | 1     |
| Lymphoma                              | 2.71*  | 2.4 - 3.0  | 2.79  | 2.34* | 2.1 - 2.5 | 2.34  |
| Hodgkin Lymphoma                      | 1.57*  | 1.1 - 2.1  | 0.18  | 1.48* | 1.1 - 1.8 | 0.15  |
| Non-Hodgkin Lymphoma                  | 2.99*  | 2.6 - 3.3  | 2.61  | 2.52* | 2.3 - 2.7 | 2.19  |
| Myeloma                               | 1.50*  | 1.0 - 2.1  | 0.14  | 1.04  | 0.8 - 1.3 | 0.01  |
| Leukemia                              | 3.45*  | 2.9 - 3.9  | 1.67  | 2.15* | 1.9 - 2.4 | 0.86  |
| Acute Lymphocytic Leukemia            | 2.51*  | 1.3 - 4.3  | 0.09  | 1.95* | 1.2 - 2.9 | 0.06  |
| Non-Lymphocytic Leukemia              | 4.98*  | 4.2 - 5.8  | 1.52  | 2.99* | 2.6 - 3.4 | 0.82  |
| Acute Non-Lymphocytic Leukemia (ANLL) | 6.66*  | 5.5 - 7.9  | 1.36  | 3.67* | 3.1 - 4.2 | 0.7   |
| Myeloid and Monocytic Leukemia        | 4.83*  | 4.0 - 5.7  | 1.36  | 3.05* | 2.6 - 3.4 | 0.78  |
| Acute Myeloid Leukemia                | 6.23*  | 5.0 - 7.5  | 1.11  | 3.64* | 3.1 - 4.2 | 0.61  |
| Acute Monocytic Leukemia              | 8.99*  | 4.4 - 16.0 | 0.12  | 4.03* | 2.1 - 6.8 | 0.05  |
| Chronic Myeloid Leukemia              | 2.03*  | 1.2 - 3.1  | 0.12  | 1.58* | 1.1 - 2.1 | 0.07  |
| Mesothelioma                          | 3.15*  | 1.3 - 6.2  | 0.07  | 0.98  | 0.3 - 2.0 | 0     |
| Kaposi Sarcoma                        | 1.71*  | 1.1 - 2.4  | 0.18  | 1.96* | 1.5 - 2.4 | 0.22  |
| Miscellaneous                         | 3.23*  | 2.5 - 3.9  | 0.78  | 1.50* | 1.2 - 1.8 | 0.2   |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

**MPC Risk by Age at 1<sup>st</sup> Primary Cancer Diagnosis.** Higher risks of MPCs were observed in AYAs diagnosed with a first primary cancer at the ages of 15 to 19 (Table 9). Risks declined with increasing age at first cancer diagnosis, but varied by type of MPC. Among AYAs diagnosed with a first cancer at ages 15 to 19, we observed higher risks of Leukemia including Acute Monocytic Leukemia (SIR=18.25, 95% CI 3.76-53.33), ANLL (SIR=12.78, 95% CI 8.74-18.04), Acute Myeloid Leukemia (SIR=12.69, 95% CI 8.43-18.34), and Non-lymphocytic Leukemia (SIR=8.94, 95% CI 6.23-12.44). Risks for leukemias remained high for all ages at first cancer diagnosis, but declined with increasing age. Individuals in the 15 to 19 age group were also at higher risks for salivary gland cancer (SIR=17.42, 95% CI 9.75-28.74), soft tissue cancer (SIR=9.64,

95% CI 6.41-13.94), and cancer of the bones and joints (SIR=6.26, 95% CI 3.00-11.52). AYAs diagnosed in their early twenties (ages 20-24) had higher risk of subsequent genital tract cancers including vaginal cancer (SIR=9.26, 95% CI 2.52-23.71) and testis cancer (SIR=4.81, 95% CI 3.86-5.92). Risk for these cancers remained elevated, but showed a slight decline as age at first cancer diagnosis increased.

TABLE 9 – Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by Age at First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                              | 15-19  |            |       | 20-24 |            |       | 25-29 |            |       | 30-34 |           |       | 35-39 |           |       |
|---------------------------------------|--------|------------|-------|-------|------------|-------|-------|------------|-------|-------|-----------|-------|-------|-----------|-------|
|                                       | SIR    | 95% CI     | EAR   | SIR   | 95% CI     | EAR   | SIR   | 95% CI     | EAR   | SIR   | 95% CI    | EAR   | SIR   | 95% CI    | EAR   |
| All sites                             | 3.03*  | 2.7 - 3.2  | 20.94 | 2.37* | 2.2 - 2.5  | 21.84 | 1.99* | 1.9 - 2.0  | 23.62 | 1.92* | 1.8 - 1.9 | 31.59 | 1.70* | 1.6 - 1.8 | 33.2  |
| All Solid Tumors                      | 3.08*  | 2.8 - 3.3  | 18.27 | 2.38* | 2.2 - 2.5  | 19.24 | 1.93* | 1.8 - 2.0  | 19.8  | 1.87* | 1.8 - 1.9 | 27.03 | 1.65* | 1.6 - 1.7 | 28.28 |
| Oral Cavity and Pharynx               | 6.33*  | 4.2 - 9.0  | 1.31  | 3.64* | 2.6 - 4.8  | 1.11  | 2.42* | 1.9 - 3.0  | 0.88  | 2.16* | 1.8 - 2.5 | 1     | 2.16* | 1.9 - 2.5 | 1.35  |
| Salivary Gland                        | 17.42* | 9.7 - 28.7 | 0.76  | 8.08* | 4.6 - 13.1 | 0.44  | 4.97* | 3.0 - 7.5  | 0.32  | 3.41* | 2.2 - 4.9 | 0.25  | 2.35* | 1.5 - 4.9 | 0.18  |
| Digestive System                      | 2.86*  | 2.1 - 3.7  | 1.89  | 2.46* | 2.0 - 2.8  | 2.66  | 1.68* | 1.4 - 1.8  | 1.98  | 1.85* | 1.7 - 2   | 3.81  | 1.60* | 1.5 - 1.7 | 3.93  |
| Respiratory System                    | 2.41*  | 1.4 - 3.7  | 0.63  | 2.50* | 1.9 - 3.1  | 1.38  | 2.14* | 1.8 - 2.4  | 1.98  | 1.55* | 1.3 - 1.7 | 1.7   | 1.54* | 1.4 - 1.6 | 2.73  |
| Bones and Joints                      | 6.26*  | 3 - 11.5   | 0.45  | 5.56* | 2.9 - 9.5  | 0.33  | 3.71* | 2.0 - 6.2  | 0.2   | 2.89* | 1.6 - 4.6 | 0.14  | 2.66* | 1.6 - 3.9 | 0.13  |
| Soft Tissue including Heart           | 9.64*  | 6.4 - 13.9 | 1.35  | 7.35* | 5.3 - 9.9  | 1.16  | 3.30* | 2.3 - 4.5  | 0.49  | 3.50* | 2.7 - 4.4 | 0.64  | 2.64* | 2.0 - 3.9 | 0.5   |
| Skin excluding Basal and Squamous     | 2.80*  | 2.1 - 3.6  | 2.11  | 2.92* | 2.4 - 3.4  | 3.14  | 2.69* | 2.3 - 3.0  | 3.51  | 2.71* | 2.4 - 2.9 | 4.23  | 2.31* | 2.1 - 2.6 | 3.73  |
| Breast                                | 2.80*  | 2.2 - 3.3  | 3.67  | 2.14* | 1.8 - 2.4  | 3.92  | 1.93* | 1.7 - 2.0  | 5.52  | 2.10* | 1.9 - 2.2 | 10.03 | 1.79* | 1.7 - 1.8 | 10.4  |
| Female Genital System                 | 1.52   | 0.9 - 2.2  | 0.48  | 1.28  | 0.9 - 1.6  | 0.41  | 1.37* | 1.1 - 1.5  | 0.86  | 1.41* | 1.2 - 1.5 | 1.4   | 1.40* | 1.2 - 1.4 | 1.89  |
| Vagina                                | 0      | 0 - 24.2   | -0.01 | 9.26* | 2.5 - 23.7 | 0.11  | 9.31* | 4.6 - 16.6 | 0.19  | 4.31* | 2.1 - 7.7 | 0.12  | 5.02* | 3.2 - 6.7 | 0.2   |
| Male Genital System                   | 2.81*  | 2.0 - 3.7  | 1.49  | 2.62* | 2.1 - 3.1  | 2.27  | 1.86* | 1.6 - 2.1  | 1.77  | 1.23* | 1.0 - 1.3 | 0.68  | 1.08  | 0.9 - 1.4 | 0.33  |
| Testis                                | 3.85*  | 2.7 - 5.2  | 1.52  | 4.81* | 3.8 - 5.9  | 2.17  | 4.67* | 3.8 - 5.6  | 1.74  | 3.46* | 2.7 - 4.2 | 0.87  | 2.42* | 1.8 - 4.2 | 0.34  |
| Urinary System                        | 3.00*  | 1.9 - 4.5  | 0.83  | 2.47* | 1.8 - 3.1  | 1.09  | 1.83* | 1.5 - 2.2  | 0.99  | 1.81* | 1.5 - 2.0 | 1.47  | 1.71* | 1.5 - 1.9 | 1.83  |
| Eye and Orbit                         | 2.16   | 0.0 - 12.0 | 0.03  | 0.86  | 0.0 - 4.7  | -0.01 | 0.75  | 0.0 - 2.7  | -0.01 | 1.62  | 0.7 - 3.1 | 0.04  | 1.77  | 0.9 - 2.2 | 0.07  |
| Brain and Other Nervous System        | 5.81*  | 4.0 - 8.0  | 1.65  | 2.63* | 1.8 - 3.6  | 0.68  | 2.07* | 1.5 - 2.7  | 0.52  | 1.85* | 1.4 - 2.3 | 0.49  | 1.59* | 1.3 - 2.2 | 0.4   |
| Endocrine System                      | 3.55*  | 2.7 - 4.5  | 2.51  | 1.98* | 1.5 - 2.4  | 1.2   | 1.76* | 1.4 - 2.0  | 1.13  | 1.70* | 1.4 - 1.9 | 1.18  | 1.55* | 1.3 - 1.8 | 1.01  |
| Lymphoma                              | 1.64*  | 1.1 - 2.3  | 0.63  | 1.99* | 1.5 - 2.4  | 1.19  | 2.39* | 2.0 - 2.7  | 2     | 2.70* | 2.4 - 3   | 2.98  | 2.42* | 2.2 - 2.5 | 3.06  |
| Hodgkin Lymphoma                      | 1      | 0.4 - 1.9  | 0     | 1.44  | 0.8 - 2.2  | 0.18  | 1.3   | 0.8 - 1.9  | 0.11  | 1.65* | 1.1 - 2.2 | 0.19  | 1.66* | 1.2 - 1.7 | 0.18  |
| Non-Hodgkin Lymphoma                  | 2.15*  | 1.3 - 3.2  | 0.63  | 2.27* | 1.7 - 2.9  | 1.01  | 2.75* | 2.3 - 3.2  | 1.9   | 2.92* | 2.6 - 3.2 | 2.78  | 2.53* | 2.3 - 2.7 | 2.89  |
| Myeloma                               | 0      | 0 - 3.5    | -0.06 | 1.72  | 0.6 - 3.7  | 0.08  | 1.12  | 0.5 - 2    | 0.02  | 1.25  | 0.8 - 1.8 | 0.08  | 1.13  | 0.8 - 1.4 | 0.06  |
| Leukemia                              | 5.99*  | 4.2 - 8.2  | 1.66  | 3.49* | 2.5 - 4.6  | 1.04  | 3.62* | 2.9 - 4.3  | 1.45  | 1.99* | 1.6 - 2.4 | 0.74  | 2.13* | 1.8 - 2.5 | 1.12  |
| Acute Lymphocytic Leukemia            | 1.48   | 0.1 - 5.3  | 0.04  | 2.1   | 0.5 - 5.3  | 0.07  | 3.33* | 1.6 - 6.1  | 0.13  | 1.16  | 0.3 - 2.7 | 0.01  | 2.26* | 1.2 - 2.3 | 0.08  |
| Non-Lymphocytic Leukemia              | 8.94*  | 6.2 - 12.4 | 1.67  | 4.77* | 3.4 - 6.5  | 0.99  | 4.87* | 3.8 - 6.0  | 1.26  | 2.69* | 2.1 - 3.3 | 0.7   | 3.06* | 2.6 - 3.8 | 1.07  |
| Acute Non-Lymphocytic Leukemia (ANLL) | 12.78* | 8.7 - 18.0 | 1.59  | 6.50* | 4.5 - 9.0  | 0.9   | 6.49* | 5.0 - 8.2  | 1.12  | 2.90* | 2.1 - 3.7 | 0.49  | 3.89* | 3.2 - 4.9 | 0.97  |
| Myeloid and Monocytic Leukemia        | 9.31*  | 6.4 - 13.0 | 1.63  | 4.72* | 3.3 - 6.5  | 0.91  | 4.84* | 3.8 - 6.0  | 1.17  | 2.86* | 2.2 - 3.5 | 0.71  | 2.93* | 2.4 - 3.8 | 0.93  |
| Acute Myeloid Leukemia                | 12.69* | 8.4 - 18.3 | 1.39  | 6.27* | 4.2 - 9    | 0.76  | 6.38* | 4.8 - 8.2  | 0.97  | 3.11* | 2.3 - 4.0 | 0.48  | 3.55* | 2.9 - 4.8 | 0.75  |
| Acute Monocytic Leukemia              | 18.25* | 3.7 - 53.3 | 0.15  | 5.97  | 0.7 - 21.5 | 0.05  | 7.37* | 2.3 - 17.2 | 0.08  | 1.64  | 0.2 - 5.9 | 0.01  | 5.69* | 2.9 - 8.0 | 0.1   |
| Chronic Myeloid Leukemia              | 2.51   | 0.5 - 7.3  | 0.1   | 1.49  | 0.4 - 3.8  | 0.04  | 1.84  | 0.8 - 3.3  | 0.09  | 2.36* | 1.4 - 3.5 | 0.17  | 1.25  | 0.7 - 1.9 | 0.04  |
| Mesothelioma                          | 7.86   | 0.2 - 43.8 | 0.05  | 9.79* | 2.6 - 25.0 | 0.11  | 0     | 0 - 3.1    | -0.02 | 1.87  | 0.6 - 4.3 | 0.03  | 1.11  | 0.4 - 2.8 | 0.01  |
| Kaposi Sarcoma                        | 0      | 0 - 1.2    | -0.16 | 0.38  | 0.0 - 1.1  | -0.15 | 1.63* | 1.0 - 2.4  | 0.18  | 2.70* | 2.0 - 3.5 | 0.45  | 2.08* | 1.4 - 2.2 | 0.21  |
| Miscellaneous                         | 5.53*  | 2.5 - 10.5 | 0.4   | 2.42* | 1.2 - 4.2  | 0.22  | 1.68* | 1.0 - 2.5  | 0.17  | 2.27* | 1.7 - 2.8 | 0.5   | 1.75* | 1.4 - 2.1 | 0.44  |

\*p-value &lt; 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

**MPC Risk by Type of 1<sup>st</sup> Primary Cancer.** Lastly, risk estimates for MPCs were stratified by type of first cancer diagnosis in survivors of AYA cancers (Table 10). Patients diagnosed first with a soft tissue sarcoma ((SIR=2.61, 95% CI 2.44-2.78), EAR=39.55) or a lymphoma ((SIR=2.58, 95% CI 2.48-2.69), EAR=45.68) had the highest risk for the development of MPCs. The latter also demonstrated the highest excess risks for MPCs. First primary cancers with the lowest risk for MPCs included miscellaneous specified neoplasms (SIR=1.57, 95% CI 1.32-1.85), germ cell and trophoblastic neoplasms (SIR=1.65, 95% CI 1.56-1.74), and melanoma and skin carcinomas (SIR=1.63, 95% CI 1.57-1.70). Those first diagnosed with either leukemia or lymphoma showed a higher risk for subsequent salivary gland cancers and leukemias, especially Acute Lymphocytic Leukemia (ANLL) and Acute Myeloid Leukemia (AML). Higher risks for lymphomas, notably Non-Hodgkin's lymphoma, were observed after a soft tissue sarcoma.

TABLE 10– Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                          | Leukemias |            |       | Lymphomas |            |       | CNS and Other Intracranial and Intraspinal Neoplasms |            |       | Osseous and Chondromatous Neoplasms |             |       | Soft Tissue Sarcomas |             |       |
|-----------------------------------|-----------|------------|-------|-----------|------------|-------|------------------------------------------------------|------------|-------|-------------------------------------|-------------|-------|----------------------|-------------|-------|
|                                   | SIR       | 95% CI     | EAR   | SIR       | 95% CI     | EAR   | SIR                                                  | 95% CI     | EAR   | SIR                                 | 95% CI      | EAR   | SIR                  | 95% CI      | EAR   |
| All sites                         | 1.80*     |            | 16.48 | 2.58*     |            | 39.55 | 1.92*                                                |            | 18.53 | 1.85*                               |             | 18.34 | 2.61*                |             | 45.68 |
| All Solid Tumors                  | 1.57*     | 1.5 - 2.0  | 10.25 | 2.30*     | 2.4 - 2.6  | 28.75 | 1.96*                                                | 1.7 - 2.1  | 17.02 | 1.61*                               | 1.5 - 2.2   | 11.62 | 1.58*                | 2.4 - 2.7   | 14.59 |
|                                   |           | 1.3 - 1.8  | 3.05  | 3.34*     | 2.1 - 2.4  | 1.78  | 3.15*                                                | 1.7 - 2.2  | 1.26  | 2.29                                | 1.3 - 1.9   | 0.84  | 2.01*                | 1.4 - 1.7   | 0.87  |
| Oral Cavity and Pharynx           | 5.71*     | 3.5 - 8.6  | 0.76  | 10.23*    | 2.6 - 4.1  | 0.78  | 9.52*                                                | 1.8 - 5.1  | 0.62  | 3.97                                | 0.7 - 5.3   | 0.22  | 1.72                 | 1.2 - 3.0   | 0.07  |
| Salivary Gland                    | 11.10*    | 3.6 - 25.9 | 1.53  | 2.27*     | 6.9 - 14.6 | 4.35  | 1.61*                                                | 3.4 - 20.7 | 1.57  | 1.12                                | 0.1 - 22.1  | 0.34  | 1.99*                | 0.2 - 6.2   | 4.11  |
| Digestive System                  | 1.71      | 1.0 - 2.2  | 1.18  | 3.50*     | 2.0 - 2.5  | 5.43  | 1.53                                                 | 1.1 - 2.2  | 0.8   | 2.43*                               | 0.5 - 2     | 2.64  | 1.56*                | 1.6 - 2.4   | 1.57  |
| Respiratory System                | 4.22      | 0.9 - 2.7  | 0.26  | 6.61*     | 3.0 - 3.9  | 0.44  | 8.96*                                                | 0.9 - 2.3  | 0.61  | 50.22*                              | 1.3 - 4     | 4.11  | 5.07*                | 1.1 - 2.0   | 0.32  |
| Bones and Joints                  | 0.78      | 0.5 - 15.2 | -0.05 | 5.66*     | 3.9 - 10.4 | 1.07  | 5.57*                                                | 3.2 - 19.5 | 0.95  | 21.09*                              | 27.4 - 84.2 | 4.28  | 18.12*               | 1.6 - 11.8  | 4.25  |
| Soft Tissue including Heart       | 0.95      | 0.0 - 4.3  | -0.09 | 1.25*     | 4.1 - 7.5  | 0.51  | 1.12                                                 | 2.6 - 10.2 | 0.23  | 0.85                                | 11.8 - 34.7 | -0.27 | 2.51*                | 13.7 - 23.4 | 3.04  |
| Skin excluding Basal and Squamous | 1.59*     | 0.4 - 1.7  | 2.19  | 2.71*     | 1 - 1.5    | 8.03  | 0.67*                                                | 0.6 - 1.7  | -1.37 | 1.03                                | 0.2 - 1.9   | 0.1   | 1.26*                | 1.9 - 3.2   | 1.42  |
| Breast                            | 1.4       | 1.1 - 2.2  | 0.58  | 1.47*     | 2.4 - 2.9  | 0.85  | 1.36                                                 | 0.4 - 0.9  | 0.58  | 0.6                                 | 0.5 - 1.7   | -0.59 | 0.61*                | 1.0 - 1.5   | -0.82 |
| Female Genital System             | 0         | 0.7 - 2.4  | -0.01 | 3.28      | 1.1 - 1.8  | 0.04  | 0                                                    | 0.8 - 2.1  | -0.02 | 0                                   | 0.1 - 1.7   | -0.01 | 0                    | 0.3 - 0.9   | -0.02 |
| Vagina                            | 1.2       | 0 - 44.5   | 0.51  | 0.93      | 0.4 - 11.8 | -0.21 | 0.61                                                 | 0 - 27.7   | -0.81 | 0.8                                 | 0 - 76.1    | -0.59 | 1                    | 0 - 13.0    | 0     |
| Male Genital System               | 0.57      | 0.7 - 1.9  | -0.26 | 0.63      | 0.7 - 1.1  | -0.2  | 0.38                                                 | 0.3 - 1.0  | -0.37 | 1.05                                | 0.3 - 1.5   | 0.03  | 1.16                 | 0.7 - 1.3   | 0.09  |
| Testis                            | 1.09      | 0.0 - 2.0  | 0.12  | 2.17*     | 0.3 - 1.1  | 1.77  | 1.37                                                 | 0.0 - 1.3  | 0.4   | 0.46                                | 0.1 - 3.7   | -0.7  | 1.28                 | 0.5 - 2.2   | 0.49  |
| Urinary System                    | 0         | 0.4 - 2.1  | -0.02 | 3.55      | 1.7 - 2.6  | 0.06  | 0                                                    | 0.7 - 2.3  | -0.02 | 0                                   | 0.0 - 1.6   | -0.02 | 0                    | 0.8 - 1.8   | -0.03 |
| Eye and Orbit                     | 3.62      | 0 - 32.5   | 0.12  | 0.53      | 0.7 - 10.3 | -0.03 | 0                                                    | 0 - 24.9   | -0.05 | 6.46                                | 0 - 53.8    | 0.25  | 0                    | 0 - 9.9     | -0.06 |
| Brain and Other Nervous System    | 1.61      | 0.0 - 20.1 | 0.7   | 3.28*     | 0.0 - 2.9  | 2.9   | 2.50*                                                | 0 - 9.2    | 1.8   | 1.88                                | 0.1 - 35.9  | 0.98  | 1.52                 | 0 - 5.1     | 0.62  |
| Endocrine System                  | 2.82*     | 0.8 - 2.8  | 2.6   | 5.27*     | 2.7 - 3.8  | 6.79  | 0.82                                                 | 1.6 - 3.6  | -0.25 | 1.04                                | 0.7 - 3.8   | 0.05  | 17.10*               | 0.9 - 2.2   | 28.07 |
| Lymphoma                          | 2.27      | 1.8 - 4.1  | 0.47  | 3.81*     | 4.6 - 5.9  | 1.04  | 0.92                                                 | 0.3 - 1.5  | -0.03 | 0                                   | 0.3 - 2.4   | -0.38 | 1.57                 | 15.4 - 18.9 | 0.2   |
| Hodgkin Lymphoma                  | 3.01*     | 0.7 - 5.2  | 2.13  | 5.71*     | 2.8 - 5.0  | 5.75  | 0.79                                                 | 0.1 - 2.6  | -0.22 | 1.4                                 | 0 - 2.9     | 0.43  | 21.01*               | 0.6 - 3.2   | 27.87 |
| Non-Hodgkin Lymphoma              | 0.92      | 1.8 - 4.7  | -0.01 | 2.17*     | 5.0 - 6.4  | 0.26  | 0                                                    | 0.3 - 1.6  | -0.16 | 1.55                                | 0.4 - 3.2   | 0.11  | 1.34                 | 18.9 - 23.2 | 0.1   |
| Myeloma                           | 6.34*     | 0.0 - 5.1  | 2.97  | 5.97*     | 1.2 - 3.4  | 3.12  | 3.97*                                                | 0 - 2.6    | 1.55  | 11.54*                              | 0.0 - 8.6   | 6.02  | 1.82*                | 0.4 - 3.1   | 0.57  |
| Leukemia                          |           | 3.9 - 9.6  |       |           | 4.9 - 7.0  |       |                                                      | 2.3 - 6.2  |       |                                     | 7.2 - 17.4  |       |                      | 1.0 - 2.9   |       |

|                                       |        |            |       |        |             |       |            |       |        |             |       |       |            |       |
|---------------------------------------|--------|------------|-------|--------|-------------|-------|------------|-------|--------|-------------|-------|-------|------------|-------|
|                                       | 20.32* |            | 1.28  | 4.13*  | 0.2         | 1.84  |            | 0.05  | 17.35* |             | 1.13  | 2.53  |            | 0.1   |
| Acute Lymphocytic Leukemia            |        | 8.7 - 40.0 |       |        | 1.8 - 7.8   |       |            |       |        |             |       |       |            |       |
|                                       | 6.80*  |            | 1.86  | 9.52*  | 2.99        | 4.49* | 0.0 - 10.2 | 1.08  | 15.87* | 4.7 - 44.4  | 4.77  | 2.45* | 0.3 - 9.1  | 0.56  |
| Non-Lymphocytic Leukemia              |        | 3.6 - 11.6 |       |        | 7.8 - 11.4  |       |            |       |        |             |       |       |            |       |
|                                       | 9.35*  |            | 1.65  | 13.69* | 2.75        | 6.68* | 2.3 - 7.8  | 1.08  | 20.93* | 9.2 - 25.4  | 3.99  | 3.32* | 1.2 - 4.2  | 0.55  |
| Acute Non-Lymphocytic Leukemia (ANLL) |        | 4.6 - 16.7 |       |        | 11.1 - 16.6 |       |            |       |        |             |       |       |            |       |
|                                       | 7.30*  |            | 1.89  | 9.10*  | 2.64        | 4.42* | 3.3 - 11.9 | 0.98  | 16.05* | 11.4 - 35.1 | 4.49  | 2.64* | 1.5 - 6.1  | 0.59  |
| Myeloid and Monocytic Leukemia        |        | 3.8 - 12.4 |       |        | 7.4 - 11.0  |       |            |       |        |             |       |       |            |       |
|                                       | 10.60* |            | 1.67  | 12.67* | 2.23        | 6.90* | 2.2 - 7.9  | 0.99  | 22.03* | 9.1 - 26.0  | 3.72  | 3.38* | 1.3 - 4.6  | 0.5   |
| Acute Myeloid Leukemia                |        | 5.2 - 18.9 |       |        | 10.1 - 15.6 |       |            |       |        |             |       |       |            |       |
|                                       | 0      |            | -0.01 | 16.36* | 0.22        | 0     | 3.3 - 12.6 | -0.01 | 0      | 11.7 - 37.6 | -0.01 | 5.31  | 1.5 - 6.4  | 0.06  |
| Acute Monocytic Leukemia              |        | 0 - 48.6   |       |        | 7.0 - 32.2  |       |            |       |        |             |       |       |            |       |
|                                       | 0      |            | -0.11 | 2.03   | 0.12        | 1.14  | 0 - 34.4   | 0.01  | 5.86   | 0 - 84.8    | 0.5   | 1.26  | 0.1 - 29.6 | 0.03  |
| Chronic Myeloid Leukemia              |        | 0 - 5.9    |       |        | 0.8 - 4     |       |            |       |        |             |       |       |            |       |
|                                       | 7.51   | 0.1 - 41.8 | 0.15  | 2.96   | 0.06        | 0     | 0.0 - 6.3  | -0.02 | 0      | 0.7 - 21.1  | -0.03 | 0     | 0.1 - 4.5  | -0.03 |
| Mesothelioma                          |        |            |       |        | 0.6 - 8.6   |       |            |       |        |             |       |       |            |       |
| Kaposi Sarcoma                        | 0      | 0 - 2.1    | -0.29 | 6.37*  | 4.9 - 8     | 1.77  | 0 - 21.1   | -0.32 | 0      | 0 - 43.3    | -0.28 | 0.54  | 0 - 8.9    | -0.2  |
| Miscellaneous                         | 4.21*  | 1.5 - 9.1  | 0.77  | 3.23*  | 2.2 - 4.5   | 0.66  | 0 - 1.3    | 0.24  | 3.57   | 0 - 3.9     | 0.65  | 2.40* | 0.1 - 1.5  | -0.2  |
|                                       |        |            |       |        |             |       | 0.5 - 5.2  |       |        | 0.7 - 10.4  |       |       | 1.2 - 4.3  | 0.51  |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

TABLE 10— Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer by First Cancer Diagnosis, SEER 9 1973-2012 (Continued)

|                                       | Germ Cell and Trophoblastic Neoplasms |             |       | Melanoma and Skin Carcinomas |           |       | Carcinomas |           |       | Miscellaneous Specified Neoplasms |            |       | Unspecified Malignant Neoplasms |            |       |
|---------------------------------------|---------------------------------------|-------------|-------|------------------------------|-----------|-------|------------|-----------|-------|-----------------------------------|------------|-------|---------------------------------|------------|-------|
|                                       | SIR                                   | 95% CI      | EAR   | SIR                          | 95% CI    | EAR   | SIR        | 95% CI    | EAR   | SIR                               | 95% CI     | EAR   | SIR                             | 95% CI     | EAR   |
| <b>MPC Site</b>                       |                                       |             |       |                              |           |       |            |           |       |                                   |            |       |                                 |            |       |
| All sites                             | 1.65*                                 |             | 17.08 | 1.63*                        |           | 22.35 | 1.79*      | 1.7 - 1.8 | 30.53 | 1.57*                             |            | 17.84 | 1.98*                           |            | 31.2  |
| All Solid Tumors                      | 1.67*                                 | 1.5 - 1.7   | 15.42 | 1.69*                        | 1.5 - 1.7 | 21.85 | 1.82*      | 1.7 - 1.8 | 28.9  | 1.51*                             | 1.3 - 1.8  | 14.5  | 1.86*                           | 1.5 - 2.5  | 24.84 |
| Oral Cavity and Pharynx               | 1.02                                  | 1.5 - 1.7   | 0.02  | 1.06                         | 1.6 - 1.7 | 0.06  | 2.90*      | 1.8 - 3.2 | 1.48  | 2.11                              | 1.2 - 1.8  | 0.78  | 1.27                            | 1.4 - 2.4  | 0.2   |
| Salivary Gland                        | 2.46                                  | 0.7 - 1.4   | 0.14  | 2.20*                        | 0.7 - 1.4 | 0.13  | 3.12*      | 2.2 - 4.1 | 0.23  | 7.83                              | 0.5 - 5.4  | 0.65  | 0                               | 0.0 - 7.0  | -0.1  |
| Digestive System                      | 1.43*                                 | 0.9 - 5.0   | 1.92  | 0.87                         | 1.0 - 4.1 | -0.61 | 1.93*      | 1.8 - 2.0 | 4.5   | 1.66                              | 0.9 - 28.2 | 2.66  | 2.73*                           | 0 - 35.7   | 7.16  |
| Respiratory System                    | 1.19                                  | 1.2 - 1.6   | 0.51  | 0.76*                        | 0.7 - 1.0 | -0.79 | 1.65*      | 1.5 - 1.7 | 2.36  | 2.26*                             | 0.9 - 2.6  | 3.52  | 2.63*                           | 1.4 - 4.7  | 4.67  |
| Bones and Joints                      | 0.39                                  | 0.9 - 1.4   | -0.05 | 1.58                         | 0.6 - 0.9 | 0.05  | 2.30*      | 1.4 - 3.4 | 0.1   | 0                                 | 1.3 - 3.6  | -0.07 | 0                               | 1.1 - 5.1  | -0.07 |
| Soft Tissue including Heart           | 2.52*                                 | 0.0 - 2.1   | 0.4   | 1.80*                        | 0.5 - 3.6 | 0.21  | 2.33*      | 1.8 - 2.9 | 0.34  | 7.76*                             | 0 - 18.7   | 1.62  | 0                               | 0 - 47.3   | -0.24 |
| Skin excluding Basal and Squamous     | 1.02                                  | 1.5 - 3.8   | 0.04  | 9.28*                        | 1.0 - 2.8 | 23.15 | 1.11       |           | 0.26  | 1.12                              | 2.5 - 18.1 | 0.24  | 1.8                             | 0 - 14.4   | 1.67  |
| Breast                                | 0.97                                  | 0.8 - 1.2   | -0.03 | 0.86*                        | 8.7 - 9.8 | -1.17 | 2.16*      | 1 - 1.2   | 14.58 | 0.98                              | 0.4 - 2.4  | -0.16 | 1.33                            | 0.4 - 4.6  | 3.01  |
| Female Genital System                 | 0.71                                  | 0.6 - 1.3   | -0.11 | 0.86                         | 0.7 - 0.9 | -0.43 | 1.54*      | 2.0 - 2.2 | 2.52  | 1.48                              | 0.6 - 1.4  | 1.69  | 1.91                            | 0.7 - 2.2  | 3.14  |
| Vagina                                | 0                                     | 0.3 - 1.4   | 0     | 0.82                         | 0.7 - 1.0 | -0.01 | 6.90*      | 1.6 - 9.2 | 0.29  | 19.84*                            | 0.8 - 2.4  | 0.71  | 0                               | 0.7 - 3.9  | -0.04 |
| Male Genital System                   | 2.58*                                 | 0 - 32.5    | 9.87  | 1.1                          | 0.0 - 4.5 | 0.39  | 0.92       | 5.0 - 9.2 | -0.15 | 0.63                              | 2.4 - 71.6 | -0.65 | 0.86                            | 0 - 93.9   | -0.3  |
| Testis                                | 11.20*                                | 2.3 - 2.8   | 9.76  | 0.67                         | 0.9 - 1.2 | -0.13 | 1.27       | 0.8 - 1.0 | 0.04  | 1.32                              | 0.1 - 1.8  | 0.09  | 7.02                            | 0.1 - 3.1  | 1.62  |
| Urinary System                        | 1.94*                                 | 10.0 - 12.5 | 2.13  | 1                            | 0.3 - 1.2 | 0     | 2.09*      | 1.8 - 2.2 | 1.86  | 1.58                              | 0.0 - 7.3  | 0.81  | 1.25                            | 0.8 - 25.3 | 0.37  |
| Eye and Orbit                         | 4.66*                                 | 1.6 - 2.3   | 0.13  | 0.71                         | 0.7 - 1.2 | -0.01 | 3.02*      | 1.6 - 5.0 | 0.07  | 0                                 | 0.5 - 3.4  | -0.03 | 0                               | 0.1 - 4.5  | -0.03 |
| Brain and Other Nervous System        | 0.98                                  | 1.5 - 10.8  | 0     | 3.39*                        | 0.0 - 3.9 | 0.18  | 1.33       | 0.6 - 2.3 | 0.02  | 0                                 | 0 - 53.4   | -0.05 | 0                               | 0 - 127.7  | -0.06 |
| Endocrine System                      | 1.95*                                 | 0.1 - 3.5   | 0.78  | 1.52*                        | 1.6 - 6.2 | 0.89  | 1.51*      | 1.3 - 1.6 | 0.97  | 2.52*                             | 0 - 25.5   | 2.46  | 1.72                            | 0 - 62.0   | 1.19  |
| Lymphoma                              | 1.09                                  | 1.4 - 2.5   | 0.17  | 1.18                         | 1.2 - 1.8 | 0.34  | 1.20*      | 1.0 - 1.3 | 0.33  | 1.43                              | 1.2 - 4.5  | 0.67  | 1.77                            | 0.3 - 5.0  | 1.23  |
| Hodgkin Lymphoma                      | 0.77                                  | 0.8 - 1.3   | -0.09 | 1.24                         | 0.9 - 1.4 | 0.08  | 1.04       | 0.7 - 1.4 | 0.01  | 1.2                               | 0.5 - 3.1  | 0.06  | 2.97                            | 0.3 - 5.1  | 0.62  |
| Non-Hodgkin Lymphoma                  | 1.17                                  | 0.3 - 1.4   | 0.26  | 1.17                         | 0.7 - 2.0 | 0.26  | 1.23*      | 1.0 - 1.3 | 0.32  | 1.49                              | 0.0 - 6.7  | 0.61  | 1.47                            | 0.0 - 16.5 | 0.6   |
| Myeloma                               | 1.64                                  | 0.8 - 1.5   | 0.18  | 0.69                         | 0.9 - 1.4 | -0.09 | 0.96       | 0.7 - 1.2 | -0.01 | 5.05*                             | 0.4 - 3.4  | 1.19  | 6.33                            | 0.1 - 5.3  | 1.59  |
| Leukemia                              | 2.38*                                 | 0.9 - 2.7   | 1.1   | 1.35                         | 0.3 - 1.3 | 0.28  | 1.86*      | 1.6 - 2.1 | 0.64  | 4.04*                             | 1.3 - 12.9 | 1.96  | 1.43                            | 0.7 - 22.8 | 0.28  |
| Acute Lymphocytic Leukemia            | 0                                     | 1.8 - 3.0   | -0.07 | 0.81                         | 0.9 - 1.8 | -0.01 | 1.02       | 0.4 - 2.0 | 0     | 0                                 | 1.6 - 8.3  | -0.06 | 16.37                           | 0.0 - 7.9  | 0.88  |
| Non-Lymphocytic Leukemia              | 3.84*                                 | 0 - 1.7     | 1.16  | 1.4                          | 0.1 - 2.9 | 0.17  | 2.59*      | 2.1 - 3.0 | 0.67  | 5.90*                             | 0 - 23.8   | 1.85  | 0                               | 0.4 - 91.2 | -0.38 |
| Acute Non-Lymphocytic Leukemia (ANLL) | 5.26*                                 | 2.8 - 5.1   | 1.05  | 1.53                         | 0.8 - 2.1 | 0.14  | 2.91*      | 2.3 - 3.5 | 0.52  | 7.83*                             | 2.1 - 12.8 | 1.62  | 0                               | 0 - 9.1    | -0.24 |
|                                       |                                       | 3.7 - 7.1   |       |                              | 0.8 - 2.4 |       |            |           |       |                                   | 2.5 - 18.2 |       |                                 | 0 - 14.5   |       |

|                                |        |            |       |      |           |       |       |           |       |       |            |       |      |            |       |
|--------------------------------|--------|------------|-------|------|-----------|-------|-------|-----------|-------|-------|------------|-------|------|------------|-------|
| Myeloid and Monocytic Leukemia | 3.94*  | 2.8 - 5.2  | 1.12  | 1.31 | 0.8 - 2.0 | 0.12  | 2.63* | 2.2 - 3.1 | 0.64  | 6.38* | 2.3 - 13.8 | 1.88  | 0    | 0 - 9.8    | -0.35 |
| Acute Myeloid Leukemia         | 5.05*  | 3.4 - 7.0  | 0.88  | 1.63 | 0.9 - 2.6 | 0.15  | 2.78* | 2.2 - 3.4 | 0.43  | 8.85* | 2.8 - 20.6 | 1.65  | 0    | 0 - 16.3   | -0.21 |
| Acute Monocytic Leukemia       | 10.23* | 3.3 - 23.8 | 0.15  | 0    | 0 - 5.3   | -0.02 | 4.22* | 2.0 - 7.7 | 0.06  | 0     | 0 - 90.8   | -0.02 | 0    | 0 - 229.4  | -0.02 |
| Chronic Myeloid Leukemia       | 1.44   | 0.5 - 3.1  | 0.06  | 0.6  | 0.1 - 1.7 | -0.05 | 2.08* | 1.4 - 2.8 | 0.13  | 3.2   | 0.0 - 17.8 | 0.26  | 0    | 0 - 29.7   | -0.12 |
| Mesothelioma                   | 0.79   | 0.0 - 4.4  | -0.01 | 1.79 | 0.3 - 5.2 | 0.03  | 1.62  | 0.7 - 3.1 | 0.02  | 0     | 0 - 50.6   | -0.03 | 0    | 0 - 115.6  | -0.03 |
| Kaposi Sarcoma                 | 0.82   | 0.4 - 1.4  | -0.1  | 1.35 | 0.7 - 2.3 | 0.09  | 0.91  | 0.5 - 1.5 | -0.01 | 4.05  | 0.4 - 14.6 | 0.56  | 4.96 | 0.1 - 27.6 | 0.75  |
| Miscellaneous                  | 1.38   | 0.7 - 2.2  | 0.14  | 0.71 | 0.3 - 1.2 | -0.12 | 2.09* | 1.7 - 2.4 | 0.48  | 0     | 0 - 3.8    | -0.36 | 5.11 | 0.6 - 18.4 | 1.51  |

\*p-value < 0.05

CI = confidence interval; SIR = standardized incidence ratio; EAR = excess absolute risk

## Specific Aim 2

To determine whether demographic and disease-related factors have an effect on the risk of developing multiple primary cancers among survivors of AYA cancers, using a multivariable approach.

**Risk for All MPCs Combined.** The incidence rate ratios (IRRs) for each demographic and disease-related factor are displayed in Table 11. The model for all MPCs combined indicates that females have about a 12% reduced overall risk for the development of a MPC compared to males. Both Blacks (IRR=1.34, 95% CI 1.27-1.41) and Other race (IRR=1.34, 95% CI 1.26-1.43) have a significant increased risk for a MPC compared to Whites. The model also verifies that risk for a MPC decreases as age at first cancer diagnosis increases. AYAs diagnosed with a first cancer between the ages of 35 and 39 have nearly a 50% decreased risk for a MPC (IRR=0.53, 95% CI 0.49-0.58) compared to those diagnosed with a first cancer between the ages of 15 and 19. Type of first cancer (i.e. solid vs. non-solid cancer) was not significantly associated with the risk for a MPC, when controlling for other factors. Radiation also showed a significant association with development of a MPC. Survivors of AYA cancers who received radiation as treatment for their first primary cancer had 1.35 times increased risk for a MPC compared to those who did not receive any radiation treatment. Lastly, a decline in risk for MPC was observed as time from first cancer diagnosis increased. AYAs had a 74% reduced risk for the development of a MPC 10 or more years after the first primary cancer diagnosis (IRR=0.26, 95% CI 0.25-0.28).

**Risk for Breast MPCs.** The model for breast cancer MPCs shows that both Blacks (IRR=1.70, 95% CI 1.57-1.85) and Other race (IRR=1.25, 95% CI 1.12-1.40) have an increased risk for a breast MPC compared to Whites. AYAs diagnosed with a first cancer at 20 years of age and older have a reduced risk for the development of breast MPCs. AYAs diagnosed with a first cancer between the ages of 35 and 39 have a 50% decreased risk for a breast MPC (IRR=0.50, 95% CI 0.41-0.62) compared to those diagnosed with a first cancer between the ages of 15 and 19. Type of first cancer was not significantly associated with risk of developing a subsequent breast cancer. Survivors of AYA cancers who received radiation as treatment for their first primary cancer had a nearly 2-fold increased risk for a breast MPC compared to those who did not receive any radiation treatment (IRR=1.98, 95% CI 1.87-2.11). Lastly, a decline in risk for breast MPC was observed as time from first cancer diagnosis increased. AYAs have the lowest risk for the development of a breast MPC 10 or more years after the first primary cancer diagnosis (IRR=0.34, 95% CI 0.31-0.43).

**Risk for Lymphoma MPCs.** Females have 50% less overall risk for the development of a lymphoma MPC compared to males (IRR=0.50, 95% CI 0.44-0.57). Race was not significantly associated with the development of a subsequent lymphoma. The risk for a lymphoma MPC was shown to increase with increasing age at first cancer diagnosis. AYAs diagnosed with a first cancer between the ages of 30 and 34 had the highest risk for a lymphoma MPC (IRR=2.11, 95% CI 1.41-3.15). Patients first diagnosed with a solid cancer had a 50% reduced risk of a lymphoma MPC compared to those first diagnosed with a non-solid cancer (lymphoma or leukemia) (IRR=0.50, 95% CI 0.42-0.55). Radiation treatment did not show a significant association with

development of a lymphoma MPC. A decline in risk for lymphoma was observed as time from first cancer diagnosis increased. AYAs have the lowest risk for the development of a lymphoma MPC 10 or more years after the first primary cancer diagnosis (IRR=0.15, 95% CI 0.12-0.18).

**Risk for Leukemia MPCs.** Females had a 25% increased risk for the development of a leukemia MPC compared to males (IRR=1.25, 95% CI 1.02-1.52). Race was not significantly associated with the development of a subsequent leukemia. Risk differences by increasing age group were not notably different within each site specific cancer group. However, comparisons across site specific cancer groups demonstrated increasing risk with increasing age in lymphomas and leukemias that was not observed in breast cancers. Treatment with radiation was associated with an increased risk for leukemia MPCs (IRR=1.28, 95% 1.04-1.56). Time between first cancer diagnosis and subsequent leukemia diagnosis was generally not significantly associated with the development of leukemia in AYAs, but there was a significant increased risk 1-4 years after the first primary cancer diagnosis (IRR=3.05, 95% CI 1.55-5.09).

**TABLE 11 – Risk of Multiple Primary Cancers in Survivors of Adolescent and Young Adult Cancer, Overall and by Site using Multivariable Poisson Regression (SEER 9 1973-2012)**

|                                                                        | All MPCs<br>IRR (95% CI) | Breast Cancer<br>IRR (95% CI) | Lymphoma<br>IRR (95% CI) | Leukemia<br>IRR (95% CI) |
|------------------------------------------------------------------------|--------------------------|-------------------------------|--------------------------|--------------------------|
| <b>Sex</b>                                                             |                          |                               |                          |                          |
| Male                                                                   | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| Female                                                                 | 0.88 (0.86-0.91)*        | 1.29 (0.58-2.88)              | 0.50 (0.44-0.57)*        | 1.25 (1.02-1.52)*        |
| <b>Race</b>                                                            |                          |                               |                          |                          |
| White                                                                  | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| Black                                                                  | 1.34 (1.27-1.41)*        | 1.70 (1.57-1.85)*             | 1.13 (0.91-1.40)         | 1.07 (0.73-1.59)         |
| Other                                                                  | 1.34 (1.26-1.43)*        | 1.25 (1.12-1.40)*             | 1.13 (0.80-1.60)         | 1.27 (0.79-2.04)         |
| <b>Age at 1<sup>st</sup> Cancer Diagnosis</b>                          |                          |                               |                          |                          |
| 15-19                                                                  | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| 20-24                                                                  | 0.79 (0.72-0.88)*        | 0.78 (0.62-0.99)*             | 1.34 (0.86-2.10)         | 1.30 (0.80-2.09)         |
| 25-29                                                                  | 0.67 (0.61-0.73)*        | 0.69 (0.56-0.85)*             | 1.81 (1.19-2.73)*        | 1.08 (0.74-1.59)         |
| 30-34                                                                  | 0.63 (0.58-0.69)*        | 0.67 (0.54-0.82)*             | 2.11 (1.41-3.15)*        | 1.47 (1.14-1.90)*        |
| 35-39                                                                  | 0.53 (0.49-0.58)*        | 0.50 (0.41-0.62)*             | 2.00 (1.34-2.97)*        | 0.92 (0.72-1.17)         |
| <b>Type of 1<sup>st</sup> Primary Cancer</b>                           |                          |                               |                          |                          |
| Non-solid Cancers**                                                    | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| Solid Cancers                                                          | 0.85 (0.82-1.63)         | 0.93 (0.84-1.03)              | 0.50 (0.42-0.55)*        | 0.40 (0.32-0.50)*        |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer</b>                   |                          |                               |                          |                          |
| No Radiation                                                           | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| Any Radiation                                                          | 1.35 (1.31-1.40)*        | 1.98 (1.87-2.11)*             | 0.97 (0.85-1.10)         | 1.28 (1.04-1.56)*        |
| <b>Time Since AYA 1<sup>st</sup> Cancer Diagnosis to MPC Diagnosis</b> |                          |                               |                          |                          |
| 2-11 Months                                                            | 1.00 (ref)               | 1.00 (ref)                    | 1.00 (ref)               | 1.00 (ref)               |
| 1-4 Years                                                              | 0.62 (0.58-0.67)*        | 0.98 (0.83-1.16)              | 0.45 (0.37-0.54)*        | 3.05 (1.55-5.99)*        |
| 5-9 Years                                                              | 0.42 (0.39-0.45)*        | 0.66 (0.56-0.78)*             | 0.18 (0.15-0.23)*        | 1.57 (0.79-3.11)         |
| ≥10 Years                                                              | 0.26 (0.25-0.28)*        | 0.34 (0.31-0.43)*             | 0.15 (0.12-0.18)*        | 0.67 (0.34-1.30)         |

\*p-value < 0.05

\*\*Non-solid Cancers include Leukemias and Lymphomas

### **Specific Aim 3**

To estimate the survival rates of AYA cancer survivors after diagnosis of a second primary cancer by site of second primary cancer, gender, and race/ethnicity; and, assess the effect of patient characteristics on survival rates of AYA cancer survivors after diagnosis of a second primary cancer.

**Cohort Characteristics.** To assess survival, the study population was limited to all AYA cancer survivors who had only a second primary cancer. A total of 13,420 (79%) survivors of AYA cancers met this criterion. Characteristics of this population are shown in Table 12. Approximately 59% were alive at the time of this analysis. These individuals had a mean follow-time of nearly 6 years from time of second cancer diagnosis until death, loss to follow-up, or end of the study. The majority were White (83.6%) and female (64.9%). The mean age at second primary cancer diagnosis was 45.6 years (compared to a mean age of 32.5 years at first cancer diagnosis). Over half were diagnosed with a carcinoma (solid tumors including digestive, respiratory, endocrine, breast, reproductive cancers etc.) as their first primary cancer. A high percentage (55.3%) of second cancers developed 10 or more years after the first cancer diagnosis. Nearly 28% of second primary cancers were breast cancers, which was the largest proportion of second primary cancers observed in this population.

**TABLE 12 – Characteristics of Survivors of Adolescent and Young Adult Cancer with Only a Second Primary Cancer, SEER 9 (1973-2012)**

|                                                    | <b>Survivors with Only a Second<br/>Primary Cancer<br/>n = 13,420</b> |
|----------------------------------------------------|-----------------------------------------------------------------------|
| <b>Sex (%)</b>                                     |                                                                       |
| Male                                               | 4,711 (35.1)                                                          |
| Female                                             | 8,709 (64.9)                                                          |
| <b>Race (%)</b>                                    |                                                                       |
| White                                              | 11,223 (83.6)                                                         |
| Black                                              | 1,357 (10.1)                                                          |
| Other                                              | 829 (6.2)                                                             |
| Unknown                                            | 11 (0.1)                                                              |
| <b>Age at 1<sup>st</sup> Cancer Diagnosis (%)</b>  |                                                                       |
| 15-19                                              | 476 (3.6)                                                             |
| 20-24                                              | 970 (7.2)                                                             |
| 25-29                                              | 2,035 (15.2)                                                          |
| 30-34                                              | 3,751 (27.9)                                                          |
| 35-39                                              | 6,188 (46.1)                                                          |
| <b>Type of 1<sup>st</sup> Primary Cancer (%)</b>   |                                                                       |
| Leukemias                                          | 183 (1.4)                                                             |
| Lymphomas                                          | 1,774 (13.2)                                                          |
| CNS and Other                                      | 297 (2.2)                                                             |
| Intracranial & Intraspinal                         |                                                                       |
| Neoplasms                                          |                                                                       |
| Osseous & Chondromatous                            | 108 (0.8)                                                             |
| Neoplasms                                          |                                                                       |
| Soft Tissue Sarcomas                               | 819 (6.1)                                                             |
| Germ Cell & Trophoblastic                          | 1,081 (8.1)                                                           |
| Neoplasms                                          |                                                                       |
| Melanoma & Skin Carcinomas                         | 1,668 (12.4)                                                          |
| Carcinomas                                         | 7,330 (54.6)                                                          |
| Miscellaneous Specified Neoplasms                  | 103 (0.8)                                                             |
| Unspecified Malignant Neoplasms                    | 57 (0.4)                                                              |
| <b>Type of 2<sup>nd</sup> Primary Cancer</b>       |                                                                       |
| Oral Cavity and Pharynx                            | 367 (2.7)                                                             |
| Digestive System                                   | 1,563 (11.65)                                                         |
| Respiratory System                                 | 1,126 (8.39)                                                          |
| Bones and Joints                                   | 67 (0.5)                                                              |
| Soft Tissue (including heart)                      | 200 (1.5)                                                             |
| Skin (excluding Basal and Squamous)                | 1,194 (8.9)                                                           |
| Breast                                             | 3,728 (27.8)                                                          |
| Female Genital System                              | 943 (7.0)                                                             |
| Male Genital System                                | 888 (6.6)                                                             |
| Central Nervous System                             | 266 (2.0)                                                             |
| Eye and Orbit                                      | 19 (0.1)                                                              |
| Urinary System                                     | 612 (4.6)                                                             |
| Endocrine System                                   | 638 (4.7)                                                             |
| Lymphoma                                           | 1,001 (7.5)                                                           |
| Leukemia                                           | 431 (3.2)                                                             |
| Kaposi Sarcoma                                     | 112 (0.8)                                                             |
| Myeloma                                            | 80 (0.6)                                                              |
| Mesothelioma                                       | 13 (0.1)                                                              |
| Miscellaneous                                      | 172 (1.3)                                                             |
| <b>Year of 1<sup>st</sup> Cancer Diagnosis (%)</b> |                                                                       |
| 1973-1979                                          | 1,610 (13.2)                                                          |

|                                                                                      |              |
|--------------------------------------------------------------------------------------|--------------|
| 1980-1989                                                                            | 4,780 (39.2) |
| 1990-1999                                                                            | 3,761 (30.9) |
| 2000-2012                                                                            | 2,042 (16.7) |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer (%)</b>                             |              |
| Any Radiation                                                                        | 4,623 (34.5) |
| No Radiation                                                                         | 8,578 (63.9) |
| Unknown                                                                              | 219 (1.6)    |
| <b>Time Since AYA 1<sup>st</sup> Cancer Diagnosis to Second Cancer Diagnosis (%)</b> |              |
| 2-11 Months                                                                          | 935 (7.0)    |
| 1-4 Years                                                                            | 2,676 (19.9) |
| 5-9 Years                                                                            | 2,394 (17.8) |
| ≥10 Years                                                                            | 7,415 (55.3) |
| <b>Mean Age at 2nd Cancer Diagnosis (SD)</b>                                         | 45.6 (10.6)  |
| <b>Vital Status (%)</b>                                                              |              |
| Alive                                                                                | 7,917 (59.0) |
| Dead                                                                                 | 5,503 (41.0) |
| <b>Mean Follow-up Time in Years (SD)*</b>                                            | 5.9 (6.6)    |

\*Follow-up time measured from time of second cancer diagnosis until death, loss to follow-up, or end of study

**Univariate Analysis.** Table 13 presents the overall median survival times after a second primary cancer. Median survivals were lowest for leukemias and cancers targeting the respiratory system (respiratory cancers and mesothelioma), and Kaposi sarcoma. Conversely, median survivals of greater than 10 years were observed for breast, female genital system, urinary, and oral cancers. The Kaplan Meier survival analysis indicates that survival after a second primary cancer significantly differs by sex, race, age at first cancer diagnosis, type of first primary cancer, type of 2<sup>nd</sup> primary cancer, age at second cancer diagnosis, whether radiation was used as treatment for the first cancer, and time between first and second cancer diagnosis (log rank p-values <0.0001).

**TABLE 13 – Overall Median Survival Times after a Second Primary Cancer in Survivors of Adolescent and Young Adult Cancer  
(n = 13,420), SEER 9 1973-2012**

|                                                   | Median Survival Time<br>(months) | 95% CI        | Log Rank p-<br>value |
|---------------------------------------------------|----------------------------------|---------------|----------------------|
| <b>Sex</b>                                        |                                  |               |                      |
| Male                                              | 104.0                            | 85.0 – 130.0  | <0.0001              |
| Female                                            | 219.0                            | 183.0 – 257.0 |                      |
| <b>Race</b>                                       |                                  |               |                      |
| White                                             | 195.0                            | 176.0 – 220.0 | <0.0001              |
| Black                                             | 49.0                             | 42.0 – 61.0   |                      |
| Other                                             | 148.0                            | 107.0 – 168.0 |                      |
| <b>Age at 1<sup>st</sup> Cancer Diagnosis</b>     |                                  |               |                      |
| 15-19                                             | 294.0                            | 138.0 – n/a   | <0.0001              |
| 20-24                                             | 252.0                            | 164.0 – 321.0 |                      |
| 25-29                                             | 253.0                            | 192.0 – 289.0 |                      |
| 30-34                                             | 183.0                            | 156.0 – 230.0 |                      |
| 35-39                                             | 129.0                            | 116.0 – 146.0 |                      |
| <b>Type of 1<sup>st</sup> Primary Cancer</b>      |                                  |               |                      |
| Leukemias                                         | 40.0                             | 27.0 – 78.0   | <0.0001              |
| Lymphomas                                         | 84.0                             | 67.0 – 108.0  |                      |
| CNS and Other Intracranial Intrasplinal Neoplasms | 50.0                             | 34.0 – 62.0   |                      |
| Osseous & Chondromatous Neoplasms                 | 93.0                             | 39.0 – 311.0  |                      |
| Soft Tissue Sarcomas                              | 11.0                             | 8.0 – 14.0    |                      |
| Germ Cell & Trophoblastic Neoplasms               | 366.0                            | 321.0 – n/a   |                      |
| Melanoma & Skin Carcinomas                        | N/A                              | N/A           |                      |
| Carcinomas                                        | 148.0                            | 133.0 – 166.0 |                      |
| Miscellaneous Specified Neoplasms                 | 122.0                            | 64.0 – 278.0  |                      |
| Unspecified Malignant Neoplasms                   | 263.0                            | 78.0 – 347.0  |                      |
| <b>Type of 2<sup>nd</sup> Primary Cancer</b>      |                                  |               |                      |
| Oral Cavity and Pharynx                           | 234.0                            | 119.0 – 281.0 | <0.0001              |
| Digestive System                                  | 35.0                             | 31.0 – 41.0   |                      |
| Respiratory System                                | 14.0                             | 12.0 – 15.0   |                      |
| Bones and Joints                                  | 48.0                             | 22.0 – 311.0  |                      |
| Soft Tissue (including heart)                     | 39.0                             | 28.0 – 68.0   |                      |
| Skin (excluding Basal and Squamous)               | N/A                              | N/A           |                      |
| Breast                                            | 267.0                            | 240.0 – 294.0 |                      |
| Female Genital System                             | 187.0                            | 130.0 – 263.0 |                      |
| Male Genital System                               | N/A                              | N/A           |                      |
| Central Nervous System                            | 30.0                             | 20.0 – 42.0   |                      |
| Eye and Orbit                                     | N/A                              | N/A           |                      |
| Urinary System                                    | 253.0                            | 212.0 – 314.0 |                      |
| Endocrine System                                  | N/A                              | N/A           |                      |
| Lymphoma                                          | 23.0                             | 14.0 – 33.0   |                      |

|                                                                                          |       |               |         |
|------------------------------------------------------------------------------------------|-------|---------------|---------|
| Leukemia                                                                                 | 13.0  | 11.0 – 17.0   |         |
| Kaposi Sarcoma                                                                           | 10.0  | 7.0 – 15.0    |         |
| Myeloma                                                                                  | 105.0 | 43.0 – 155.0  |         |
| Mesothelioma                                                                             | 13.0  | 1.0 – 43.0    |         |
| Miscellaneous                                                                            | 10.0  | 7.0 – 15.0    |         |
| <b>Age at 2<sup>nd</sup> Cancer Diagnosis</b>                                            |       |               |         |
| 15-19                                                                                    | N/A   | N/A           | <0.0001 |
| 20-29                                                                                    | 314.0 | 176.0 – 397.0 |         |
| 30-39                                                                                    | 108.0 | 89.0 – 140.0  |         |
| 40-49                                                                                    | 179.0 | 158.0 – 217.0 |         |
| 50-59                                                                                    | 173.0 | 153.0 – 198.0 |         |
| 60-69                                                                                    | 142.0 | 123.0 – n/a   |         |
| ≥70                                                                                      | 49.0  | 35.0 – n/a    |         |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer (%)</b>                                 |       |               |         |
| Any Radiation                                                                            | 106.0 | 93.0 – 126.0  | <0.0001 |
| No Radiation                                                                             | 218.0 | 190.0 – 248.0 |         |
| Unknown                                                                                  | 77.0  | 42.0 – 146.0  |         |
| <b>Time Since AYA 1<sup>st</sup> Cancer Diagnosis to 2<sup>nd</sup> Cancer Diagnosis</b> |       |               |         |
| 2-11 Months                                                                              | 78.0  | 49.0 – 113.0  | <0.0001 |
| 1-4 Years                                                                                | 74.0  | 62.0 – 87.0   |         |
| 5-9 Years                                                                                | 249.0 | 201.0 – 299.0 |         |
| ≥10 Years                                                                                | 195.0 | 173.0 – 226.0 |         |

**Multivariable Analysis.** The results of the Cox proportional hazards analysis are presented in Table 14. Females had a 27% reduced risk of death after a second primary cancer (SPC) compared to males (HR = 0.73, 95% CI 0.68-0.78). Blacks (HR = 1.23, 95% CI 1.18-1.38) had an increased risk of dying after a second primary cancer compared to Whites. Conversely, Other race (HR = 0.89, 95% CI 0.79-0.99) had over a 10% reduced risk for death compared to Whites. Age at first cancer diagnosis was not significantly associated with risk of death after a SPC. Patients first diagnosed with a soft tissue sarcoma had an increased risk of death after a SPC (HR=1.38, 95% CI 1.10-1.72). The type of second primary cancer was also associated with mortality. Those with Mesothelioma (HR = 12.60, 95% CI 6.62-23.98), respiratory system cancers (HR = 10.27, 95% CI 8.63-12.23), and miscellaneous cancers (HR = 11.13, 95% CI 8.80-14.07) have the highest risk of dying after developing a SPC. Leukemia, Kaposi Sarcoma, Brain and other nervous system cancers, and digestive system cancers also demonstrated risks greater than 5.0 for mortality. AYAs who received radiation treatment for their 1<sup>st</sup> primary cancer had a 16% increased risk of dying after developing their second cancer (HR=1.16, 95% CI 1.10-1.23). Patients diagnosed with an SPC a year or more after the first cancer diagnosis demonstrated reduced risks for SPCs. Those diagnosed with a SPC 10 or more years after the first cancer had a 40% reduced risk of mortality (HR=0.60, 95% CI 0.55-0.69).

**Table 14. Risk of Mortality After a Second Primary Cancer (SPC) in Survivors of Adolescent and Young Adult Cancer, using Multivariable Cox Proportional Hazards Regression (SEER 9 1973-2012)**

|                 | Hazard Ratio<br>(HR) | 95% CI      | p-value |
|-----------------|----------------------|-------------|---------|
| <b>Sex</b>      |                      |             |         |
| Male            | 1.00 (Ref)           | ---         | ---     |
| Female          | 0.73                 | 0.68 - 0.78 | <0.0001 |
| <b>Race (%)</b> |                      |             |         |
| White           | 1.00 (Ref)           | ---         | ---     |
| Black           | 1.23                 | 1.18 – 1.38 | <0.0001 |
| Other           | 0.89                 | 0.79 – 0.99 | 0.04    |

|                                                                                          |            |              |         |
|------------------------------------------------------------------------------------------|------------|--------------|---------|
| <b>Age at 1<sup>st</sup> Cancer Diagnosis</b>                                            |            |              |         |
| 15-19                                                                                    | 1.00 (Ref) | ---          | ---     |
| 20-24                                                                                    | 1.04       | 0.86 – 1.26  | 0.66    |
| 25-29                                                                                    | 1.04       | 0.87 – 1.25  | 0.67    |
| 30-34                                                                                    | 1.01       | 0.83 – 1.22  | 0.89    |
| 35-39                                                                                    | 1.08       | 0.89 – 1.31  | 0.56    |
| <b>Type of 1<sup>st</sup> Primary Cancer</b>                                             |            |              |         |
| Leukemias                                                                                | 1.00 (Ref) | ---          | ---     |
| Lymphomas                                                                                | 0.81       | 0.65 – 1.00  | 0.05    |
| CNS and Other Intracranial & Intraspinal Neoplasms                                       | 0.86       | 0.66 – 1.11  | 0.24    |
| Osseous & Chondromatous Neoplasms                                                        | 0.66       | 0.46 – 0.94  | 0.02    |
| Soft Tissue Sarcomas                                                                     | 1.38       | 1.10 – 1.72  | 0.004   |
| Germ Cell & Trophoblastic Neoplasms                                                      | 0.61       | 0.49 – 0.78  | <0.0001 |
| Melanoma & Skin Carcinomas                                                               | 0.53       | 0.42 – 0.67  | <0.0001 |
| Carcinomas                                                                               | 0.72       | 0.58 – 0.88  | 0.001   |
| Miscellaneous Specified Neoplasms                                                        | 0.68       | 0.48 – 0.97  | 0.03    |
| Unspecified Malignant Neoplasms                                                          | 0.49       | 0.31 – 0.77  | 0.002   |
| <b>Type of 2<sup>nd</sup> Primary Cancer</b>                                             |            |              |         |
| Skin (excluding Basal and Squamous)                                                      | 1.0 (Ref)  | ---          | ---     |
| Oral Cavity and Pharynx                                                                  | 3.03       | 2.42 – 3.80  | <0.0001 |
| Digestive System                                                                         | 5.98       | 5.02 – 7.12  | <0.0001 |
| Respiratory System                                                                       | 10.27      | 8.63 – 12.23 | <0.0001 |
| Bones and Joints                                                                         | 3.87       | 2.66 – 5.64  | <0.0001 |
| Soft Tissue (including heart)                                                            | 4.18       | 3.27 – 5.35  | <0.0001 |
| Breast                                                                                   | 2.60       | 2.19 – 3.09  | <0.0001 |
| Female Genital System                                                                    | 3.39       | 2.80 – 4.12  | <0.0001 |
| Male Genital System                                                                      | 0.54       | 0.41 – 0.71  | <0.0001 |
| Brain and Other Nervous System                                                           | 6.13       | 4.90 – 7.68  | <0.0001 |
| Eye and Orbit                                                                            | 3.55       | 1.67 – 7.57  | 0.001   |
| Urinary System                                                                           | 2.47       | 2.00 – 3.05  | <0.0001 |
| Endocrine System                                                                         | 0.97       | 0.75 – 1.27  | 0.85    |
| Lymphoma                                                                                 | 5.22       | 4.37 – 6.25  | <0.0001 |
| Leukemia                                                                                 | 8.63       | 7.09 – 10.51 | <0.0001 |
| Kaposi Sarcoma                                                                           | 7.78       | 5.98 – 10.12 | <0.0001 |
| Myeloma                                                                                  | 3.68       | 2.52 – 5.37  | <0.0001 |
| Mesothelioma                                                                             | 12.60      | 6.62 – 23.98 | <0.0001 |
| Miscellaneous                                                                            | 11.13      | 8.80 – 14.07 | <0.0001 |
| <b>Age at 2<sup>nd</sup> Cancer Diagnosis</b>                                            |            |              |         |
| 15-19                                                                                    | 1.00 (Ref) | ---          | ---     |
| 20-29                                                                                    | 1.45       | 0.90 – 2.33  | 0.13    |
| 30-39                                                                                    | 1.73       | 1.07 – 2.79  | 0.03    |
| 40-49                                                                                    | 1.58       | 0.96 – 2.58  | 0.07    |
| 50-59                                                                                    | 1.69       | 1.02 – 2.81  | 0.04    |
| 60-69                                                                                    | 1.97       | 1.18 – 3.31  | 0.01    |
| ≥70                                                                                      | 2.32       | 1.31 – 4.13  | 0.004   |
| <b>Radiation Treatment for 1<sup>st</sup> Cancer (%)</b>                                 |            |              |         |
| No Radiation                                                                             | 1.00 (Ref) | ---          | ---     |
| Any Radiation                                                                            | 1.16       | 1.10 – 1.23  | <0.0001 |
| <b>Time Since AYA 1<sup>st</sup> Cancer Diagnosis to 2<sup>nd</sup> Cancer Diagnosis</b> |            |              |         |
| 2-11 Months                                                                              | 1.00 (Ref) | ---          | ---     |
| 1-4 Years                                                                                | 0.92       | 0.82 – 1.02  | 0.11    |
| 5-9 Years                                                                                | 0.62       | 0.55 – 0.70  | <0.0001 |
| ≥10 Years                                                                                | 0.60       | 0.52 – 0.69  | <0.0001 |

## CHAPTER V

### DISCUSSION

This study of a nationally representative sample of AYA cancer survivors found a strong risk of developing at least one subsequent cancer. We observed risks for MPCs exceeding 3x for subsequent salivary gland cancers, soft tissue cancers, cancers of the bones and joints, testicular and vaginal cancers, and most subtypes of leukemia. Overall, survivors diagnosed with their first cancer at a young age and survivors who received radiotherapy were at more risk of a subsequent cancer. Risks for MPCs also varied by gender, race, latency period, and type of first primary cancer.

We were pleased to see a manuscript recently published (Lee et al., 2016) after our analysis was finished that used similar SEER data (1973-2011) to explore secondary cancers in AYAs. Our results largely agreed with Lee et al. We observed that nearly 7% of AYAs develop at least one subsequent cancer and have a nearly 2-fold increased overall risk ( $SIR=1.86$ ) for a MPC. Lee et al. observed a nearly 2-fold increased risk ( $SIR=1.97$ ) of a SMN in those diagnosed with a first cancer between the ages of 15 and 39 (Lee et al, 2016). A possible explanation for our inability to replicate Lee's finding is that we investigated risk of at least one subsequent cancer (identifying risk of secondary and multiple subsequent cancers combined) and we included all AYA's with any cancer, not just the seven most common primary cancers. A second possibility is that we included an additional year of SEER data that moved the risk estimate, but only slightly.

Our results are also in contrast to smaller international studies which observed larger risks with subsequent cancers in AYAs. One Dutch study was conducted among

patients diagnosed with a first cancer at the ages 12 to 24 (n=1118) and only 21 (2%) second primary cancers were observed in the study population. Findings from this study showed a 30-fold increase in risk (SIR=30.55, 95% CI 19.96-44.76) for second cancers in survivors of AYA cancer (van Gaal et al., 2009). A subsequent larger Dutch study investigated risk for second primary cancers in a cohort of patients with a first cancer diagnosis at the ages of 15 to 29 (n=23,161). In this study, 884 (4%) developed a second cancer and male AYA cancer survivors had a higher risk (SIR=6.2, 95% CI 5.6-6.9) of developing a second cancer compared to female AYA cancer survivors (SIR=4.8, 95% CI 4.4-5.2) (Aben et al., 2012). The third study was conducted among young adults in British Columbia (ages 20-24) where only 62 (5%) second primary cancers were observed in the cohort (n=1248) during the follow-up period. The results showed a three-fold increased risk (SIR=3.0, 95% CI, 2.3-3.8) of second primary cancer in survivors of cancers diagnosed during young adulthood (Zhang et al., 2012). The larger increased risks for subsequent cancers observed in these studies compared to our study may be attributed to the younger age and smaller size of the study cohorts. Additionally, different criteria used to define MPCs in these studies could have led to misclassification of subsequent cancers and could have played a role in the higher risk estimates observed in these studies.

As another useful measure of risk to evaluate the overall burden of multiple primary cancers in this population, excess absolute risks have been observed to be higher for survivors of AYA cancers, compared to those in survivors of childhood and older adult cancers (Curtis et al., 2006; Lee et al., 2016). Research shows the EAR in AYAs ranges from 22 to ~40 excess cancer cases per 10,000 person years, while the

EARs in childhood cancer survivors and adult cancer survivors (aged  $\geq 40$  years) are approximately 16 and 23 excess cancer cases per 10,000 person years, respectively (Curtis et al., 2006; Lee et al., 2016). We observed an EAR of  $\sim 29$  excess cancer cases per 10,000 person years in this study. As expected, the cancer sites with the highest EARs did not necessarily correspond with those sites with highest SIRs. High SIRs can be associated with low EARs when the baseline cancer incidence rate in the general population is low, such as in the AYA general population (Curtis et al., 2006). Similarly, we found the risk for a MPC was highest in those diagnosed with a first primary cancer at a younger age (e.g. 15-19 years), and decreased with increasing age at first cancer diagnosis, while the EARs for MPCs increased with increasing age. This likely reflects the higher baseline cancer incidence rate with increasing age in the general population (MacArthur et al., 2007).

In our study, breast cancers, followed by cancers of the digestive system, and skin cancers (excluding Basal and Squamous cell cancers) were the most commonly diagnosed MPCs among survivors of AYA cancers. These cancers also displayed the highest excess risks. Our results largely agree with the most common subsequent cancers found in other studies assessing MPC risk in survivors of AYA cancers (Aben et al., 2012; Lee et al., 2016). While it is unclear why these types are more commonly diagnosed as a MPC, these types of cancers are more easily and commonly screened. Previous studies suggest genetic predisposition and treatment of first primary cancer are the main contributors to MPCs in younger patients (Inskip & Curtis, 2007; Schiffman et al., 2013). Younger patients who received chest radiation are at a higher risk for subsequent breast cancers because the developing breast tissue is more susceptible to

the carcinogenic effects of radiation. Obesity has also been associated with an increased risk for MPCs (Wood et al., 2012). Obesity is a risk factor for a number of cancers including breast and colon cancers. Research suggests that there is a significantly higher prevalence of obesity in AYA cancer survivors and this increased rate of obesity may be contributing to a portion of the common MPCs observed in AYA cancer survivors (Tai et al., 2012).

We found survivors of AYA cancers have high overall risks of developing a number of different types of multiple primary cancers including leukemias, lymphomas, soft tissue cancers, cancers of the bones and joints, and salivary gland cancers. An unexpected finding of this study was the high observed overall risk (5x) for subsequent vaginal cancers among females. Previous studies assessing MPC risk in AYAs have not observed such a high risk for subsequent vaginal cancers. Typically, vaginal cancers are rare and more prevalent in older adult women, with only 15% of cases found in women under the age of 40 (ACS, 2015). Risk factors for vaginal cancers include smoking and alcohol use, and HIV infection (ACS, 2015). Another U.S. study using SEER data to examine risks for HPV-related second malignancies in survivors of AYA cancers found that females have a 40% increased risk for second HPV-related malignancies, and the highest risk observed in females was for subsequent vaginal cancers (SIR=6.1, 95% CI 3.0, 11) (Ojha et al., 2013). These findings suggest that HPV infection may contribute to a portion of multiple primary cancers in survivors of AYA cancers.

As suspected, we found that survivors of AYA cancers who received radiation treatment for their first cancer had a significantly increased overall risk for the

development of MPCs (SIR=2.44, 95% CI 2.38-2.51), particularly for subsequent leukemias, lymphomas, soft tissue cancers, and salivary gland cancers. Numerous studies have shown that radiation treatment increases the risk of developing subsequent leukemias, breast, thyroid, lung, brain and central nervous system, non-melanoma skin, bone, and soft tissue cancers in survivors of childhood and adolescent cancers (ACS, 2009; Inskip & Curtis, 2007). In young adults, radiation increases the risk for subsequent solid tumors, especially in areas that received large doses of radiation exposure (Curtis et al., 2006).

To our knowledge, our study is the first to estimate the risk for MPCs specifically in survivors of AYA cancers by race. We found Blacks and Other race have a higher risk for developing MPCs compared to Whites. Potential explanations for this finding are known risk factors for MPCs such as obesity, diabetes, and physical inactivity are more prevalent in Blacks (Crawford et al., 2010). Health equity is also likely a key driver to the disparate risks, survival, and prevention efforts observed between races.

Following our stratified analyses of risk for MPCs in survivors of AYA cancers, we utilized a multivariable approach to identify risk factors for MPCs. We used a Poisson regression to directly model the SIR, while controlling for confounders. This approach allowed us to account for the natural increase in risk for subsequent cancers with increasing age. No other studies have used this method in evaluating MPC risk in the AYA population. Despite the suggestion of an association, we had limited power to run risk analysis for specific subsequent cancers. Rather, we evaluated risk for all MPCs, and for MPCs observed to be more common: breast cancer MPCs, leukemia MPCs, and lymphoma MPCs. The results from the multivariable analysis confirm the general

findings from our first aim. Similar to our results in aim 1, females had a lower overall risk for MPCs compared to males, risk for MPCs was highest in those aged 15-19 at the time of first cancer diagnosis and declined with increasing age, and risk for MPCs declined as time between first cancer diagnosis and MPC cancer diagnosis increased. Again, we found that minorities (Blacks and Other race) and those treated with radiation treatment were at an increased risk for developing MPCs, but the results were less pronounced after controlling for other factors. We also found that survivors of AYA cancers first diagnosed with a non-solid cancer (e.g. leukemia or lymphoma) had a higher risk of developing an MPC compared to those first diagnosed with a solid cancer. A proportion of the risks for subsequent cancers can be attributed to alkylating agents and radiotherapy used to treat non-solid cancers, especially in those diagnosed at the lower end of the AYA age spectrum (Curtis et al., 2006; Maule et al., 2007; Morton et al., 2010). Underlying immune dysfunction and shared risk factors, such as genetic susceptibility, immunodeficiency, infection (eg. HIV and Epstein Barr), and lifestyle factors may also contribute to the increased risks for MPCs after a non-solid cancer (Curtis et al., 2006; Maule et al., 2007; Morton et al., 2010).

To our knowledge, this is the first study to assess survival rates and risk factors for death after a second primary cancer (SPC) in survivors of AYA cancers. We utilized a Cox proportional model because censoring of participants as well as time to each event was important to account for the expected migratory nature of AYAs as they move to college and career opportunities.

The factors significantly affecting survival after a second primary cancer included gender, race, type of first primary cancer, the type of second primary cancer, radiation treatment for the first cancer, and time between first and second cancer diagnosis.

Our results show that females have a 23% reduced risk of death after a second primary cancer compared to males. The median survival time in males was approximately 8.5 years, whereas it was over 18 years in females. Research shows that cancer mortality is higher in males for a majority of different cancer types (Cook et al., 2011). Though there is not one direct cause, it is hypothesized that this discrepancy is driven by the general higher incidence of cancer in males compared to females, and by extension, differences in lifestyle factors (smoking and alcohol), viral infections, and hormones (Cook et al., 2011). However, in our analysis only 35% of second primary cancers were diagnosed in males. This suggests that other factors, such as differences between the sexes in screening, healthcare behaviors, comorbid conditions, and tumor biology may contribute to the higher risk of mortality after SPC in male survivors of AYA cancers.

We observed a significant racial disparity in risk for death after a SPC. Black survivors of AYA cancers had a 23% increased risk for death compared to Whites, and the median survival time for Blacks after SPC was only about 4 years compared to over 16 years in Whites. The factors associated with decreased survival from primary cancers in Black adults appear to be similar to those factors that decrease survival after SPC among Blacks AYA. These factors include limited healthcare access, lack of health insurance, late stage of diagnosis, risky lifestyle/environmental factors, and different

tumor biology (Chen et al., 1997; Eley et al., 1994; Hill et al., 1996; Howard et al., 1992; Mayberry et al., 1995; Keegan et al., 2013; Keegan et al., 2016).

Research shows the more time that elapses between a first primary cancer and a second primary cancer, the better the prognosis for the subsequent cancer (Friedrich, 2007; Amer, 2014). We observed a risk reduction for death when SPCs were diagnosed a year or more past the first primary cancer diagnosis. One reason for poorer prognosis of a SPC diagnosed within a year of the first primary could be reductions in the effectiveness of therapy when treating two different cancers at the same time (Friedrich, 2007). Similarly, we observed in aims 1 and 2 that risk for MPCs decreased with increasing time between first and subsequent cancer. Increased survival as time progresses may play a role in the reduced risks for MPCs observed in the later years after first cancer diagnosis.

This study is one of the first and largest studies to provide a wide overview of the risk and survival of MPCs in survivors of adolescent and young adult cancers. It utilized the most current data from the SEER program, which is considered the most authoritative source of cancer data in the United States. A major strength of this study is the large number of second and subsequent cancer cases in survivors of AYA cancers, as well as up to 39 years of follow-up time. Additionally, SEER has nearly 100% ascertainment of incident cancer cases which likely reduced the chance for selection bias. SEER has strict guidelines for classifying multiple primary cancers which reduced the potential for misclassification of MPCs. Lastly, SEER has more than a 97% rate of follow-up for vital status because it actively traces all living patients, including those who have migrated out of the SEER regions, and links with state and national death

registries. This reduced the potential for loss-to-follow-up for the survival analyses portion of this study.

There are limitations of this study that are noted. Despite the large SEER program, cancers in AYAs are still rare. Appreciating that cancers are heterogeneous, site specific analysis are preferred but are characteristically underpowered due to small numbers. In order to obtain enough numbers to stratify by first primary cancer site, we utilized the adapted classification scheme for tumors of adolescents and young adults. This classification scheme groups cancer sites into 10 broad categories of cancer types that are common among AYAs. Additionally, we had to dichotomize type of first primary cancer into solid and non-solid cancers (leukemias and lymphomas) in order to obtain enough power to conduct the multivariable Poisson regression analysis in aim 2. Site specific analysis should be interpreted with caution and viewed as exploratory in nature.

Another limitation of this study is that only radiation information was available in SEER. We were not able to investigate risks for MPCs after chemotherapy or hormone therapy for first primary cancers. Additionally, we did not have information on co-morbid conditions or socioeconomic factors that may potentially influence the risk for MPCs and survival after developing a second primary cancer.

In conclusion, we successfully demonstrated that survivors of AYA cancers have an increased risk for the development of multiple primary cancers and we confirmed many of the established risk factors for the development of MPCs in this population. Given the larger burden of MPCs in survivors of AYA cancers, interventions and screening programs should be tailored to MPC risk reduction. The findings from this

study may help educate providers on surveillance and follow-up care of AYA cancer patients in order to improve quality of life and survival outcomes in this population.

## APPENDIX

| Table 1. Recent Studies Assessing Risk for Multiple Primary Cancers |                                             |                                                                                                                                                                      |                                                                                                                            |                                                                                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study/Investigator                                                  | Study Type                                  | Study Population                                                                                                                                                     | Outcomes Measured                                                                                                          | Summary of Findings                                                                                                                                                                                                                                                                                                        |
| <b>Curtis et al, 2006</b>                                           | Population-based retrospective cohort study | Cancer survivors of all ages from 1973-2000 identified in SEER program                                                                                               | Risk for multiple primary cancers (standardized incidence ratio, SIR)                                                      | Survivors of all ages have 14 times the risk for MPC; six-fold increased risk for MPC for those diagnosed with a first cancer during childhood, a 2-to-3-fold increased risk in those diagnosed during young adulthood (ages 18-39), and a 1.4-to-1.6-fold increased risk among those diagnosed between the ages 40 and 59 |
| <b>Inskip &amp; Curtis, 2007</b>                                    | Population-based retrospective cohort study | Childhood cancer survivors 1 <sup>st</sup> diagnosed with cancer before the age of 18 years and between calendar years 1973 and 2002 identified from SEER            | Risk for multiple primary cancers (standardized incidence ratio, SIR)                                                      | Childhood cancer survivors had 6-fold risk of developing a new cancer ( $SIR = 5.9$ , 95% CI: 5.4–6.5). Most common SPCs were female breast, central nervous system, bone, thyroid gland and soft tissue.                                                                                                                  |
| <b>Meadows et al., 2009</b>                                         | Population-based retrospective cohort study | Childhood cancer survivors 1 <sup>st</sup> diagnosed with cancer before the age of 21 years identified from CCSS cohort                                              | Cumulative incidence and risk for a subsequent neoplasm (standardized incidence ratio, SIR)                                | The 30-year cumulative incidence of SMNs was 9.3%; had 6-fold risk of developing a new cancer ( $SIR = 6.4$ ); risks differ by SN subtype, but include radiotherapy, age at diagnosis, sex, family history of cancer, and primary childhood cancer diagnosis.                                                              |
| <b>Olsen et al., 2009</b>                                           | Population-based retrospective cohort study | Childhood cancer survivors 1 <sup>st</sup> diagnosed with cancer at ages 0-19 years identified from registries from Nordic countries                                 | risk for a second primary cancer (standardized incidence ratio, SIR)                                                       | Overall SIR of 3.3 (95% confidence interval = 3.1 to 3.5).                                                                                                                                                                                                                                                                 |
| <b>Friedman et al., 2010</b>                                        | Population-based retrospective cohort study | 5-year childhood cancer survivors 1 <sup>st</sup> diagnosed with cancer before the age of 21 years identified from CCSS cohort                                       | Cumulative incidence and risk for subsequent primary cancers (standardized incidence ratio, SIR)                           | The 30-year cumulative incidence of SMNs was 20.7%; had 6-fold risk of developing a new cancer ( $SIR = 6.0$ , 95% CI 5.5-6.4); risks differ by sex, age at diagnosis, treatment era, diagnosis of Hodgkin lymphoma, and treatment with radiation therapy                                                                  |
| <b>de Gonzalez et al., 2011</b>                                     | Population-based retrospective cohort study | Cancer survivors treated with radiotherapy and 1 <sup>st</sup> diagnosed with cancer at ages 20 and older, between calendar years 1973 and 2002 identified from SEER | Relative risks (RRs) for second cancer in patients treated with radiotherapy versus patients not treated with radiotherapy | RR varied from 1.08 (95% CI 0.79-1.46) after cancers of the eye and orbit to 1.43 (1.13-1.84) after cancer of the testes; RR decreased with increasing age at diagnosis, and increased with time since diagnosis. only 8% of subsequent cancers in adults can be attributed to radiotherapy;                               |

**Table 2. Original Classification of Potential Confounding Variables**

| Variable                                                                    | Variable Type                                        | Variable Categories                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age at first primary cancer diagnosis                                       | Categorical                                          | 15-19<br>20-24<br>25-29<br>30-34<br>35-39                                                                                                                                                                                                                                                                                       |
| Age at subsequent cancer diagnosis                                          | Continuous                                           | Range 15-78                                                                                                                                                                                                                                                                                                                     |
| Sex                                                                         | Categorical                                          | Male<br>Female                                                                                                                                                                                                                                                                                                                  |
| Race                                                                        | Categorical                                          | White<br>Black<br>Other (American Indian/AK native,<br>Asian/Pacific Islander)<br>Unknown                                                                                                                                                                                                                                       |
| Type of first primary cancer                                                | Categorical<br>(AYA site recode ICD-O-3/WHO<br>2008) | Leukemias<br>Lymphomas<br>CNS and other intracranial and intraspinal<br>neoplasms (all behaviors)<br>Osseous and chondromatous neoplasms<br>Soft tissue sarcomas<br>Germ cell and trophoblastic neoplasms<br>Melanoma and skin carcinomas<br>Carcinomas<br>Miscellaneous specified neoplasms<br>Unspecified malignant neoplasms |
| Year of diagnosis of first primary cancer                                   | Categorical                                          | 1973-1979<br>1980-1989<br>1990-1999<br>2000-2011                                                                                                                                                                                                                                                                                |
| Years since diagnosis of first cancer until<br>development of second cancer | Categorical                                          | <1 year<br>1-4 years<br>5-9 years<br>≥10 years                                                                                                                                                                                                                                                                                  |
| Treatment                                                                   | Categorical                                          | None<br>Radiation<br>Surgery<br>Surgery/Radiation                                                                                                                                                                                                                                                                               |

## Tables Including Risks for All Multiple Primary Sites

**TABLE 3 – Risk of MPCs in Survivors of AYA Cancer by Sex, SEER 9 1973-2012**

| MPC Site                                                 | Males |          |       |               |       | Females |          |       |               |       |
|----------------------------------------------------------|-------|----------|-------|---------------|-------|---------|----------|-------|---------------|-------|
|                                                          | O     | E        | SIR   | 95% CI        | EAR   | O       | E        | SIR   | 95% CI        | EAR   |
| All sites                                                | 5,863 | 2,946.97 | 1.99* | (1.94 – 2.04) | 28.02 | 11,138  | 6,175.40 | 1.80* | (1.77 – 1.84) | 29.24 |
| All sites (excluding non-Melanoma skin)                  | 5,822 | 2,932.68 | 1.99* | (1.93 – 2.04) | 27.76 | 11,089  | 6,153.99 | 1.80* | (1.77 – 1.84) | 29.08 |
| All Solid Tumors                                         | 4,723 | 2,545.12 | 1.86* | (1.80 – 1.91) | 20.93 | 10,237  | 5,682.92 | 1.80* | (1.77 – 1.84) | 26.84 |
| Oral Cavity and Pharynx                                  | 322   | 133.66   | 2.41* | (2.15 – 2.69) | 1.81  | 215     | 92.87    | 2.31* | (2.02 – 2.65) | 0.72  |
| Salivary Gland                                           | 50    | 10.45    | 4.78* | (3.55 – 6.31) | 0.38  | 58      | 17.01    | 3.41* | (2.59 – 4.41) | 0.24  |
| Digestive System                                         | 980   | 525.71   | 1.86* | (1.75 – 1.98) | 4.36  | 1,108   | 675.88   | 1.64* | (1.54 – 1.74) | 2.55  |
| Esophagus                                                | 64    | 41.02    | 1.56* | (1.20 – 1.99) | 0.22  | 38      | 17.16    | 2.21* | (1.57 – 3.04) | 0.12  |
| Stomach                                                  | 116   | 48.02    | 2.42* | (2.00 – 2.90) | 0.65  | 91      | 48.85    | 1.86* | (1.50 – 2.29) | 0.25  |
| Small Intestine                                          | 43    | 15.88    | 2.71* | (1.96 – 3.65) | 0.26  | 44      | 22.35    | 1.97* | (1.43 – 2.64) | 0.13  |
| Colon, Rectum and Anus                                   | 509   | 276.73   | 1.84* | (1.68 – 2.01) | 2.23  | 670     | 423.46   | 1.58* | (1.46 – 1.71) | 1.45  |
| Colon and Rectum                                         | 446   | 263.41   | 1.69* | (1.54 – 1.86) | 1.75  | 624     | 395.23   | 1.58* | (1.46 – 1.71) | 1.35  |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 100   | 76.09    | 1.31* | (1.07 – 1.60) | 0.23  | 97      | 57.02    | 1.70* | (1.38 – 2.08) | 0.24  |
| Liver                                                    | 74    | 61.03    | 1.21  | (0.95 – 1.52) | 0.12  | 42      | 28.72    | 1.46* | (1.05 – 1.98) | 0.08  |
| Gallbladder                                              | 4     | 2.7      | 1.48  | (0.4 – 3.8)   | 0.01  | 11      | 11.46    | 0.96  | (0.48 – 1.72) | 0     |
| Pancreas                                                 | 121   | 61.22    | 1.98* | (1.64 – 2.36) | 0.57  | 125     | 85.36    | 1.46* | (1.22 – 1.72) | 0.23  |
| Respiratory System                                       | 572   | 332.29   | 1.72* | (1.58 – 1.87) | 2.3   | 826     | 515.37   | 1.60* | (1.50 – 1.72) | 1.83  |
| Nose, Nasal Cavity and Middle Ear                        | 19    | 6.48     | 2.93* | (1.76 – 4.58) | 0.12  | 15      | 7.27     | 2.06* | (1.15 – 3.40) | 0.05  |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 506   | 288.02   | 1.76* | (1.61 – 1.92) | 2.09  | 783     | 488.21   | 1.60* | (1.49 – 1.72) | 1.74  |
| Lung and Bronchus                                        | 499   | 285.28   | 1.75* | (1.60 – 1.91) | 2.05  | 782     | 486.78   | 1.61* | (1.50 – 1.72) | 1.74  |
| Bones and Joints                                         | 41    | 9.14     | 4.48* | (3.22 – 6.08) | 0.31  | 33      | 12.01    | 2.75* | (1.89 – 3.86) | 0.12  |
| Soft Tissue including Heart                              | 115   | 29.06    | 3.96* | (3.27 – 4.75) | 0.83  | 136     | 39.01    | 3.49* | (2.93 – 4.12) | 0.57  |
| Skin excluding Basal and Squamous Melanoma of the Skin   | 679   | 248.24   | 2.74* | (2.53 – 2.95) | 4.14  | 960     | 393.18   | 2.44* | (2.29 – 2.60) | 3.34  |
| Breast                                                   | 638   | 233.95   | 2.73* | (2.52 – 2.95) | 3.88  | 911     | 371.77   | 2.45* | (2.29 – 2.61) | 3.18  |
| Female Breast                                            | 11    | 6.16     | 1.79  | (0.89 – 3.20) | 0.05  | 4,626   | 2,398.69 | 1.93* | (1.87 – 1.98) | 13.13 |
| Female Genital System                                    | 0     | 0        | 0     | 0             | 0     | 4,626   | 2,398.69 | 1.93* | (1.87 – 1.98) | 13.13 |
| Cervix Uteri                                             | 0     | 0        | 0     | 0             | 0     | 1,258   | 902.93   | 1.39* | (1.32 – 1.47) | 2.09  |
| Corpus and Uterus, NOS                                   | 0     | 0        | 0     | 0             | 0     | 173     | 208.81   | 0.83* | (0.71 – 0.96) | -0.21 |
| Corpus Uteri                                             | 0     | 0        | 0     | 0             | 0     | 495     | 416.66   | 1.19* | (1.09 – 1.30) | 0.46  |
| Uterus, NOS                                              | 0     | 0        | 0     | 0             | 0     | 484     | 408.87   | 1.18* | (1.08 – 1.29) | 0.44  |
| Ovary                                                    | 0     | 0        | 0     | 0             | 0     | 11      | 7.79     | 1.41  | (0.7 – 2.53)  | 0.02  |
| Vagina                                                   | 0     | 0        | 0     | 0             | 0     | 452     | 221      | 2.05* | (1.86 – 2.24) | 1.36  |
| Male Genital System                                      | 1,063 | 787.32   | 1.35* | (1.27 – 1.43) | 2.65  | 51      | 9.3      | 5.49* | (4.08 – 7.21) | 0.25  |
| Prostate                                                 | 666   | 679.8    | 0.98  | (0.91 – 1.06) | -0.13 | 0       | 0        | 0     | 0             | 0     |
| Testis                                                   | 387   | 101.8    | 3.80* | (3.43 – 4.20) | 2.74  | 0       | 0        | 0     | 0             | 0     |
| Penis                                                    | 7     | 4.08     | 1.71  | (0.69 – 3.53) | 0.03  | 0       | 0        | 0     | 0             | 0     |
| Urinary System                                           | 511   | 270.51   | 1.89* | (1.73 – 2.06) | 2.31  | 357     | 208.92   | 1.71* | (1.54 – 1.9)  | 0.87  |
| Urinary Bladder                                          | 200   | 138      | 1.45* | (1.26 – 1.66) | 0.6   | 140     | 80.69    | 1.74* | (1.46 – 2.05) | 0.35  |
| Kidney and Renal Pelvis                                  | 283   | 128.39   | 2.20* | (1.95 – 2.48) | 1.49  | 196     | 124.23   | 1.58* | (1.36 – 1.81) | 0.42  |
| Kidney                                                   | 266   | 124.04   | 2.14* | (1.89 – 2.42) | 1.36  | 190     | 119.83   | 1.59* | (1.37 – 1.83) | 0.41  |
| Renal Pelvis                                             | 17    | 4.36     | 3.90* | (2.27 – 6.24) | 0.12  | 6       | 4.4      | 1.36  | (0.5 – 2.97)  | 0.01  |
| Eye and Orbit                                            | 11    | 7.46     | 1.47  | (0.74 – 2.64) | 0.03  | 16      | 10.22    | 1.57  | (0.89 – 2.54) | 0.03  |
| Brain and Other Nervous System                           | 163   | 69.84    | 2.33* | (1.99 – 2.72) | 0.9   | 146     | 84.42    | 1.73* | (1.46 – 2.03) | 0.36  |
| Brain                                                    | 149   | 65.84    | 2.26* | (1.91 – 2.66) | 0.8   | 128     | 78       | 1.64* | (1.37 – 1.95) | 0.29  |
| Endocrine System                                         | 175   | 71.94    | 2.43* | (2.09 – 2.82) | 0.99  | 591     | 365.07   | 1.62* | (1.49 – 1.75) | 1.33  |
| Thyroid                                                  | 163   | 65.86    | 2.47* | (2.11 – 2.89) | 0.93  | 573     | 355.61   | 1.61* | (1.48 – 1.75) | 1.28  |
| Adrenal Gland                                            | 2     | 1.75     | 1.15  | (0.14 – 4.14) | 0     | 7       | 3.54     | 1.98  | (0.79 – 4.07) | 0.02  |
| All Lymphatic and Hematopoietic Diseases                 | 1,028 | 344.4    | 2.98* | (2.81 – 3.17) | 6.57  | 714     | 408.05   | 1.75* | (1.62 – 1.88) | 1.8   |
| Lymphoma                                                 | 759   | 219.12   | 3.46* | (3.22 – 3.72) | 5.19  | 383     | 251.16   | 1.52* | (1.38 – 1.69) | 0.78  |
| Hodgkin Lymphoma                                         | 80    | 41.04    | 1.95* | (1.55 – 2.43) | 0.37  | 50      | 46.32    | 1.08  | (0.8 – 1.42)  | 0.02  |
| Non-Hodgkin Lymphoma                                     | 679   | 178.09   | 3.81* | (3.53 – 4.11) | 4.81  | 333     | 204.83   | 1.63* | (1.46 – 1.81) | 0.76  |
| Myeloma                                                  | 52    | 34.38    | 1.51* | (1.13 – 1.98) | 0.17  | 45      | 48.29    | 0.93  | (0.68 – 1.25) | -0.02 |
| Leukemia                                                 | 217   | 90.9     | 2.39* | (2.08 – 2.73) | 1.21  | 286     | 108.61   | 2.63* | (2.34 – 2.96) | 1.05  |
| Lymphocytic Leukemia                                     | 50    | 45.24    | 1.11  | (0.82 – 1.46) | 0.05  | 58      | 43.88    | 1.32* | (1.00 – 1.71) | 0.08  |
| Acute Lymphocytic Leukemia                               | 15    | 7.58     | 1.98* | (1.11 – 3.26) | 0.07  | 20      | 9.19     | 2.18* | (1.33 – 3.36) | 0.06  |
| Chronic Lymphocytic Leukemia                             | 28    | 30.77    | 0.91  | (0.60 – 1.32) | -0.03 | 37      | 31.11    | 1.19  | (0.84 – 1.64) | 0.03  |
| Other Lymphocytic Leukemia                               | 7     | 6.89     | 1.02  | (0.41 – 2.09) | 0     | 1       | 3.58     | 0.28  | (0.01 – 1.56) | -0.02 |
| Non-Lymphocytic Leukemia                                 | 167   | 45.66    | 3.66* | (3.12 – 4.26) | 1.17  | 228     | 64.73    | 3.52* | (3.08 – 4.01) | 0.96  |
| Acute Non-Lymphocytic Leukemia (ANLL)                    | 132   | 27.52    | 4.80* | (4.01 – 5.69) | 1     | 185     | 42.39    | 4.36* | (3.76 – 5.04) | 0.84  |
| Myeloid and Monocytic Leukemia                           | 151   | 42.47    | 3.56* | (3.01 – 4.17) | 1.04  | 215     | 59.98    | 3.58* | (3.12 – 4.10) | 0.91  |
| Acute Myeloid Leukemia                                   | 113   | 24.2     | 4.67* | (3.85 – 5.61) | 0.85  | 158     | 37.49    | 4.21* | (3.58 – 4.92) | 0.71  |
| Acute Monocytic Leukemia                                 | 8     | 1.8      | 4.45* | (1.92 – 8.76) | 0.06  | 16      | 2.7      | 5.92* | (3.38 – 9.61) | 0.08  |
| Chronic Myeloid Leukemia                                 | 26    | 15.58    | 1.67* | (1.09 – 2.45) | 0.1   | 32      | 18.24    | 1.75* | (1.20 – 2.48) | 0.08  |
| Mesothelioma                                             | 7     | 5.28     | 1.33  | (0.53 – 2.73) | 0.02  | 9       | 4.52     | 1.99  | (0.91 – 3.78) | 0.03  |
| Kaposi Sarcoma                                           | 114   | 62.79    | 1.82* | (1.50 – 2.18) | 0.49  | 5       | 1.23     | 4.07* | (1.32 – 9.50) | 0.02  |
| Miscellaneous                                            | 71    | 43.16    | 1.64* | (1.28 – 2.07) | 0.27  | 138     | 63.02    | 2.19* | (1.84 – 2.59) | 0.44  |

\*p-value < 0.05

TABLE 4 – Risk of MPCs in Survivors of AYA Cancer by Race, SEER 9 1973-2012

| MPC Site                                                 | White  |       |             |       | Black |       |              |       | Other |        |              |       | Unknown |       |              |       |
|----------------------------------------------------------|--------|-------|-------------|-------|-------|-------|--------------|-------|-------|--------|--------------|-------|---------|-------|--------------|-------|
|                                                          | O      | SIR   | 95% CI      | EAR   | O     | SIR   | 95% CI       | EAR   | O     | SIR    | 95% CI       | EAR   | O       | SIR   | 95% CI       | EAR   |
| All sites                                                | 14,250 | 1.80* | 1.77 - 1.83 | 27.24 | 1,695 | 2.45* | 2.34 - 2.57  | 47.36 | 1,043 | 2.59*  | 2.34 - 2.57  | 37.31 |         |       | 0.07 - 0.22  | -     |
| All sites (excluding non-Melanoma skin)                  | 14,183 | 1.80* | 1.77 - 1.83 | 27.08 | 1,683 | 2.45* | 2.33 - 2.57  | 46.94 | 1,032 | 2.57*  | 2.33 - 2.57  | 36.75 | 13      | 0.13* | 0.07 - 0.22  | 27.03 |
| All Solid Tumors                                         | 12,544 | 1.75* | 1.72 - 1.79 | 23.24 | 1,486 | 2.41* | 2.28 - 2.53  | 40.96 | 918   | 2.48*  | 2.28 - 2.53  | 31.93 | 12      | 0.13* | 0.07 - 0.23  | -     |
| Oral Cavity and Pharynx                                  | 456    | 2.34* | 2.13 - 2.56 | 1.12  | 51    | 2.95* | 2.2 - 3.88   | 1.59  | 30    | 2.60*  | 2.2 - 3.88   | 1.08  |         |       |              |       |
| Salivary Gland                                           | 94     | 4.03* | 3.26 - 4.93 | 0.3   | 4     | 1.92  | 0.52 - 4.92  | 0.09  | 10    | 5.76*  | 0.52 - 4.92  | 0.48  | 0       | 0     | 0 - 1.42     | -0.79 |
| Digestive System                                         | 1,671  | 1.68* | 1.6 - 1.76  | 2.91  | 229   | 1.89* | 1.65 - 2.15  | 5.08  | 187   | 2.60*  | 1.65 - 2.15  | 6.7   | 0       | 0     | 11.86        | -0.09 |
| Esophagus                                                | 85     | 1.72* | 1.37 - 2.12 | 0.15  | 12    | 1.86  | 0.96 - 3.25  | 0.26  | 5     | 3.18*  | 0.96 - 3.25  | 0.2   | 1       | 0.08* | 0 - 0.44     | -3.59 |
| Stomach                                                  | 154    | 2.05* | 1.74 - 2.4  | 0.34  | 28    | 2.47* | 1.64 - 3.57  | 0.79  | 25    | 2.69*  | 1.64 - 3.57  | 0.92  | 0       | 0     | 0 - 5.66     | -0.2  |
| Small Intestine                                          | 71     | 2.21* | 1.73 - 2.79 | 0.17  | 10    | 2.20* | 1.05 - 4.04  | 0.26  | 6     | 5.13*  | 1.05 - 4.04  | 0.28  | 0       | 0     | 0 - 3.75     | -0.3  |
| Colon, Rectum and Anus                                   | 943    | 1.61* | 1.51 - 1.71 | 1.54  | 129   | 1.90* | 1.59 - 2.26  | 2.89  | 106   | 2.77*  | 1.59 - 2.26  | 3.95  | 0       | 0     | 0 - 8.89     | -0.13 |
| Colon and Rectum                                         | 857    | 1.56* | 1.46 - 1.67 | 1.32  | 110   | 1.72* | 1.41 - 2.07  | 2.16  | 102   | 2.72*  | 1.41 - 2.07  | 3.76  | 1       | 0.13* | 0 - 0.74     | -1.98 |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 152    | 1.46* | 1.24 - 1.71 | 0.21  | 23    | 1.64* | 1.04 - 2.47  | 0.43  | 22    | 1.62*  | 1.04 - 2.47  | 0.49  | 1       | 0.14* | 0 - 0.79     | -1.84 |
| Liver                                                    | 82     | 1.2   | 0.95 - 1.49 | 0.06  | 18    | 1.74* | 1.03 - 2.76  | 0.36  | 16    | 1.58   | 1.03 - 2.76  | 0.34  | 0       | 0     | 0 - 2.72     | -0.41 |
| Gallbladder                                              | 13     | 1.15  | 0.61 - 1.97 | 0.01  | 2     | 1.17  | 0.14 - 4.21  | 0.01  | 0     | 0      | 0.14 - 4.21  | -0.06 | 0       | 0     | 0 - 4.05     | -0.28 |
| Pancreas                                                 | 207    | 1.68* | 1.46 - 1.92 | 0.36  | 23    | 1.53  | 0.97 - 2.3   | 0.38  | 16    | 2.39*  | 0.97 - 2.3   | 0.54  | 0       | 0     | 27.09        | -0.04 |
| Respiratory System                                       | 1,148  | 1.58* | 1.49 - 1.67 | 1.82  | 185   | 2.21* | 1.9 - 2.55   | 4.78  | 65    | 2.27*  | 1.9 - 2.55   | 37.31 | 0       | 0     | 0 - 2.39     | -0.47 |
| Nose, Nasal Cavity and Middle Ear                        | 27     | 2.31* | 1.53 - 3.37 | 0.07  | 2     | 1.8   | 0.22 - 6.5   | 0.04  | 5     | 6.07*  | 0.22 - 6.5   | 0.24  | 0       | 0.00* | 0 - 0.41     | -2.72 |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 1,059  | 1.59* | 1.5 - 1.69  | 1.7   | 172   | 2.26* | 1.93 - 2.62  | 4.52  | 58    | 2.16*  | 1.93 - 2.62  | 1.82  | 0       | 0     | 23.77        | -0.05 |
| Lung and Bronchus                                        | 1,052  | 1.59* | 1.5 - 1.69  | 1.68  | 171   | 2.26* | 1.93 - 2.62  | 4.49  | 58    | 2.18*  | 1.93 - 2.62  | 1.83  | 0       | 0.00* | 0 - 0.46     | -2.47 |
| Bones and Joints                                         | 57     | 3.04* | 2.3 - 3.93  | 0.16  | 4     | 2.98  | 0.81 - 7.64  | 0.13  | 13    | 16.92* | 0.81 - 7.64  | 0.71  | 0       | 0.00* | 0 - 0.46     | -2.46 |
| Soft Tissue including Heart                              | 198    | 3.42* | 2.96 - 3.93 | 0.6   | 30    | 4.89* | 3.3 - 6.98   | 1.13  | 23    | 7.00*  | 3.3 - 6.98   | 1.15  | 0       | 0     | 14.07        | -0.08 |
| Skin excluding Basal and Squamous                        | 1,593  | 2.55* | 2.43 - 2.68 | 4.17  | 15    | 3.31* | 1.85 - 5.46  | 0.49  | 24    | 5.81*  | 1.85 - 5.46  | 1.16  | 0       | 0     | 0 - 4.68     | -0.24 |
| Melanoma of the Skin                                     | 1,526  | 2.57* | 2.44 - 2.7  | 4.02  | 3     | 2.06  | 0.42 - 6.01  | 0.07  | 13    | 4.64*  | 0.42 - 6.01  | 0.59  | 7       | 0.82  | 0.33 - 1.69  | -0.46 |
| Breast                                                   | 3,638  | 1.78* | 1.72 - 1.84 | 6.86  | 667   | 3.30* | 3.05 - 3.56  | 21.92 | 331   | 2.51*  | 3.05 - 3.56  | 11.62 | 7       | 0.86  | 0.35 - 1.78  | -0.34 |
| Female Breast                                            | 3,629  | 1.78* | 1.72 - 1.84 | 6.84  | 665   | 3.30* | 3.05 - 3.56  | 21.85 | 331   | 2.52*  | 3.05 - 3.56  | 11.63 | 1       | 0.04* | 0 - 0.22     | -7.27 |
| Female Genital System                                    | 1,041  | 1.35* | 1.27 - 1.44 | 1.17  | 116   | 1.73* | 1.43 - 2.07  | 2.31  | 99    | 1.73*  | 1.43 - 2.07  | 2.44  | 1       | 0.04* | 0 - 0.23     | -7.25 |
| Cervix Uteri                                             | 137    | 0.81* | 0.68 - 0.96 | -0.14 | 27    | 1.17  | 0.77 - 1.71  | 0.19  | 9     | 0.64   | 0.77 - 1.71  | -0.3  | 2       | 0.21* | 0.03 - 0.77  | -2.26 |
| Corpus and Uterus, NOS                                   | 406    | 1.13* | 1.02 - 1.25 | 0.2   | 40    | 1.55* | 1.11 - 2.12  | 0.67  | 49    | 1.75*  | 1.11 - 2.12  | 1.23  | 0       | 0     | 0 - 1.63     | -0.69 |
| Corpus Uteri                                             | 397    | 1.13* | 1.02 - 1.24 | 0.19  | 38    | 1.56* | 1.1 - 2.14   | 0.64  | 49    | 1.78*  | 1.1 - 2.14   | 1.25  | 0       | 0.00* | 0 - 0.88     | -1.29 |
| Uterus, NOS                                              | 9      | 1.5   | 0.68 - 2.84 | 0.01  | 2     | 1.54  | 0.19 - 5.55  | 0.03  | 0     | 0      | 0.19 - 5.55  | -0.02 | 0       | 0.00* | 0 - 0.89     | -1.26 |
| Ovary                                                    | 387    | 2.01* | 1.81 - 2.22 | 0.84  | 30    | 2.28* | 1.54 - 3.25  | 0.79  | 34    | 2.63*  | 1.54 - 3.25  | 1.23  | 0       | 0     | 50.23 - 0.01 | -0.02 |
| Vagina                                                   | 37     | 4.86* | 3.42 - 6.7  | 0.13  | 9     | 7.42* | 3.4 - 14.09  | 0.37  | 4     | 10.44* | 3.4 - 14.09  | 0.21  | 1       | 0.43  | 0.24 - 0.28  | -0.4  |
| Male Genital System                                      | 969    | 1.37* | 1.28 - 1.45 | 1.12  | 58    | 1.07  | 0.81 - 1.39  | 0.19  | 36    | 2.54*  | 0.81 - 1.39  | 1.27  | 1       | 10.96 | 61.06        | 0.28  |
| Prostate                                                 | 594    | 0.98  | 0.9 - 1.06  | -0.06 | 52    | 0.99  | 0.74 - 1.3   | -0.02 | 20    | 1.69*  | 0.74 - 1.3   | 0.47  | 0       | 0.00* | 0 - 0.38     | -2.95 |
| Testis                                                   | 368    | 3.80* | 3.42 - 4.21 | 1.17  | 3     | 2.31  | 0.48 - 6.74  | 0.08  | 16    | 7.48*  | 0.48 - 6.74  | 0.81  | 0       | 0.00* | 0 - 0.45     | -2.49 |
| Penis                                                    | 5      | 1.36  | 0.44 - 3.17 | 0.01  | 2     | 8.21  | 0.99 - 29.64 | 0.08  | 0     | 0      | 0.99 - 29.64 | -0.01 | 0       | 0     | 0 - 2.52     | -0.45 |
| Urinary System                                           | 760    | 1.77* | 1.64 - 1.9  | 1.42  | 71    | 2.39* | 1.87 - 3.02  | 1.95  | 37    | 2.72*  | 1.87 - 3.02  | 1.36  | 0       | 0     | 71.23        | -0.02 |
| Urinary Bladder                                          | 308    | 1.51* | 1.35 - 1.69 | 0.45  | 18    | 2.28* | 1.35 - 3.61  | 0.48  | 14    | 3.30*  | 1.35 - 3.61  | 0.57  | 0       | 0.00* | 0 - 0.66     | -1.71 |
| Kidney and Renal Pelvis                                  | 408    | 1.86* | 1.68 - 2.05 | 0.81  | 49    | 2.33* | 1.72 - 3.08  | 1.32  | 22    | 2.43*  | 1.72 - 3.08  | 0.75  | 0       | 0     | 0 - 1.41     | -0.8  |
| Kidney                                                   | 386    | 1.82* | 1.65 - 2.01 | 0.75  | 49    | 2.38* | 1.76 - 3.15  | 1.34  | 21    | 2.38*  | 1.76 - 3.15  | 0.71  | 0       | 0     | 0 - 1.27     | -0.88 |
| Renal Pelvis                                             | 22     | 2.76* | 1.73 - 4.18 | 0.06  | 0     | 0     | 0 - 7.93     | -0.02 | 1     | 4.24   | 0 - 7.93     | 0.04  | 0       | 0     | 0 - 1.32     | -0.85 |
| Eye and Orbit                                            | 26     | 1.53  | 1 - 2.24    | 0.04  | 0     | 0     | 0 - 17.12    | -0.01 | 1     | 3.98   | 0 - 17.12    | 0.04  | 0       | 0     | 37.24 - 0    | -0.03 |
| Brain and Other Nervous System                           | 276    | 1.95* | 1.73 - 2.2  | 0.58  | 14    | 2.16* | 1.18 - 3.62  | 0.35  | 19    | 4.09*  | 1.18 - 3.62  | 0.84  | 0       | 0     | 16.45        | -0.07 |
| Brain                                                    | 248    | 1.88* | 1.65 - 2.13 | 0.5   | 13    | 2.27* | 1.21 - 3.89  | 0.34  | 16    | 3.84*  | 1.21 - 3.89  | 0.69  | 0       | 0     | 0 - 1.93     | -0.58 |
| Endocrine System                                         | 657    | 1.72* | 1.59 - 1.85 | 1.18  | 47    | 2.31* | 1.7 - 3.07   | 1.26  | 61    | 2.14*  | 1.7 - 3.07   | 1.89  | 0       | 0     | 0 - 2.06     | -0.55 |
|                                                          |        |       |             |       |       |       |              |       |       |        |              |       | 1       | 0.19  | 0 - 1.03     | -1.34 |

|                                          |       |       |             |       |     |       |             |       |    |       |             |       |   |       |             |       |
|------------------------------------------|-------|-------|-------------|-------|-----|-------|-------------|-------|----|-------|-------------|-------|---|-------|-------------|-------|
| Thyroid                                  | 635   | 1.72* | 1.58 - 1.85 | 1.14  | 43  | 2.29* | 1.66 - 3.09 | 1.14  | 57 | 2.08* | 1.66 - 3.09 | 1.73  | 1 | 0.19  | 0 - 1.07    | -1.29 |
| Adrenal Gland                            | 8     | 1.75  | 0.75 - 3.44 | 0.01  | 1   | 2.46  | 0.06 - 13.7 | 0.03  | 0  | 0     | 0.06 - 13.7 | -0.01 | 0 | 0     | 0 - 60.97   | -0.02 |
| All Lymphatic and Hematopoietic Diseases | 1,472 | 2.24* | 2.12 - 2.36 | 3.51  | 171 | 2.89* | 2.48 - 3.36 | 5.28  | 98 | 3.65* | 2.48 - 3.36 | 4.15  | 1 | 0.11* | 0 - 0.64    | -2.36 |
| Lymphoma                                 | 984   | 2.37* | 2.22 - 2.52 | 2.45  | 104 | 3.14* | 2.57 - 3.81 | 3.35  | 53 | 3.33* | 2.57 - 3.81 | 2.16  | 1 | 0.18  | 0 - 1       | -1.39 |
| Hodgkin Lymphoma                         | 110   | 1.42* | 1.16 - 1.71 | 0.14  | 13  | 1.99* | 1.06 - 3.4  | 0.31  | 6  | 3.05* | 1.06 - 3.4  | 0.24  | 1 | 0.88  | 0.02 - 4.89 | -0.04 |
| Non-Hodgkin Lymphoma                     | 874   | 2.59* | 2.42 - 2.76 | 2.31  | 91  | 3.43* | 2.76 - 4.21 | 3.04  | 47 | 3.37* | 2.76 - 4.21 | 1.93  | 0 | 0.00* | 0 - 0.83    | -1.35 |
| Myeloma                                  | 76    | 1.17  | 0.92 - 1.46 | 0.05  | 16  | 1.18  | 0.67 - 1.91 | 0.11  | 5  | 1.66  | 0.67 - 1.91 | 0.12  | 0 | 0     | 0 - 4.49    | -0.25 |
| Leukemia                                 | 412   | 2.33* | 2.11 - 2.57 | 1.01  | 51  | 4.11* | 3.06 - 5.41 | 1.82  | 40 | 5.06* | 3.06 - 5.41 | 1.87  | 0 | 0     | 0 - 1.59    | -0.71 |
| Lymphocytic Leukemia                     | 87    | 1.06  | 0.85 - 1.31 | 0.02  | 14  | 3.52* | 1.93 - 5.91 | 0.47  | 7  | 3.48* | 1.93 - 5.91 | 0.29  | 0 | 0     | 0 - 3.48    | -0.32 |
| Acute Lymphocytic Leukemia               | 23    | 1.57  | 1 - 2.36    | 0.04  | 8   | 8.34* | 3.6 - 16.43 | 0.33  | 4  | 3.98* | 3.6 - 16.43 | 0.17  | 0 | 0     | 0 - 18.05   | -0.06 |
| Chronic Lymphocytic Leukemia             | 57    | 0.99  | 0.75 - 1.28 | 0     | 5   | 1.86  | 0.6 - 4.34  | 0.11  | 3  | 3.81  | 0.6 - 4.34  | 0.13  | 0 | 0     | 0 - 5.1     | -0.22 |
| Other Lymphocytic Leukemia               | 7     | 0.72  | 0.29 - 1.47 | -0.01 | 1   | 3.07  | 0.08 - 17.1 | 0.03  | 0  | 0     | 0.08 - 17.1 | -0.01 | 0 | 0     | 0 - 27.69   | -0.04 |
| Non-Lymphocytic Leukemia                 | 325   | 3.43* | 3.07 - 3.82 | 0.99  | 37  | 4.39* | 3.09 - 6.05 | 1.35  | 33 | 5.60* | 3.09 - 6.05 | 1.58  | 0 | 0     | 0 - 2.92    | -0.39 |
| Acute Non-Lymphocytic Leukemia (ANLL)    | 266   | 4.41* | 3.89 - 4.97 | 0.89  | 28  | 5.96* | 3.96 - 8.61 | 1.1   | 23 | 5.68* | 3.96 - 8.61 | 1.1   | 0 | 0     | 0 - 4.61    | -0.24 |
| Myeloid and Monocytic Leukemia           | 301   | 3.41* | 3.04 - 3.82 | 0.92  | 34  | 4.52* | 3.13 - 6.32 | 1.25  | 31 | 5.64* | 3.13 - 6.32 | 1.49  | 0 | 0     | 0 - 3.13    | -0.36 |
| Acute Myeloid Leukemia                   | 226   | 4.25* | 3.72 - 4.85 | 0.74  | 24  | 5.65* | 3.62 - 8.41 | 0.93  | 21 | 5.84* | 3.62 - 8.41 | 1.01  | 0 | 0     | 0 - 5.23    | -0.22 |
| Acute Monocytic Leukemia                 | 21    | 5.28* | 3.27 - 8.08 | 0.07  | 2   | 9.08* | 1.1 - 32.78 | 0.08  | 1  | 3.89  | 1.1 - 32.78 | 0.04  | 0 | 0     | 0 - 70.24   | -0.02 |
| Chronic Myeloid Leukemia                 | 41    | 1.41* | 1.01 - 1.92 | 0.05  | 8   | 2.83* | 1.22 - 5.58 | 0.24  | 9  | 5.69* | 1.22 - 5.58 | 0.43  | 0 | 0     | 0 - 9.39    | -0.12 |
| Mesothelioma                             | 16    | 1.77* | 1.01 - 2.87 | 0.03  | 0   | 0     | 0 - 9.84    | -0.02 | 0  | 0     | 0 - 9.84    | -0.01 | 0 | 0     | 0 - 31.87   | -0.04 |
| Kaposi Sarcoma                           | 105   | 1.87* | 1.53 - 2.26 | 0.21  | 11  | 1.82  | 0.91 - 3.25 | 0.23  | 3  | 3.06  | 0.91 - 3.25 | 0.12  | 0 | 0     | 0 - 4.86    | -0.23 |
| Miscellaneous                            | 167   | 1.87* | 1.6 - 2.18  | 0.33  | 26  | 2.31* | 1.51 - 3.39 | 0.7   | 16 | 3.52* | 1.51 - 3.39 | 0.67  | 0 | 0     | 0 - 3.29    | -0.34 |

TABLE 5 – Risk of MPCs in Survivors of AYA Cancer by Time Since First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                                                 | 2-11 Months |        |                      |       | 1-4 Years |        |              |       | 5-9 Years |       |              |       | ≥10 Years |       |             |       |
|----------------------------------------------------------|-------------|--------|----------------------|-------|-----------|--------|--------------|-------|-----------|-------|--------------|-------|-----------|-------|-------------|-------|
|                                                          | O           | SIR    | 95% CI               | EAR   | O         | SIR    | 95% CI       | EAR   | O         | SIR   | 95% CI       | EAR   | O         | SIR   | 95% CI      | EAR   |
| All sites                                                | 1,026       | 5.60*  | 5.27 - 5.96          | 47.4  | 3,066     | 3.47*  | 3.34 - 3.59  | 32.35 | 2,919     | 2.33* | 2.25 - 2.42  | 26.43 | 9,990     | 1.47* | 1.44 - 1.5  | 25.4  |
| All sites (excluding non-Melanoma skin)                  | 1,023       | 5.63*  | 5.29 - 5.99          | 47.31 | 3,051     | 3.47*  | 3.35 - 3.6   | 32.21 | 2,895     | 2.32* | 2.24 - 2.41  | 26.15 | 9,942     | 1.47* | 1.44 - 1.5  | 25.19 |
| All Solid Tumors                                         | 804         | 5.11*  | 4.76 - 5.48          | 36.37 | 2,505     | 3.23*  | 3.11 - 3.36  | 25.65 | 2,587     | 2.31* | 2.22 - 2.4   | 23.27 | 9,064     | 1.47* | 1.44 - 1.5  | 23.01 |
| Oral Cavity and Pharynx                                  | 22          | 6.04*  | 3.78 - 9.14          | 1.03  | 67        | 3.71*  | 2.87 - 4.71  | 0.73  | 101       | 3.47* | 2.83 - 4.22  | 1.14  | 347       | 1.97* | 1.77 - 2.19 | 1.36  |
| Salivary Gland                                           | 4           | 4.30*  | 1.17 - 11.02         | 0.17  | 17        | 4.32*  | 2.52 - 6.91  | 0.19  | 20        | 4.37* | 2.67 - 6.75  | 0.24  | 67        | 3.72* | 2.88 - 4.72 | 0.39  |
| Digestive System                                         | 69          | 5.00*  | 3.89 - 6.32          | 3.1   | 202       | 2.73*  | 2.36 - 3.13  | 1.9   | 263       | 2.08* | 1.83 - 2.34  | 2.16  | 1,554     | 1.57* | 1.5 - 1.65  | 4.52  |
| Esophagus                                                | 3           | 9.17*  | 1.89 - 26.79         | 0.15  | 7         | 3.43*  | 1.38 - 7.07  | 0.07  | 11        | 2.43* | 1.21 - 4.35  | 0.1   | 81        | 1.58* | 1.25 - 1.96 | 0.24  |
| Stomach                                                  | 7           | 4.27*  | 1.72 - 8.79          | 0.3   | 20        | 2.45*  | 1.49 - 3.78  | 0.18  | 29        | 2.36* | 1.58 - 3.39  | 0.26  | 151       | 2.02* | 1.71 - 2.37 | 0.61  |
| Small Intestine                                          | 3           | 5.95*  | 1.23 - 17.4          | 0.14  | 12        | 4.48*  | 2.32 - 7.83  | 0.14  | 10        | 2.26* | 1.08 - 4.15  | 0.09  | 62        | 2.03* | 1.55 - 2.6  | 0.25  |
| Colon, Rectum and Anus                                   | 42          | 4.83*  | 3.48 - 6.53          | 1.87  | 134       | 2.86*  | 2.39 - 3.38  | 1.29  | 165       | 2.09* | 1.78 - 2.43  | 1.36  | 838       | 1.48* | 1.38 - 1.59 | 2.17  |
| Colon and Rectum                                         | 39          | 4.76*  | 3.38 - 6.5           | 1.73  | 115       | 2.62*  | 2.16 - 3.15  | 1.05  | 141       | 1.92* | 1.61 - 2.26  | 1.07  | 775       | 1.45* | 1.35 - 1.56 | 1.93  |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 3           | 2.7    | 0.56 - 7.9           | 0.11  | 13        | 2.19*  | 1.17 - 3.75  | 0.1   | 20        | 1.81* | 1.11 - 2.8   | 0.14  | 161       | 1.40* | 1.19 - 1.63 | 0.37  |
| Liver                                                    | 2           | 2.87   | 0.35 - 10.38         | 0.07  | 8         | 2.26   | 0.98 - 4.46  | 0.07  | 11        | 1.59  | 0.79 - 2.84  | 0.06  | 95        | 1.21  | 0.98 - 1.48 | 0.13  |
| Gallbladder                                              | 0           | 0      | 0 -                  | -0.01 | 1         | 1.27   | 0.03 - 7.1   | 0     | 3         | 2.18  | 0.45 - 6.38  | 0.03  | 11        | 0.93  | 0.46 - 1.66 | -0.01 |
| Pancreas                                                 | 10          | 9.15*  | 28.82 - 4.39 - 16.82 | 0.5   | 12        | 1.92   | 0.99 - 3.36  | 0.09  | 20        | 1.66* | 1.01 - 2.56  | 0.13  | 204       | 1.60* | 1.39 - 1.84 | 0.61  |
| Respiratory System                                       | 26          | 4.33*  | 2.83 - 6.34          | 1.12  | 144       | 4.05*  | 3.42 - 4.77  | 1.61  | 166       | 2.34* | 2 - 2.72     | 1.51  | 1,062     | 1.44* | 1.36 - 1.53 | 2.6   |
| Nose, Nasal Cavity and Middle Ear                        | 1           | 2.81   | 0.07 - 15.64         | 0.04  | 4         | 2.47   | 0.67 - 6.33  | 0.04  | 7         | 3.28* | 1.32 - 6.76  | 0.08  | 22        | 2.28* | 1.43 - 3.45 | 0.1   |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 23          | 4.46*  | 2.83 - 6.7           | 1     | 135       | 4.36*  | 3.65 - 5.16  | 1.54  | 150       | 2.38* | 2.01 - 2.79  | 1.38  | 981       | 1.45* | 1.36 - 1.54 | 2.42  |
| Lung and Bronchus                                        | 23          | 4.70*  | 2.98 - 7.05          | 1.02  | 132       | 4.39*  | 3.67 - 5.21  | 1.51  | 147       | 2.36* | 2 - 2.78     | 1.34  | 979       | 1.45* | 1.36 - 1.54 | 2.42  |
| Bones and Joints                                         | 3           | 2.48   | 0.51 - 7.23          | 0.1   | 25        | 5.62*  | 3.63 - 8.29  | 0.3   | 15        | 3.46* | 1.94 - 5.7   | 0.17  | 31        | 2.78* | 1.89 - 3.95 | 0.16  |
| Soft Tissue including Heart                              | 12          | 4.53*  | 2.34 - 7.91          | 0.53  | 49        | 4.47*  | 3.31 - 5.91  | 0.56  | 51        | 4.17* | 3.1 - 5.48   | 0.61  | 139       | 3.29* | 2.77 - 3.89 | 0.77  |
| Skin excluding Basal and Squamous                        | 164         | 7.47*  | 6.37 - 8.7           | 7.99  | 380       | 3.87*  | 3.49 - 4.28  | 4.18  | 325       | 2.76* | 2.47 - 3.08  | 3.29  | 770       | 1.91* | 1.78 - 2.05 | 2.92  |
| Melanoma of the Skin                                     | 161         | 7.83*  | 6.66 - 9.13          | 7.9   | 365       | 3.95*  | 3.56 - 4.38  | 4.04  | 301       | 2.70* | 2.41 - 3.03  | 3.01  | 722       | 1.89* | 1.76 - 2.04 | 2.71  |
| Breast                                                   | 171         | 4.02*  | 3.44 - 4.67          | 7.23  | 930       | 3.83*  | 3.59 - 4.08  | 10.19 | 1,009     | 2.58* | 2.42 - 2.74  | 9.79  | 2,527     | 1.46* | 1.41 - 1.52 | 6.37  |
| Female Breast                                            | 171         | 4.03*  | 3.45 - 4.68          | 7.23  | 929       | 3.83*  | 3.59 - 4.09  | 10.18 | 1,008     | 2.58* | 2.42 - 2.74  | 9.79  | 2,518     | 1.46* | 1.4 - 1.52  | 6.34  |
| Female Genital System                                    | 87          | 3.92*  | 3.14 - 4.83          | 3.64  | 200       | 1.90*  | 1.65 - 2.19  | 1.41  | 215       | 1.55* | 1.35 - 1.78  | 1.22  | 756       | 1.19* | 1.1 - 1.27  | 0.95  |
| Cervix Uteri                                             | 19          | 1.65   | 0.99 - 2.58          | 0.42  | 39        | 0.8    | 0.57 - 1.09  | -0.15 | 44        | 0.87  | 0.63 - 1.17  | -0.11 | 71        | 0.73* | 0.57 - 0.92 | -0.21 |
| Corpus and Uterus, NOS                                   | 25          | 5.22*  | 3.38 - 7.71          | 1.14  | 49        | 1.83*  | 1.36 - 2.42  | 0.33  | 75        | 1.67* | 1.31 - 2.09  | 0.48  | 346       | 1.02  | 0.91 - 1.13 | 0.05  |
| Corpus Uteri                                             | 25          | 5.39*  | 3.49 - 7.95          | 1.14  | 48        | 1.85*  | 1.36 - 2.45  | 0.33  | 72        | 1.64* | 1.28 - 2.06  | 0.45  | 339       | 1.01  | 0.91 - 1.13 | 0.04  |
| Uterus, NOS                                              | 0           | 0      | 0 -                  | -0.01 | 1         | 1.38   | 0.03 - 7.68  | 0     | 3         | 2.82  | 0.58 - 8.24  | 0.03  | 7         | 1.2   | 0.48 - 2.46 | 0.01  |
| Ovary                                                    | 35          | 7.51*  | 5.23 - 10.45         | 1.71  | 90        | 3.86*  | 3.1 - 4.74   | 0.99  | 72        | 2.10* | 1.64 - 2.64  | 0.6   | 255       | 1.61* | 1.42 - 1.82 | 0.77  |
| Vagina                                                   | 5           | 27.41* | 8.9 - 63.96          | 0.27  | 10        | 11.25* | 5.39 - 20.69 | 0.14  | 7         | 5.46* | 2.2 - 11.26  | 0.09  | 29        | 4.18* | 2.8 - 6     | 0.18  |
| Male Genital System                                      | 32          | 3.61*  | 2.47 - 5.1           | 1.3   | 142       | 4.03*  | 3.39 - 4.75  | 1.58  | 156       | 3.39* | 2.88 - 3.97  | 1.75  | 733       | 1.05  | 0.98 - 1.13 | 0.29  |
| Prostate                                                 | 5           | 14.71* | 4.78 - 34.32         | 0.26  | 8         | 2.13   | 0.92 - 4.2   | 0.06  | 33        | 1.86* | 1.28 - 2.62  | 0.24  | 620       | 0.94  | 0.87 - 1.02 | -0.3  |
| Testis                                                   | 26          | 3.09*  | 2.02 - 4.52          | 0.99  | 133       | 4.28*  | 3.59 - 5.08  | 1.51  | 121       | 4.40* | 3.65 - 5.26  | 1.48  | 107       | 3.07* | 2.52 - 3.71 | 0.58  |
| Penis                                                    | 1           | 16.31  | 0.41 - 90.89         | 0.05  | 1         | 3.01   | 0.08 - 16.78 | 0.01  | 1         | 1.9   | 0.05 - 10.61 | 0.01  | 4         | 1.26  | 0.34 - 3.23 | 0.01  |
| Urinary System                                           | 63          | 11.50* | 8.84 - 14.72         | 3.23  | 107       | 3.66*  | 3 - 4.42     | 1.15  | 83        | 1.68* | 1.34 - 2.09  | 0.53  | 615       | 1.56* | 1.43 - 1.68 | 1.75  |
| Urinary Bladder                                          | 16          | 7.23*  | 4.13 - 11.74         | 0.78  | 29        | 2.55*  | 1.71 - 3.66  | 0.26  | 32        | 1.67* | 1.14 - 2.35  | 0.2   | 263       | 1.41* | 1.25 - 1.6  | 0.61  |
| Kidney and Renal Pelvis                                  | 43          | 13.49* | 9.77 - 18.18         | 2.24  | 70        | 4.00*  | 3.12 - 5.05  | 0.78  | 48        | 1.63* | 1.2 - 2.16   | 0.29  | 318       | 1.57* | 1.4 - 1.75  | 0.92  |
| Kidney                                                   | 4           | 25.29* | 6.89 - 64.76         | 0.22  | 9         | 11.20* | 5.12 - 21.26 | 0.12  | 5         | 3.75* | 1.22 - 8.75  | 0.06  | 54        | 3.70* | 2.78 - 4.83 | 0.31  |
| Renal Pelvis                                             | 43          | 13.85* | 10.02 - 18.65        | 2.24  | 69        | 4.04*  | 3.15 - 5.12  | 0.77  | 46        | 1.60* | 1.17 - 2.13  | 0.27  | 298       | 1.53* | 1.36 - 1.71 | 0.82  |
| Eye and Orbit                                            | 0           | 0      | 45.09                | 0     | 1         | 2.29   | 0.06 - 12.76 | 0.01  | 2         | 2.75  | 0.33 - 9.93  | 0.02  | 20        | 2.66* | 1.63 - 4.11 | 0.1   |
| Brain and Other Nervous System                           | 0           | 0      | 0 -                  | -0.02 | 4         | 1.97   | 0.54 - 5.04  | 0.03  | 5         | 1.86  | 0.6 - 4.34   | 0.04  | 18        | 1.44  | 0.85 - 2.27 | 0.04  |
| Brain                                                    | 19          | 3.14*  | 1.89 - 4.9           | 0.73  | 74        | 2.94*  | 2.31 - 3.69  | 0.72  | 69        | 2.46* | 1.92 - 3.12  | 0.65  | 147       | 1.55* | 1.31 - 1.82 | 0.41  |

|                                          |     |        |               |       |     |        |               |       |     |       |             |      |     |       |             |       |
|------------------------------------------|-----|--------|---------------|-------|-----|--------|---------------|-------|-----|-------|-------------|------|-----|-------|-------------|-------|
| Endocrine System                         | 91  | 4.92*  | 3.96 - 6.04   | 4.08  | 156 | 1.94*  | 1.65 - 2.27   | 1.12  | 130 | 1.45* | 1.21 - 1.72 | 0.64 | 389 | 1.56* | 1.41 - 1.73 | 1.12  |
| Thyroid                                  | 88  | 4.90*  | 3.93 - 6.04   | 3.94  | 148 | 1.90*  | 1.6 - 2.23    | 1.04  | 125 | 1.44* | 1.2 - 1.72  | 0.61 | 375 | 1.57* | 1.42 - 1.74 | 1.09  |
| Adrenal Gland                            | 0   | 0      | 0 - 20.05     | -0.01 | 4   | 4.98*  | 1.36 - 12.75  | 0.05  | 1   | 1.04  | 0.03 - 5.8  | 0    | 4   | 1.2   | 0.33 - 3.06 | 0.01  |
| All Lymphatic and Hematopoietic Diseases | 210 | 9.26*  | 8.05 - 10.6   | 10.53 | 521 | 5.47*  | 5.01 - 5.96   | 6.31  | 275 | 2.42* | 2.15 - 2.73 | 2.56 | 736 | 1.41* | 1.31 - 1.52 | 1.71  |
| Lymphoma                                 | 188 | 11.32* | 9.76 - 13.06  | 9.64  | 338 | 4.94*  | 4.43 - 5.5    | 4     | 157 | 2.01* | 1.71 - 2.36 | 1.25 | 459 | 1.49* | 1.36 - 1.64 | 1.21  |
| Hodgkin Lymphoma                         | 14  | 2.01*  | 1.1 - 3.38    | 0.4   | 42  | 1.68*  | 1.21 - 2.27   | 0.25  | 27  | 1.29  | 0.85 - 1.88 | 0.1  | 47  | 1.36  | 1 - 1.81    | 0.1   |
| Non-Hodgkin Lymphoma                     | 174 | 18.03* | 15.45 - 20.92 | 9.24  | 296 | 6.82*  | 6.06 - 7.64   | 3.75  | 130 | 2.28* | 1.9 - 2.7   | 1.16 | 412 | 1.51* | 1.37 - 1.66 | 1.11  |
| Myeloma                                  | 4   | 6.04*  | 1.65 - 15.46  | 0.19  | 6   | 1.52   | 0.56 - 3.32   | 0.03  | 10  | 1.32  | 0.63 - 2.42 | 0.04 | 77  | 1.09  | 0.86 - 1.37 | 0.05  |
| Leukemia                                 | 18  | 3.32*  | 1.97 - 5.25   | 0.71  | 177 | 7.70*  | 6.61 - 8.93   | 2.28  | 108 | 3.87* | 3.17 - 4.67 | 1.27 | 200 | 1.40* | 1.21 - 1.6  | 0.45  |
| Lymphocytic Leukemia                     | 5   | 3.25*  | 1.05 - 7.57   | 0.19  | 14  | 2.05*  | 1.12 - 3.44   | 0.11  | 16  | 1.67  | 0.95 - 2.71 | 0.1  | 73  | 1.03  | 0.8 - 1.29  | 0.01  |
| Acute Lymphocytic Leukemia               | 5   | 5.08*  | 1.65 - 11.86  | 0.23  | 12  | 3.34*  | 1.73 - 5.84   | 0.12  | 8   | 2.43* | 1.05 - 4.78 | 0.07 | 10  | 1.12  | 0.54 - 2.07 | 0.01  |
| Chronic Lymphocytic Leukemia             | 0   | 0      | 0 - 11.77     | -0.02 | 1   | 0.5    | 0.01 - 2.79   | -0.01 | 6   | 1.34  | 0.49 - 2.92 | 0.02 | 58  | 1.05  | 0.8 - 1.36  | 0.02  |
| Other Lymphocytic Leukemia               | 0   | 0      | 0 - 15.16     | -0.01 | 1   | 0.81   | 0.02 - 4.51   | 0     | 2   | 1.1   | 0.13 - 3.99 | 0    | 5   | 0.7   | 0.23 - 1.63 | -0.02 |
| Non-Lymphocytic Leukemia                 | 13  | 3.35*  | 1.78 - 5.73   | 0.51  | 163 | 10.09* | 8.6 - 11.77   | 2.18  | 92  | 5.02* | 4.05 - 6.16 | 1.17 | 127 | 1.76* | 1.47 - 2.1  | 0.44  |
| Acute Non-Lymphocytic Leukemia (ANLL)    | 11  | 4.56*  | 2.28 - 8.16   | 0.48  | 140 | 14.05* | 11.82 - 16.59 | 1.93  | 73  | 6.51* | 5.1 - 8.18  | 0.98 | 93  | 2.01* | 1.62 - 2.46 | 0.37  |
| Myeloid and Monocytic Leukemia           | 12  | 3.35*  | 1.73 - 5.86   | 0.47  | 147 | 9.84*  | 8.31 - 11.57  | 1.96  | 87  | 5.13* | 4.11 - 6.33 | 1.11 | 120 | 1.79* | 1.49 - 2.14 | 0.42  |
| Acute Myeloid Leukemia                   | 10  | 4.77*  | 2.29 - 8.77   | 0.44  | 113 | 13.04* | 10.75 - 15.68 | 1.55  | 67  | 6.86* | 5.32 - 8.71 | 0.91 | 81  | 1.97* | 1.56 - 2.45 | 0.32  |
| Acute Monocytic Leukemia                 | 1   | 7.3    | 0.18 - 40.67  | 0.05  | 15  | 24.51* | 13.72 - 40.43 | 0.21  | 2   | 2.75  | 0.33 - 9.94 | 0.02 | 6   | 1.98  | 0.73 - 4.31 | 0.02  |
| Chronic Myeloid Leukemia                 | 0   | 0      | 0 - 2.95      | -0.07 | 14  | 2.65*  | 1.45 - 4.45   | 0.13  | 17  | 2.81* | 1.63 - 4.49 | 0.17 | 27  | 1.27  | 0.84 - 1.85 | 0.05  |
| Mesothelioma                             | 0   | 0      | 0 - 26.56     | -0.01 | 0   | 0      | 0 - 5.44      | -0.01 | 3   | 2.97  | 0.61 - 8.67 | 0.03 | 13  | 1.63  | 0.87 - 2.79 | 0.04  |
| Kaposi Sarcoma                           | 48  | 9.21*  | 6.79 - 12.22  | 2.41  | 40  | 2.11*  | 1.51 - 2.88   | 0.31  | 20  | 1.08  | 0.66 - 1.67 | 0.02 | 11  | 0.52* | 0.26 - 0.92 | -0.08 |
| Miscellaneous                            | 9   | 5.26*  | 2.4 - 9.98    | 0.41  | 25  | 2.95*  | 1.91 - 4.35   | 0.24  | 33  | 2.56* | 1.76 - 3.6  | 0.32 | 142 | 1.71* | 1.44 - 2.01 | 0.47  |

TABLE 6 – Risk of MPCs in Survivors of AYA Cancer by Radiation Treatment for First Cancer, SEER 9 1973-2012

| MPC Site                                                 | Any Radiation |        |              |       | No Radiation |       |             |       | Unknown |       |              |       |
|----------------------------------------------------------|---------------|--------|--------------|-------|--------------|-------|-------------|-------|---------|-------|--------------|-------|
|                                                          | O             | SIR    | 95% CI       | EAR   | O            | SIR   | 95% CI      | EAR   | O       | SIR   | 95% CI       | EAR   |
| All sites                                                | 5,873         | 2.44*  | 2.38 - 2.51  | 44    | 10,889       | 1.65* | 1.62 - 1.68 | 22.37 | 239     | 2.17* | 1.9 - 2.46   | 36.32 |
| All sites (excluding non-Melanoma skin)                  | 5,847         | 2.44*  | 2.38 - 2.51  | 43.8  | 10,825       | 1.64* | 1.61 - 1.68 | 22.16 | 239     | 2.18* | 1.91 - 2.47  | 36.45 |
| All Solid Tumors                                         | 5,192         | 2.40*  | 2.34 - 2.47  | 38.42 | 9,553        | 1.60* | 1.57 - 1.63 | 18.74 | 215     | 2.16* | 1.89 - 2.47  | 32.65 |
| Oral Cavity and Pharynx                                  | 221           | 3.54*  | 3.09 - 4.04  | 2.01  | 314          | 1.95* | 1.74 - 2.17 | 0.8   | 2       | 0.72  | 0.09 - 2.6   | -0.22 |
| Salivary Gland                                           | 52            | 6.90*  | 5.15 - 9.05  | 0.56  | 56           | 2.86* | 2.16 - 3.71 | 0.19  | 0       | 0     | 0 - 10.78    | -0.1  |
| Digestive System                                         | 727           | 2.29*  | 2.13 - 2.46  | 5.2   | 1,327        | 1.53* | 1.44 - 1.61 | 2.39  | 34      | 2.34* | 1.62 - 3.27  | 5.49  |
| Esophagus                                                | 54            | 3.46*  | 2.6 - 4.51   | 0.49  | 44           | 1.05  | 0.76 - 1.41 | 0.01  | 4       | 5.49* | 1.5 - 14.05  | 0.92  |
| Stomach                                                  | 78            | 2.96*  | 2.34 - 3.7   | 0.66  | 126          | 1.82* | 1.51 - 2.16 | 0.3   | 3       | 2.5   | 0.51 - 7.3   | 0.51  |
| Small Intestine                                          | 25            | 2.47*  | 1.6 - 3.65   | 0.19  | 60           | 2.17* | 1.66 - 2.8  | 0.17  | 2       | 4.17  | 0.51 - 15.07 | 0.43  |
| Colon, Rectum and Anus                                   | 383           | 2.08*  | 1.87 - 2.3   | 2.52  | 775          | 1.53* | 1.42 - 1.64 | 1.4   | 21      | 2.48* | 1.54 - 3.8   | 3.54  |
| Colon and Rectum                                         | 343           | 1.98*  | 1.77 - 2.2   | 2.15  | 707          | 1.48* | 1.37 - 1.59 | 1.2   | 20      | 2.52* | 1.54 - 3.89  | 3.4   |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 68            | 1.88*  | 1.46 - 2.38  | 0.4   | 127          | 1.33* | 1.11 - 1.59 | 0.17  | 2       | 1.24  | 0.15 - 4.48  | 0.11  |
| Liver                                                    | 41            | 1.63*  | 1.17 - 2.21  | 0.2   | 75           | 1.18  | 0.93 - 1.48 | 0.06  | 0       | 0     | 0 - 3.32     | -0.31 |
| Gallbladder                                              | 6             | 1.7    | 0.63 - 3.71  | 0.03  | 9            | 0.86  | 0.39 - 1.63 | -0.01 | 0       | 0     | 0 - 22.15    | -0.05 |
| Pancreas                                                 | 21            | 2.76*  | 1.71 - 4.22  | 0.17  | 43           | 2.02* | 1.46 - 2.72 | 0.11  | 2       | 5.99  | 0.73 - 21.63 | 0.47  |
| Respiratory System                                       | 93            | 2.49*  | 2.01 - 3.05  | 0.71  | 151          | 1.41* | 1.19 - 1.65 | 0.23  | 2       | 1.15  | 0.14 - 4.16  | 0.07  |
| Nose, Nasal Cavity and Middle Ear                        | 554           | 2.61*  | 2.4 - 2.84   | 4.34  | 819          | 1.31* | 1.22 - 1.4  | 1.01  | 25      | 2.51* | 1.62 - 3.7   | 4.24  |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 17            | 4.52*  | 2.63 - 7.23  | 0.17  | 17           | 1.73* | 1.01 - 2.77 | 0.04  | 0       | 0     | 0 - 21.94    | -0.05 |
| Lung and Bronchus                                        | 513           | 2.66*  | 2.44 - 2.9   | 4.06  | 752          | 1.31* | 1.22 - 1.41 | 0.93  | 24      | 2.64* | 1.69 - 3.93  | 4.21  |
| Bones and Joints                                         | 509           | 2.66*  | 2.43 - 2.9   | 4.03  | 748          | 1.31* | 1.22 - 1.41 | 0.92  | 24      | 2.66* | 1.7 - 3.96   | 4.23  |
| Soft Tissue including Heart                              | 36            | 5.99*  | 4.2 - 8.29   | 0.38  | 38           | 2.55* | 1.81 - 3.51 | 0.12  | 0       | 0     | 0 - 13.78    | -0.08 |
| Skin excluding Basal and Squamous Melanoma of the Skin   | 111           | 5.87*  | 4.83 - 7.07  | 1.17  | 133          | 2.75* | 2.31 - 3.26 | 0.44  | 7       | 8.12* | 3.27 - 16.74 | 1.73  |
| Breast                                                   | 228           | 1.29*  | 1.13 - 1.47  | 0.65  | 1,397        | 3.05* | 2.9 - 3.22  | 4.91  | 14      | 1.85* | 1.01 - 3.1   | 1.81  |
| Female Breast                                            | 202           | 1.21*  | 1.05 - 1.39  | 0.45  | 1,333        | 3.09* | 2.92 - 3.26 | 4.71  | 14      | 1.96* | 1.07 - 3.29  | 1.94  |
| Female Genital System                                    | 1,944         | 3.18*  | 3.04 - 3.33  | 16.91 | 2,609        | 1.48* | 1.42 - 1.54 | 4.41  | 84      | 2.90* | 2.31 - 3.59  | 15.54 |
| Cervix Uteri                                             | 1,940         | 3.18*  | 3.04 - 3.33  | 16.88 | 2,602        | 1.48* | 1.42 - 1.54 | 4.4   | 84      | 2.91* | 2.32 - 3.6   | 15.56 |
| Corpus and Uterus, NOS                                   | 362           | 1.58*  | 1.42 - 1.76  | 1.69  | 882          | 1.33* | 1.24 - 1.42 | 1.14  | 14      | 1.32  | 0.72 - 2.21  | 0.95  |
| Corpus Uteri                                             | 49            | 0.86   | 0.64 - 1.14  | -0.1  | 121          | 0.81* | 0.67 - 0.97 | -0.15 | 3       | 1.09  | 0.23 - 3.2   | 0.07  |
| Uterus, NOS                                              | 127           | 1.24*  | 1.04 - 1.48  | 0.32  | 360          | 1.16* | 1.04 - 1.29 | 0.26  | 8       | 1.72  | 0.74 - 3.38  | 0.94  |
| Ovary                                                    | 125           | 1.25*  | 1.04 - 1.49  | 0.32  | 351          | 1.15* | 1.04 - 1.28 | 0.24  | 8       | 1.75  | 0.76 - 3.45  | 0.97  |
| Vagina                                                   | 2             | 1.02   | 0.12 - 3.67  | 0     | 9            | 1.57  | 0.72 - 2.99 | 0.02  | 0       | 0     | 0 - 36.53    | -0.03 |
| Male Genital System                                      | 128           | 2.31*  | 1.92 - 2.74  | 0.92  | 321          | 1.97* | 1.76 - 2.2  | 0.83  | 3       | 1.18  | 0.24 - 3.45  | 0.13  |
| Prostate                                                 | 24            | 10.42* | 6.68 - 15.51 | 0.28  | 27           | 3.92* | 2.59 - 5.71 | 0.11  | 0       | 0     | 0 - 32.16    | -0.03 |
| Testis                                                   | 347           | 1.59*  | 1.42 - 1.76  | 1.63  | 692          | 1.24* | 1.15 - 1.33 | 0.7   | 24      | 2.42* | 1.55 - 3.6   | 3.97  |
| Penis                                                    | 185           | 1      | 0.86 - 1.15  | -0.01 | 464          | 0.96  | 0.87 - 1.05 | -0.11 | 17      | 1.98* | 1.15 - 3.17  | 2.37  |
| Urinary System                                           | 156           | 4.96*  | 4.21 - 5.8   | 1.58  | 224          | 3.24* | 2.83 - 3.7  | 0.81  | 7       | 5.53* | 2.22 - 11.38 | 1.62  |
| Urinary Bladder                                          | 4             | 3.42   | 0.93 - 8.76  | 0.04  | 3            | 1.05  | 0.22 - 3.06 | 0     | 0       | 0     | 0 - 72.25    | -0.01 |
| Kidney and Renal Pelvis                                  | 255           | 2.01*  | 1.77 - 2.27  | 1.62  | 611          | 1.76* | 1.63 - 1.91 | 1.38  | 2       | 0.35  | 0.04 - 1.26  | -1.05 |
| Kidney                                                   | 109           | 1.91*  | 1.56 - 2.3   | 0.66  | 230          | 1.45* | 1.27 - 1.65 | 0.37  | 1       | 0.39  | 0.01 - 2.2   | -0.43 |
| Renal Pelvis                                             | 128           | 1.89*  | 1.57 - 2.24  | 0.76  | 350          | 1.93* | 1.73 - 2.14 | 0.88  | 1       | 0.32  | 0.01 - 1.81  | -0.59 |
| Eye and Orbit                                            | 123           | 1.87*  | 1.56 - 2.23  | 0.73  | 332          | 1.89* | 1.7 - 2.11  | 0.82  | 1       | 0.34  | 0.01 - 1.87  | -0.56 |
| Brain and Other Nervous System                           | 5             | 2.26   | 0.73 - 5.26  | 0.04  | 18           | 2.79* | 1.65 - 4.41 | 0.06  | 0       | 0     | 0 - 37.05    | -0.03 |
| Brain                                                    | 5             | 1.06   | 0.34 - 2.46  | 0     | 21           | 1.65* | 1.02 - 2.52 | 0.04  | 1       | 4.88  | 0.12 - 27.21 | 0.22  |
| Endocrine System                                         | 124           | 2.91*  | 2.42 - 3.47  | 1.03  | 183          | 1.67* | 1.43 - 1.93 | 0.38  | 2       | 1.07  | 0.13 - 3.87  | 0.04  |
| Thyroid                                                  | 262           | 2.11*  | 1.86 - 2.38  | 1.75  | 499          | 1.62* | 1.48 - 1.77 | 1     | 5       | 0.91  | 0.3 - 2.13   | -0.13 |
| Adrenal Gland                                            | 249           | 2.08*  | 1.83 - 2.35  | 1.64  | 482          | 1.63* | 1.48 - 1.78 | 0.97  | 5       | 0.95  | 0.31 - 2.21  | -0.08 |
| All Lymphatic and Hematopoietic Diseases                 | 3             | 2.08   | 0.43 - 6.08  | 0.02  | 6            | 1.59  | 0.58 - 3.45 | 0.01  | 0       | 0     | 0 - 56.04    | -0.02 |
| Lymphoma                                                 | 566           | 2.78*  | 2.56 - 3.02  | 4.6   | 1,156        | 2.14* | 2.02 - 2.27 | 3.22  | 20      | 2.16* | 1.32 - 3.34  | 3.03  |
| Hodgkin Lymphoma                                         | 349           | 2.71*  | 2.43 - 3.01  | 2.79  | 784          | 2.34* | 2.17 - 2.5  | 2.34  | 9       | 1.55  | 0.71 - 2.94  | 0.9   |
| Non-Hodgkin Lymphoma                                     | 40            | 1.57*  | 1.12 - 2.14  | 0.18  | 90           | 1.48* | 1.19 - 1.82 | 0.15  | 0       | 0     | 0 - 3.19     | -0.33 |
| Myeloma                                                  | 309           | 2.99*  | 2.67 - 3.34  | 2.61  | 694          | 2.52* | 2.34 - 2.72 | 2.19  | 9       | 1.94  | 0.89 - 3.68  | 1.23  |
|                                                          | 32            | 1.50*  | 1.03 - 2.12  | 0.14  | 63           | 1.04  | 0.8 - 1.34  | 0.01  | 2       | 1.9   | 0.23 - 6.88  | 0.27  |

|                                       |     |       |              |       |     |       |             |       |   |       |              |       |
|---------------------------------------|-----|-------|--------------|-------|-----|-------|-------------|-------|---|-------|--------------|-------|
| Leukemia                              | 185 | 3.45* | 2.97 - 3.99  | 1.67  | 309 | 2.15* | 1.92 - 2.41 | 0.86  | 9 | 3.76* | 1.72 - 7.13  | 1.86  |
| Lymphocytic Leukemia                  | 35  | 1.49* | 1.04 - 2.08  | 0.15  | 73  | 1.13  | 0.89 - 1.42 | 0.04  | 0 | 0     | 0 - 3.55     | -0.29 |
| Acute Lymphocytic Leukemia            | 12  | 2.51* | 1.3 - 4.38   | 0.09  | 23  | 1.95* | 1.24 - 2.93 | 0.06  | 0 | 0     | 0 - 17.62    | -0.06 |
| Chronic Lymphocytic Leukemia          | 21  | 1.34  | 0.83 - 2.04  | 0.07  | 44  | 0.97  | 0.7 - 1.3   | -0.01 | 0 | 0     | 0 - 5.22     | -0.2  |
| Other Lymphocytic Leukemia            | 2   | 0.68  | 0.08 - 2.46  | -0.01 | 6   | 0.81  | 0.3 - 1.76  | -0.01 | 0 | 0     | 0 - 29.51    | -0.04 |
| Non-Lymphocytic Leukemia              | 150 | 4.98* | 4.22 - 5.85  | 1.52  | 236 | 2.99* | 2.62 - 3.4  | 0.82  | 9 | 6.64* | 3.04 - 12.61 | 2.16  |
| Acute Non-Lymphocytic Leukemia (ANLL) | 126 | 6.66* | 5.55 - 7.93  | 1.36  | 184 | 3.67* | 3.16 - 4.24 | 0.7   | 7 | 8.28* | 3.33 - 17.07 | 1.74  |
| Myeloid and Monocytic Leukemia        | 135 | 4.83* | 4.05 - 5.71  | 1.36  | 223 | 3.05* | 2.66 - 3.47 | 0.78  | 8 | 6.38* | 2.75 - 12.57 | 1.9   |
| Acute Myeloid Leukemia                | 104 | 6.23* | 5.09 - 7.54  | 1.11  | 161 | 3.64* | 3.1 - 4.25  | 0.61  | 6 | 8.04* | 2.95 - 17.5  | 1.48  |
| Acute Monocytic Leukemia              | 11  | 8.99* | 4.49 - 16.09 | 0.12  | 13  | 4.03* | 2.15 - 6.89 | 0.05  | 0 | 0     | 0 - 67.94    | -0.02 |
| Chronic Myeloid Leukemia              | 19  | 2.03* | 1.22 - 3.16  | 0.12  | 38  | 1.58* | 1.12 - 2.17 | 0.07  | 1 | 2.37  | 0.06 - 13.18 | 0.16  |
| Mesothelioma                          | 8   | 3.15* | 1.36 - 6.21  | 0.07  | 7   | 0.98  | 0.39 - 2.02 | 0     | 1 | 8.8   | 0.22 - 49.02 | 0.25  |
| Kaposi Sarcoma                        | 34  | 1.71* | 1.19 - 2.4   | 0.18  | 85  | 1.96* | 1.57 - 2.43 | 0.22  | 0 | 0     | 0 - 4.24     | -0.25 |
| Miscellaneous                         | 89  | 3.23* | 2.59 - 3.97  | 0.78  | 116 | 1.50* | 1.24 - 1.8  | 0.2   | 4 | 3.11  | 0.85 - 7.95  | 0.77  |

TABLE 7 – Risk of MPCs in Survivors of AYA Cancer by Age at First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                                                 | 15-19 |        |              |       | 20-24 |       |              |       | 25-29 |       |              |       | 30-34 |       |             |       | 35-39 |       |             |       |
|----------------------------------------------------------|-------|--------|--------------|-------|-------|-------|--------------|-------|-------|-------|--------------|-------|-------|-------|-------------|-------|-------|-------|-------------|-------|
|                                                          | O     | SIR    | 95% CI       | EAR   | O     | SIR   | 95% CI       | EAR   | O     | SIR   | 95% CI       | EAR   | O     | SIR   | 95% CI      | EAR   | O     | SIR   | 95% CI      | EAR   |
| All sites                                                | 580   | 3.03*  | 2.79 - 3.29  | 20.94 | 1,212 | 2.37* | 2.24 - 2.51  | 21.84 | 2,485 | 1.99* | 1.91 - 2.07  | 23.62 | 4,817 | 1.92* | 1.86 - 1.97 | 31.59 | 7,907 | 1.70* | 1.66 - 1.83 | 33.2  |
| All sites (excluding non-Melanoma skin)                  | 578   | 3.04*  | 2.8 - 3.3    | 20.9  | 1,207 | 2.38* | 2.24 - 2.51  | 21.78 | 2,470 | 1.99* | 1.91 - 2.07  | 23.45 | 4,787 | 1.91* | 1.86 - 1.97 | 31.31 | 7,869 | 1.69* | 1.66 - 1.83 | 32.97 |
| All Solid Tumors                                         | 502   | 3.08*  | 2.82 - 3.37  | 18.27 | 1,065 | 2.38* | 2.24 - 2.53  | 19.24 | 2,152 | 1.93* | 1.85 - 2.01  | 19.8  | 4,241 | 1.87* | 1.81 - 1.93 | 27.03 | 7,000 | 1.65* | 1.61 - 1.79 | 28.28 |
| Oral Cavity and Pharynx                                  | 29    | 6.33*  | 4.24 - 9.09  | 1.31  | 49    | 3.64* | 2.69 - 4.81  | 1.11  | 78    | 2.42* | 1.91 - 3.02  | 0.88  | 136   | 2.16* | 1.81 - 2.56 | 1     | 245   | 2.18* | 1.79 - 2.56 | 1.35  |
| Salivary Gland                                           | 15    | 17.42* | 9.75 - 28.74 | 0.76  | 16    | 8.08* | 4.62 - 13.12 | 0.44  | 21    | 4.97* | 3.07 - 7.59  | 0.32  | 26    | 3.41* | 2.23 - 4.99 | 0.25  | 30    | 2.35* | 1.59 - 4.93 | 0.18  |
| Digestive System                                         | 54    | 2.86*  | 2.15 - 3.74  | 1.89  | 144   | 2.46* | 2.07 - 2.89  | 2.66  | 257   | 1.68* | 1.48 - 1.89  | 1.98  | 605   | 1.85* | 1.71 - 2    | 3.81  | 1,028 | 1.60* | 1.5 - 1.76  | 3.93  |
| Esophagus                                                | 3     | 4.4    | 0.91 - 12.86 | 0.12  | 4     | 1.54  | 0.42 - 3.95  | 0.04  | 12    | 1.66  | 0.86 - 2.9   | 0.09  | 22    | 1.38  | 0.86 - 2.09 | 0.08  | 61    | 1.92* | 1.47 - 2.12 | 0.3   |
| Stomach                                                  | 8     | 4.70*  | 2.03 - 9.26  | 0.34  | 19    | 3.79* | 2.2 - 5.92   | 0.44  | 25    | 1.98* | 1.28 - 2.92  | 0.24  | 65    | 2.45* | 1.89 - 3.13 | 0.53  | 90    | 1.76* | 1.42 - 2.4  | 0.4   |
| Small Intestine                                          | 4     | 5.68*  | 1.55 - 14.54 | 0.18  | 11    | 5.34* | 2.67 - 9.56  | 0.28  | 10    | 1.94  | 0.93 - 3.57  | 0.09  | 22    | 2.09* | 1.31 - 3.16 | 0.16  | 40    | 2.02* | 1.45 - 2.79 | 0.21  |
| Colon, Rectum and Anus                                   | 22    | 1.90*  | 1.19 - 2.88  | 0.56  | 72    | 2.08* | 1.63 - 2.62  | 1.16  | 131   | 1.46* | 1.22 - 1.74  | 0.79  | 346   | 1.82* | 1.64 - 2.03 | 2.14  | 608   | 1.62* | 1.5 - 1.71  | 2.38  |
| Colon and Rectum                                         | 20    | 1.87*  | 1.14 - 2.88  | 0.5   | 64    | 1.99* | 1.53 - 2.54  | 0.99  | 119   | 1.43* | 1.18 - 1.71  | 0.68  | 310   | 1.74* | 1.55 - 1.94 | 1.8   | 557   | 1.57* | 1.45 - 1.67 | 2.08  |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 5     | 2.53   | 0.82 - 5.9   | 0.16  | 12    | 1.73  | 0.89 - 3.02  | 0.16  | 27    | 1.5   | 0.99 - 2.19  | 0.17  | 58    | 1.58* | 1.2 - 2.04  | 0.29  | 95    | 1.37* | 1.11 - 1.71 | 0.26  |
| Liver                                                    | 5     | 3.54*  | 1.15 - 8.26  | 0.19  | 10    | 1.96  | 0.94 - 3.6   | 0.15  | 17    | 1.33  | 0.77 - 2.12  | 0.08  | 36    | 1.44* | 1.01 - 1.99 | 0.15  | 48    | 1.06  | 0.78 - 1.49 | 0.03  |
| Gallbladder                                              | 0     | 0      | 0 - 22.45    | -0.01 | 0     | 0     | 0 - 6.98     | -0.02 | 3     | 1.93  | 0.4 - 5.63   | 0.03  | 3     | 0.8   | 0.16 - 2.33 | -0.01 | 9     | 1.1   | 0.5 - 1.97  | 0.01  |
| Pancreas                                                 | 8     | 4.67*  | 2.02 - 9.2   | 0.34  | 23    | 3.86* | 2.45 - 5.79  | 0.53  | 40    | 2.33* | 1.66 - 3.17  | 0.44  | 67    | 1.69* | 1.31 - 2.14 | 0.37  | 108   | 1.32* | 1.08 - 1.92 | 0.27  |
| Respiratory System                                       | 20    | 2.41*  | 1.47 - 3.73  | 0.63  | 74    | 2.50* | 1.96 - 3.14  | 1.38  | 194   | 2.14* | 1.85 - 2.46  | 1.98  | 349   | 1.55* | 1.39 - 1.73 | 1.7   | 761   | 1.54* | 1.43 - 1.67 | 2.73  |
| Nose, Nasal Cavity and Middle Ear                        | 0     | 0      | 0 - 9.96     | -0.02 | 2     | 2.23  | 0.27 - 8.04  | 0.03  | 10    | 5.00* | 2.4 - 9.19   | 0.15  | 9     | 2.37* | 1.08 - 4.49 | 0.07  | 13    | 1.94* | 1.04 - 3.37 | 0.06  |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 19    | 2.64*  | 1.59 - 4.12  | 0.64  | 70    | 2.68* | 2.09 - 3.39  | 1.37  | 176   | 2.16* | 1.85 - 2.5   | 1.81  | 314   | 1.53* | 1.37 - 1.71 | 1.49  | 710   | 1.56* | 1.44 - 1.69 | 2.59  |
| Lung and Bronchus                                        | 19    | 2.75*  | 1.65 - 4.29  | 0.65  | 70    | 2.74* | 2.13 - 3.46  | 1.38  | 175   | 2.16* | 1.86 - 2.51  | 1.8   | 308   | 1.51* | 1.35 - 1.69 | 1.42  | 709   | 1.56* | 1.45 - 1.69 | 2.6   |
| Bones and Joints                                         | 10    | 6.26*  | 3 - 11.52    | 0.45  | 13    | 5.56* | 2.96 - 9.5   | 0.33  | 14    | 3.71* | 2.03 - 6.22  | 0.42  | 16    | 2.89* | 1.65 - 4.69 | 0.14  | 21    | 2.66* | 1.64 - 3.93 | 0.13  |
| Soft Tissue including Heart                              | 28    | 9.64*  | 6.41 - 13.94 | 1.35  | 43    | 7.35* | 5.32 - 9.9   | 1.16  | 37    | 3.30* | 2.33 - 4.55  | 0.9   | 65    | 3.50* | 2.7 - 4.46  | 0.64  | 78    | 2.64* | 2.09 - 3.93 | 0.5   |
| Skin excluding Basal and Squamous                        | 61    | 2.80*  | 2.14 - 3.6   | 2.11  | 153   | 2.92* | 2.48 - 3.43  | 3.14  | 292   | 2.69* | 2.39 - 3.02  | 3.51  | 489   | 2.71* | 2.48 - 2.97 | 4.23  | 644   | 2.31* | 2.14 - 2.68 | 3.73  |
| Melanoma of the Skin                                     | 59    | 2.88*  | 2.19 - 3.72  | 2.07  | 148   | 3.00* | 2.53 - 3.52  | 3.07  | 277   | 2.70* | 2.39 - 3.04  | 3.34  | 459   | 2.70* | 2.45 - 2.95 | 3.95  | 606   | 2.30* | 2.12 - 2.7  | 3.51  |
| Breast                                                   | 106   | 2.80*  | 2.29 - 3.39  | 3.67  | 236   | 2.14* | 1.88 - 2.44  | 3.92  | 598   | 1.93* | 1.78 - 2.09  | 5.52  | 1,400 | 2.10* | 1.99 - 2.21 | 10.03 | 2,297 | 1.79* | 1.72 - 1.84 | 10.4  |
| Female Breast                                            | 106   | 2.81*  | 2.3 - 3.4    | 3.68  | 234   | 2.13* | 1.87 - 2.42  | 3.87  | 598   | 1.94* | 1.79 - 2.1   | 5.54  | 1,398 | 2.10* | 1.99 - 2.21 | 10.03 | 2,290 | 1.79* | 1.72 - 1.84 | 10.36 |
| Female Genital System                                    | 26    | 1.52   | 0.99 - 2.23  | 0.48  | 60    | 1.28  | 0.98 - 1.65  | 0.41  | 168   | 1.37* | 1.17 - 1.59  | 0.86  | 353   | 1.41* | 1.27 - 1.56 | 1.4   | 651   | 1.40* | 1.29 - 1.44 | 1.89  |
| Cervix Uteri                                             | 8     | 1.2    | 0.52 - 2.36  | 0.07  | 14    | 0.85  | 0.47 - 1.43  | -0.08 | 34    | 0.94  | 0.65 - 1.31  | -0.04 | 50    | 0.83  | 0.61 - 1.09 | -0.14 | 67    | 0.75* | 0.58 - 0.96 | -0.23 |
| Corpus and Uterus, NOS                                   | 10    | 1.95   | 0.93 - 3.58  | 0.26  | 23    | 1.39  | 0.88 - 2.09  | 0.2   | 55    | 1.09  | 0.82 - 1.42  | 0.09  | 138   | 1.21* | 1.01 - 1.43 | 0.32  | 269   | 1.17* | 1.03 - 1.25 | 0.4   |
| Corpus Uteri                                             | 10    | 2      | 0.98 - 3.68  | 0.27  | 22    | 1.36  | 0.85 - 2.06  | 0.18  | 54    | 1.09  | 0.85 - 1.43  | 0.09  | 132   | 1.18  | 0.98 - 1.4  | 0.27  | 266   | 1.18* | 1.04 - 1.24 | 0.41  |
| Uterus, NOS                                              | 0     | 0      | 0 - 27.67    | -0.01 | 1     | 2.7   | 0.07 - 15.06 | 0.02  | 1     | 1.02  | 0.03 - 5.66  | 0     | 6     | 2.80* | 1.03 - 6.09 | 0.05  | 3     | 0.72  | 0.15 - 2.84 | -0.01 |
| Ovary                                                    | 5     | 1.21   | 0.39 - 2.83  | 0.05  | 14    | 1.29  | 0.7 - 2.16   | 0.1   | 57    | 1.99* | 1.51 - 2.58  | 0.54  | 132   | 2.19* | 1.83 - 2.6  | 0.98  | 244   | 2.08* | 1.83 - 2.22 | 1.3   |
| Vagina                                                   | 0     | 0      | 0 - 24.22    | -0.01 | 4     | 9.26* | 2.52 - 23.71 | 0.11  | 11    | 9.31* | 4.65 - 16.66 | 0.19  | 11    | 4.31* | 2.15 - 7.71 | 0.12  | 25    | 5.02* | 3.25 - 6.7  | 0.2   |
| Male Genital System                                      | 43    | 2.81*  | 2.03 - 3.78  | 1.49  | 118   | 2.62* | 2.17 - 3.14  | 2.27  | 200   | 1.86* | 1.61 - 2.14  | 1.77  | 268   | 1.93* | 1.69 - 2.19 | 0.68  | 434   | 1.08  | 0.98 - 1.45 | 0.33  |
| Prostate                                                 | 4     | 0.75   | 0.2 - 1.92   | -0.07 | 29    | 1.1   | 0.74 - 1.58  | 0.08  | 82    | 2.1   | 0.8 - 1.25   | 0.01  | 176   | 0.92* | 0.79 - 1.07 | -0.2  | 375   | 1     | 0.9 - 1.06  | -0.01 |
| Testis                                                   | 38    | 3.85*  | 2.73 - 5.29  | 1.52  | 88    | 4.81* | 3.86 - 5.92  | 2.17  | 116   | 4.67* | 3.86 - 5.61  | 1.74  | 89    | 3.46* | 2.78 - 4.26 | 0.87  | 56    | 2.42* | 1.83 - 4.21 | 0.34  |
| Penis                                                    | 1     | 12.44  | 0.32 - 69.33 | 0.05  | 0     | 0     | 0 - 14.86    | -0.01 | 2     | 3.37  | 0.41 - 12.19 | 0.03  | 2     | 1.75  | 0.21 - 6.31 | 0.01  | 2     | 0.99  | 0.12 - 3.17 | 0     |
| Urinary System                                           | 23    | 3.00*  | 1.9 - 4.5    | 0.83  | 59    | 2.47* | 1.88 - 3.19  | 1.09  | 114   | 1.83* | 1.51 - 2.2   | 0.99  | 239   | 1.81* | 1.59 - 2.06 | 1.47  | 433   | 1.71* | 1.55 - 1.9  | 1.83  |
| Urinary Bladder                                          | 4     | 1.43   | 0.39 - 3.65  | 0.06  | 15    | 1.57  | 0.89 - 2.58  | 0.17  | 39    | 1.46* | 0.82 - 2.2   | 0.24  | 95    | 1.59* | 1.29 - 1.95 | 0.48  | 187   | 1.56* | 1.34 - 1.69 | 0.69  |
| Kidney and Renal Pelvis                                  | 19    | 3.96*  | 2.39 - 6.19  | 0.76  | 39    | 2.79* | 1.98 - 3.81  | 0.78  | 71    | 2.05* | 1.6 - 2.59   | 0.7   | 129   | 1.84* | 1.54 - 2.19 | 0.81  | 221   | 1.71* | 1.49 - 2.05 | 0.94  |
| Kidney                                                   | 18    | 3.82*  | 2.27 - 6.04  | 0.72  | 38    | 2.78* | 1.97 - 3.82  | 0.76  | 68    | 2.02* | 1.57 - 2.56  | 0.66  | 124   | 1.83* | 1.52 - 2.18 | 0.77  | 208   | 1.67* | 1.45 - 2.01 | 0.86  |
| Renal Pelvis                                             | 1     | 11.57  | 0.29 - 64.46 | 0.05  | 1     | 3.08  | 0.08 - 17.14 | 0.02  | 3     | 3.13  | 0.65 - 9.15  | 0.04  | 5     | 2.16  | 0.7 - 5.03  | 0.04  | 13    | 2.56* | 1.36 - 4.18 | 0.08  |
| Eye and Orbit                                            | 1     | 2.16   | 0.05 - 12.06 | 0.03  | 1     | 0.86  | 0.02 - 4.77  | -0.01 | 2     | 0.75  | 0.09 - 2.71  | -0.01 | 8     | 1.62  | 0.7 - 3.19  | 0.04  | 15    | 1.77  | 0.99 - 2.24 | 0.07  |
| Brain and Other Nervous System                           | 37    | 5.81*  | 4.09 - 8.01  | 1.65  | 35    | 2.63* | 1.83 - 3.66  | 0.68  | 53    | 2.07* | 1.55 - 2.7   | 0.52  | 78    | 1.85* | 1.46 - 2.31 | 0.49  | 106   | 1.59* | 1.3 - 2.2   | 0.4   |
| Brain                                                    | 33    | 5.60*  | 3.85 - 7.86  | 1.46  | 33    | 2.67* | 1.84 - 3.75  | 0.64  | 45    | 1.89* | 1.38 - 2.52  | 0.4   | 71    | 1.80* | 1.41 - 2.28 | 0.43  | 95    | 1.52* | 1.23 - 2.13 | 0.33  |
| Endocrine System                                         | 65    | 3.55*  | 2.74 - 4.52  | 2.51  | 78    | 1.98* | 1.57 - 2.47  | 1.2   | 136   | 1.76* | 1.48 - 2.09  | 1.13  | 208   | 1.70* | 1.48 - 1.95 | 1.18  | 279   | 1.55* | 1.37 - 1.85 | 1.01  |
| Thyroid                                                  | 62    | 3.49*  | 2.68 - 4.48  | 2.38  | 75    | 1.97* | 1.55 - 2.46  | 1.15  | 133   | 1.78* | 1.49 - 2.11  | 1.11  | 203   | 1.72* | 1.5 - 1.88  | 1.17  | 263   | 1.52* | 1.34 - 1.85 | 0.92  |
| Adrenal Gland                                            | 0     | 0      | 0 - 22.44    | -0.01 | 1     | 2.7   | 0.07 - 15.02 | 0.02  | 3     | 3.71  | 0.77 - 10.84 | 0.04  | 0     | 0     | 0 - 2.5     | -0.02 | 5     | 2.02  | 0.66 - 3.44 | 0.03  |
| All Lymphatic and Hematopoietic Diseases                 | 67    | 2.63*  | 2.04 - 3.34  | 2.24  | 130   | 2.33* | 1.95 - 2.77  | 2.31  | 296   | 2.60* | 2.31 - 2.91  | 3.48  | 481   | 2.35* | 2.15 - 2.57 | 3.79  | 768   | 2.18* | 2.03 - 2.36 | 4.24  |
| Lymphoma                                                 | 30    | 1.64*  | 1.11 - 2.35  | 0.63  | 77    | 1.99* | 1.57 - 2.48  | 1.19  | 180   | 2.39* | 2.06 - 2.77  | 2     | 345   | 2.70* | 2.43 - 3    | 2.98  | 510   | 2.42* | 2.22 - 2.52 | 3.06  |
| Hodgkin Lymphoma                                         | 8     | 1      | 0.43 - 1.97  | 0     | 19    | 1.44  | 0.87 - 2.25  | 0.18  | 24    | 1.3   | 0.83 - 1.93  | 0.11  | 36    | 1.65* | 1.15 - 2.29 | 0.19  | 43    | 1.66* | 1.2 - 2.17  | 0.18  |
| Non-Hodgkin Lymphoma                                     | 22    | 2.15*  | 1.35 - 3.25  | 0.63  | 58    | 2.27* | 1.72 - 2.93  | 1.01  | 156   | 2.75* | 2.33 - 3.21  | 1.9   | 309   | 2.92* | 2.61 - 3.27 | 2.78  | 467   | 2.53* | 2.31 - 2.76 | 2.89  |
| Myeloma                                                  | 0     | 0      | 0 - 3.5      | -0.06 | 6     | 1.72  | 0.63 - 3.75  | 0.08  | 11    | 1.12  | 0.56 - 2     | 0.02  | 28    | 1.25  | 0.83 - 1.8  | 0.08  | 52    | 1.13  | 0.85 - 1.46 | 0.06  |
| Leukemia                                                 | 37    | 5.99*  | 4.22 - 8.26  | 1.66  | 47    | 3.49* | 2.56 - 4.64  | 1.04  | 105   | 3.62* | 2.96 - 4.38  | 1.45  | 108   | 1.99* | 1.63 - 2.4  | 0.74  | 206   | 2.13* | 1.85 - 2.57 | 1.12  |
| Lymphocytic Leukemia                                     | 2     | 0.88   | 0.11 - 3.19  | -0.01 | 7     | 1.38  | 0.55 - 2.83  | 0.06  | 22    | 1.84* | 1.15 - 2.78  | 0.19  | 27    | 1.12  | 0.74 - 1.63 | 0.04  | 50    | 1.1   | 0.81 - 1.31 | 0.04  |
| Acute Lymphocytic Leukemia                               | 2     | 1.48   | 0.18 - 5.36  | 0.04  | 4     | 2.1   | 0.57 - 5.38  | 0.07  | 10    | 3.33* | 1.6 - 6.13   | 0.13  | 5     | 1.16  | 0.38 - 2.7  | 0.01  | 14    | 2.28* | 1.23 - 2.36 | 0.08  |
| Chronic Lymphocytic Leukemia                             | 0     | 0      | 0 - 5.6      | -0.04 | 3     | 1.21  | 0.25 - 3.54  | 0.02  | 11    |       |              |       |       |       |             |       |       |       |             |       |

|                |   |       |                |       |    |       |                 |       |    |       |                |       |    |       |                |      |     |       |                |      |
|----------------|---|-------|----------------|-------|----|-------|-----------------|-------|----|-------|----------------|-------|----|-------|----------------|------|-----|-------|----------------|------|
| Mesothelioma   | 1 | 7.86  | 0.2 -<br>43.81 | 0.05  | 4  | 9.79* | 2.67 -<br>25.05 | 0.11  | 0  | 0     | 0 - 3.14       | -0.02 | 5  | 1.87  | 0.61 -<br>4.38 | 0.03 | 6   | 1.11  | 0.41 -<br>2.87 | 0.01 |
| Kaposi Sarcoma | 0 | 0     | 0 - 1.27       | -0.16 | 3  | 0.38  | 0.08 -<br>1.1   | -0.15 | 24 | 1.63* | 1.05 -<br>2.43 | 0.18  | 52 | 2.70* | 2.02 -<br>3.55 | 0.45 | 40  | 2.08* | 1.49 -<br>2.26 | 0.21 |
|                | 9 | 5.53* |                | 0.4   | 12 | 2.42* | 1.25 -<br>4.22  | 0.22  | 22 | 1.68* |                | 0.17  | 65 | 2.27* |                | 0.5  | 101 | 1.75* |                | 0.44 |
| Miscellaneous  |   |       | 2.53 -<br>10.5 |       |    |       |                 |       |    |       | 1.05 -<br>2.54 |       |    |       | 1.75 -<br>2.89 |      |     |       | 1.42 -<br>2.18 |      |

TABLE 8 -- Risk of MPCs in Survivors of AYA Cancer by First Cancer Diagnosis, SEER 9 1973-2012

| MPC Site                                                 | Leukemias |        |              |       | Lymphomas |        |              |       | CNS and Other Intracranial and Intraspinal Neoplasms |        |               |       | Osseous and Chondromatous Neoplasms |        |               |       | Soft Tissue Sarcomas |        |               |       |
|----------------------------------------------------------|-----------|--------|--------------|-------|-----------|--------|--------------|-------|------------------------------------------------------|--------|---------------|-------|-------------------------------------|--------|---------------|-------|----------------------|--------|---------------|-------|
|                                                          | O         | SIR    | 95% CI       | EAR   | O         | SIR    | 95% CI       | EAR   | O                                                    | SIR    | 95% CI        | EAR   | O                                   | SIR    | 95% CI        | EAR   | O                    | SIR    | 95% CI        | EAR   |
|                                                          |           |        |              |       |           |        |              |       |                                                      |        |               |       |                                     |        |               |       |                      |        |               |       |
| All sites                                                | 220       | 1.80*  | 1.57 - 2.06  | 16.48 | 2,240     | 2.58*  | 2.48 - 2.69  | 39.55 | 335                                                  | 1.92*  | 1.72 - 2.14   | 18.53 | 133                                 | 1.85*  | 1.55 - 2.2    | 18.34 | 940                  | 2.61*  | 2.44 - 2.78   | 45.68 |
| All sites (excluding non-Melanoma skin)                  | 220       | 1.81*  | 1.58 - 2.07  | 16.58 | 2,237     | 2.59*  | 2.49 - 2.7   | 39.58 | 333                                                  | 1.92*  | 1.72 - 2.14   | 18.4  | 133                                 | 1.86*  | 1.56 - 2.21   | 18.45 | 915                  | 2.55*  | 2.38 - 2.72   | 43.84 |
| All Solid Tumors                                         | 168       | 1.57*  | 1.34 - 1.83  | 10.25 | 1,766     | 2.30*  | 2.19 - 2.41  | 28.75 | 301                                                  | 1.96*  | 1.75 - 2.2    | 17.02 | 102                                 | 1.61*  | 1.32 - 1.96   | 11.62 | 505                  | 1.58*  | 1.44 - 1.72   | 14.59 |
| Oral Cavity and Pharynx                                  | 22        | 5.71*  | 3.58 - 8.65  | 3.05  | 88        | 3.34*  | 2.68 - 4.12  | 1.78  | 16                                                   | 3.15*  | 1.8 - 5.12    | 1.26  | 5                                   | 2.29   | 0.74 - 5.34   | 0.84  | 22                   | 2.01*  | 1.26 - 3.04   | 0.87  |
| Salivary Gland                                           | 5         | 11.10* | 3.6 - 25.9   | 0.76  | 30        | 10.23* | 6.9 - 14.61  | 0.78  | 6                                                    | 9.52*  | 3.49 - 20.72  | 0.62  | 1                                   | 3.97   | 0.1 - 22.12   | 0.22  | 2                    | 1.72   | 0.21 - 6.22   | 0.07  |
| Digestive System                                         | 26        | 1.54*  | 1.01 - 2.26  | 1.53  | 270       | 2.27*  | 2.01 - 2.56  | 4.35  | 36                                                   | 1.61*  | 1.13 - 2.23   | 1.57  | 11                                  | 1.12   | 0.56 - 2      | 0.34  | 105                  | 1.99*  | 1.52 - 2.4    | 4.11  |
| Esophagus                                                | 2         | 2.19   | 0.27 - 7.92  | 0.18  | 26        | 3.82*  | 2.5 - 5.6    | 0.55  | 2                                                    | 1.78   | 0.22 - 6.44   | 0.1   | 1                                   | 1.76   | 0.04 - 9.82   | 0.13  | 5                    | 1.69   | 0.55 - 3.95   | 0.16  |
| Stomach                                                  | 2         | 1.34   | 0.16 - 4.85  | 0.09  | 48        | 4.71*  | 3.48 - 6.25  | 1.09  | 4                                                    | 2.07   | 0.82 - 5.29   | 0.24  | 0                                   | 0      | 0 - 4.3       | -0.26 | 11                   | 2.42*  | 1.21 - 4.33   | 0.51  |
| Small Intestine                                          | 2         | 3.63   | 0.44 - 13.1  | 0.24  | 13        | 3.36*  | 1.79 - 5.74  | 0.26  | 3                                                    | 4.04   | 0.83 - 11.8   | 0.26  | 0                                   | 0      | 0 - 11.67     | -0.09 | 4                    | 2.37   | 0.65 - 6.08   | 0.18  |
| Colon, Rectum and Anus                                   | 11        | 1.14   | 0.57 - 2.04  | 0.23  | 113       | 1.67*  | 1.38 - 2.01  | 1.31  | 18                                                   | 1.39   | 0.82 - 2.19   | 0.58  | 7                                   | 1.26   | 0.51 - 2.59   | 0.43  | 59                   | 1.99*  | 1.51 - 2.56   | 2.31  |
| Colon and Rectum                                         | 11        | 1.22   | 0.61 - 2.18  | 0.33  | 96        | 1.51*  | 1.22 - 1.85  | 0.94  | 17                                                   | 1.4    | 0.81 - 2.24   | 0.56  | 7                                   | 1.34   | 0.54 - 2.76   | 0.53  | 27                   | 0.96   | 0.64 - 1.4    | -0.08 |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 7         | 3.34*  | 1.34 - 6.88  | 0.82  | 30        | 2.07*  | 1.4 - 2.96   | 0.45  | 5                                                    | 1.89   | 0.61 - 4.4    | 0.27  | 2                                   | 1.62   | 0.2 - 5.84    | 0.23  | 15                   | 2.25*  | 1.26 - 3.71   | 0.66  |
| Liver                                                    | 6         | 3.85*  | 1.41 - 8.37  | 0.75  | 24        | 2.24*  | 1.44 - 3.34  | 0.38  | 4                                                    | 2.07   | 0.56 - 5.29   | 0.24  | 1                                   | 1.08   | 0.03 - 6.04   | 0.02  | 12                   | 2.44*  | 1.26 - 4.26   | 0.56  |
| Gallbladder                                              | 1         | 6.92   | 0.18 - 38.55 | 0.14  | 3         | 2.88   | 0.59 - 8.43  | 0.06  | 0                                                    | 0      | 0 - 18.27     | -0.02 | 0                                   | 0      | 0 - 43.24     | -0.03 | 0                    | 0      | 0 - 7.18      | -0.04 |
| Pancreas                                                 | 1         | 0.54   | 0.01 - 3     | -0.14 | 32        | 2.35*  | 1.61 - 3.32  | 0.53  | 3                                                    | 1.24   | 0.26 - 3.62   | 0.07  | 0                                   | 0      | 0 - 3.28      | -0.34 | 4                    | 0.64   | 0.17 - 1.64   | -0.18 |
| Respiratory System                                       | 17        | 1.71   | 0.99 - 2.73  | 1.18  | 264       | 3.50*  | 3.09 - 3.95  | 5.43  | 20                                                   | 1.53   | 0.93 - 2.36   | 0.8   | 15                                  | 2.43*  | 1.36 - 4.36   | 2.64  | 55                   | 1.56*  | 1.18 - 2.04   | 1.57  |
| Nose, Nasal Cavity and Middle Ear                        | 2         | 8.59*  | 1.04 - 31.05 | 0.3   | 2         | 1.32   | 0.16 - 4.76  | 0.01  | 1                                                    | 3.16   | 0.08 - 17.59  | 0.08  | 2                                   | 15.55* | 1.88 - 56.19  | 0.56  | 3                    | 4.77   | 0.98 - 13.95  | 0.19  |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 12        | 1.36   | 0.7 - 2.37   | 0.53  | 255       | 3.80*  | 3.35 - 4.3   | 5.41  | 18                                                   | 1.55   | 0.92 - 2.45   | 0.74  | 12                                  | 2.18*  | 1.13 - 3.81   | 1.95  | 47                   | 1.49*  | 1.09 - 1.98   | 1.21  |
| Lung and Bronchus                                        | 12        | 1.37   | 0.71 - 2.4   | 0.55  | 253       | 3.80*  | 3.35 - 4.3   | 5.37  | 18                                                   | 1.57   | 0.93 - 2.48   | 0.75  | 12                                  | 2.21*  | 1.14 - 3.85   | 1.96  | 45                   | 1.43*  | 1.05 - 1.92   | 1.07  |
| Bones and Joints                                         | 2         | 4.22   | 0.51 - 15.26 | 0.26  | 18        | 6.61*  | 3.92 - 10.44 | 0.44  | 6                                                    | 8.96*  | 3.29 - 19.5   | 0.61  | 14                                  | 50.22* | 27.46 - 84.27 | 4.11  | 5                    | 5.07*  | 1.65 - 11.83  | 0.32  |
| Soft Tissue including Heart                              | 1         | 0.78   | 0.02 - 4.36  | -0.05 | 45        | 5.66*  | 4.13 - 7.57  | 1.07  | 10                                                   | 5.57*  | 2.67 - 10.25  | 0.95  | 15                                  | 21.09* | 11.8 - 34.79  | 4.28  | 57                   | 18.12* | 13.72 - 23.47 | 4.25  |
| Skin excluding Basal and Squamous                        | 10        | 0.95   | 0.46 - 1.75  | -0.09 | 90        | 1.25*  | 1 - 1.53     | 0.51  | 18                                                   | 1.12   | 0.67 - 1.78   | 0.23  | 5                                   | 0.85   | 0.27 - 1.97   | -0.27 | 64                   | 2.51*  | 1.94 - 3.21   | 3.04  |
| Melanoma of the Skin                                     | 10        | 1.01   | 0.48 - 1.86  | 0.02  | 87        | 1.28*  | 1.02 - 1.58  | 0.54  | 16                                                   | 1.06   | 0.6 - 1.72    | 0.1   | 5                                   | 0.9    | 0.29 - 2.1    | -0.17 | 39                   | 1.63*  | 1.16 - 2.23   | 1.19  |
| Breast                                                   | 35        | 1.59*  | 1.11 - 2.21  | 2.19  | 442       | 2.71*  | 2.46 - 2.97  | 8.03  | 24                                                   | 0.67*  | 0.43 - 0.99   | -1.37 | 13                                  | 1.03   | 0.55 - 1.76   | 0.1   | 88                   | 1.26*  | 1.01 - 1.55   | 1.42  |
| Female Breast                                            | 33        | 1.51*  | 1.04 - 2.12  | 1.87  | 438       | 2.70*  | 2.45 - 2.97  | 7.94  | 24                                                   | 0.67*  | 0.43 - 0.99   | -1.36 | 13                                  | 1.03   | 0.55 - 1.77   | 0.13  | 87                   | 1.25*  | 1 - 1.5       | 1.37  |
| Female Genital System                                    | 12        | 1.4    | 0.72 - 2.45  | 0.58  | 92        | 1.47*  | 1.19 - 1.8   | 0.85  | 19                                                   | 1.36   | 0.82 - 2.12   | 0.58  | 3                                   | 0.6    | 0.12 - 1.77   | -0.59 | 16                   | 0.61*  | 0.35 - 0.98   | -0.82 |
| Cervix Uteri                                             | 5         | 1.98   | 0.64 - 4.63  | 0.42  | 27        | 1.54*  | 1.02 - 2.25  | 0.27  | 5                                                    | 1.17   | 0.38 - 2.73   | 0.08  | 1                                   | 0.72   | 0.02 - 3.99   | -0.12 | 1                    | 0.16*  | 0 - 0.86      | -0.43 |
| Corpus and Uterus, NOS                                   | 4         | 1.15   | 0.31 - 2.95  | 0.09  | 38        | 1.46*  | 1.03 - 2     | 0.34  | 7                                                    | 1.27   | 0.51 - 2.63   | 0.17  | 2                                   | 0.97   | 0.12 - 3.51   | -0.02 | 9                    | 0.75   | 0.35 - 1.43   | -0.23 |
| Corpus Uteri                                             | 4         | 1.18   | 0.32 - 3.01  | 0.1   | 38        | 1.49*  | 1.05 - 2.04  | 0.36  | 7                                                    | 1.3    | 0.52 - 2.68   | 0.17  | 2                                   | 0.99   | 0.12 - 3.58   | 0     | 9                    | 0.77   | 0.35 - 1.46   | -0.21 |
| Uterus, NOS                                              | 0         | 0      | 0 - 51.3     | -0.01 | 0         | 0      | 0 - 7.17     | -0.01 | 0                                                    | 0      | 0 - 33.3      | -0.01 | 0                                   | 0      | 0 - 90.45     | -0.01 | 0                    | 0      | 0 - 15.14     | -0.02 |
| Ovary                                                    | 2         | 0.98   | 0.12 - 3.54  | -0.01 | 16        | 1.06   | 0.61 - 1.72  | 0.03  | 3                                                    | 0.89   | 0.18 - 2.6    | -0.04 | 0                                   | 0      | 0 - 3.1       | -0.36 | 5                    | 0.78   | 0.25 - 1.83   | -0.11 |
| Vagina                                                   | 0         | 0      | 0 - 44.53    | -0.01 | 2         | 3.28   | 0.4 - 11.83  | 0.04  | 0                                                    | 0      | 0 - 27.77     | -0.02 | 0                                   | 0      | 0 - 76.14     | -0.01 | 0                    | 0      | 0 - 13.07     | -0.02 |
| Male Genital System                                      | 18        | 1.2    | 0.71 - 1.9   | 0.51  | 106       | 0.93   | 0.77 - 1.13  | -0.21 | 11                                                   | 0.61   | 0.3 - 1.09    | -0.81 | 8                                   | 0.8    | 0.35 - 1.58   | -0.59 | 46                   | 1      | 0.73 - 1.33   | 0     |
| Prostate                                                 | 16        | 1.42   | 0.81 - 2.3   | 0.79  | 93        | 1      | 0.8 - 1.22   | -0.01 | 9                                                    | 0.71   | 0.32 - 1.35   | -0.42 | 6                                   | 0.75   | 0.28 - 1.63   | -0.6  | 34                   | 0.88   | 0.61 - 1.22   | -0.38 |
| Testis                                                   | 2         | 0.57   | 0.07 - 2.04  | -0.26 | 12        | 0.63   | 0.32 - 1.1   | -0.2  | 2                                                    | 0.38   | 0.05 - 1.39   | -0.37 | 2                                   | 1.05   | 0.13 - 3.79   | 0.03  | 8                    | 1.16   | 0.5 - 2.29    | 0.09  |
| Penis                                                    | 0         | 0      | 0 - 41.76    | -0.01 | 1         | 1.64   | 0.04 - 9.14  | 0.01  | 0                                                    | 0      | 0 - 33.7      | -0.01 | 0                                   | 0      | 0 - 72.96     | -0.02 | 3                    | 12.21* | 2.52 - 35.67  | 0.22  |
| Urinary System                                           | 8         | 1.09   | 0.47 - 2.15  | 0.12  | 114       | 2.17*  | 1.79 - 2.61  | 1.77  | 13                                                   | 1.37   | 0.73 - 2.34   | 0.4   | 2                                   | 0.46   | 0.06 - 1.67   | -0.7  | 28                   | 1.28   | 0.85 - 1.85   | 0.67  |
| Urinary Bladder                                          | 3         | 0.93   | 0.19 - 2.71  | -0.04 | 49        | 2.03*  | 1.5 - 2.69   | 0.72  | 3                                                    | 0.72   | 0.15 - 2.12   | -0.13 | 1                                   | 0.5    | 0.01 - 2.78   | -0.3  | 11                   | 1.11   | 0.55 - 1.99   | 0.09  |
| Kidney and Renal Pelvis                                  | 5         | 1.26   | 0.41 - 2.94  | 0.17  | 61        | 2.22*  | 1.69 - 2.85  | 0.96  | 10                                                   | 1.91   | 0.92 - 3.51   | 0.55  | 1                                   | 0.44   | 0.01 - 2.47   | -0.38 | 17                   | 1.47   | 0.86 - 2.35   | 0.43  |
| Kidney                                                   | 0         | 0      | 0 - 16.9     | -0.04 | 7         | 4.29*  | 1.73 - 8.85  | 0.15  | 0                                                    | 0      | 0 - 13.14     | -0.03 | 0                                   | 0      | 0 - 27.41     | -0.04 | 0                    | 0      | 0 - 5.07      | -0.06 |
| Renal Pelvis                                             | 5         | 1.3    | 0.42 - 3.03  | 0.19  | 58        | 2.17*  | 1.65 - 2.81  | 0.9   | 10                                                   | 1.97   | 0.94 - 3.62   | 0.57  | 1                                   | 0.46   | 0.01 - 2.54   | -0.36 | 17                   | 1.52   | 0.88 - 2.43   | 0.46  |
| Eye and Orbit                                            | 1         | 3.62   | 0 - 32.51    | 0.12  | 1         | 0.53   | 0.73 - 10.37 | -0.03 | 0                                                    | 0      | 0 - 24.99     | -0.05 | 1                                   | 6.46   | 0 - 53.84     | 0.25  | 0                    | 0      | 0 - 9.93      | -0.06 |
| Brain and Other Nervous System                           | 4         | 1.41   | 0.09 - 20.16 | 0.2   | 18        | 0.99   | 0.01 - 2.93  | -0.01 | 104                                                  | 25.15* | 0 - 9.21      | 11.52 | 3                                   | 1.88   | 0.16 - 35.99  | 0.42  | 18                   | 2.62*  | 0 - 5.15      | 0.88  |
| Brain                                                    | 11        | 1.61   | 0.38 - 3.61  | 0.7   | 145       | 3.28*  | 0.59 - 1.56  | 2.9   | 26                                                   | 2.50*  | 20.55 - 30.47 | 1.8   | 7                                   | 1.88   | 0.39 - 5.51   | 0.98  | 23                   | 1.52   | 1.55 - 4.14   | 0.62  |
| Endocrine System                                         | 11        | 1.68   | 0.8 - 2.88   | 0.75  | 140       | 3.29*  | 2.77 - 3.86  | 2.81  | 24                                                   | 2.40*  | 1.63 - 3.66   | 1.61  | 7                                   | 1.96   | 0.75 - 3.86   | 1.02  | 23                   | 1.59*  | 0.96 - 2.27   | 0.67  |
| Thyroid                                                  | 0         | 0      | 0.84 - 3     | -0.01 | 1         | 1.82   | 2.77 - 3.89  | 0.01  | 0                                                    | 0      | 1.53 - 3.56   | -0.01 | 0                                   | 0      | 0.79 - 4.03   | -0.01 | 0                    | 0      | 1.01 - 2.38   | -0.02 |
| Adrenal Gland                                            | 46        | 3.56*  | 0 - 43.87    | 5.56  | 438       | 5.16*  | 0.05 - 10.14 | 10.17 | 28                                                   | 1.55*  | 0 - 29.92     | 1.14  | 28                                  | 3.79*  | 0 - 80.28     | 6.18  | 399                  | 11.52* | 0 - 16.49     | 28.74 |
| All Lymphatic and Hematopoietic Diseases                 | 24        | 2.82*  | 2.61 - 4.75  | 2.6   | 291       | 5.27*  | 4.69 - 5.67  | 6.79  | 10                                                   | 0.82   | 1.03 - 2.24   | -0.25 | 5                                   | 1.04   | 2.52 - 5.48   | 0.05  | 378                  | 17.10* | 10.42 - 12.71 | 28.07 |
| Lymphoma                                                 | 5         | 2.27   | 1.81 - 4.19  | 0.47  | 49        | 3.81*  | 4.68 - 5.91  | 1.04  | 3                                                    | 0.92   | 0.39 - 1.51   | -0.03 | 0                                   | 0      | 0.34 - 2.42   | -0.38 | 7                    | 1.57   | 15.42 - 18.91 | 0.2   |
| Hodgkin Lymphoma                                         | 19        | 3.01*  | 0.74 - 5.29  | 2.13  | 242       | 5.71*  | 2.82 - 5.03  | 5.75  | 7                                                    | 0.79   | 0.19 - 2.68   | -0.22 | 5                                   | 1.4    | 0 - 2.92      | 0.43  | 371                  | 21.01* | 0.63 - 3.24   | 27.87 |
| Non-Hodgkin Lymphoma                                     |           |        | 1.81 - 4.7   |       |           |        | 5.01 - 6.48  |       |                                                      |        | 0.32 - 1.62   |       |                                     |        | 0.46 - 3.27   |       |                      |        | 18.93 - 23.26 |       |

|                                       |    |        |              |       |     |        |              |       |    |       |              |    |        |               |       |    |       |             |       |
|---------------------------------------|----|--------|--------------|-------|-----|--------|--------------|-------|----|-------|--------------|----|--------|---------------|-------|----|-------|-------------|-------|
| Myeloma                               | 1  | 0.92   | 0.02 - 5.14  | -0.01 | 17  | 2.17*  | 1.26 - 3.47  | 0.26  | 0  | 0     | -0.16        | 1  | 1.55   | 0.04 - 8.61   | 0.11  | 5  | 1.34  | 0.44 - 3.13 | 0.1   |
|                                       | 21 | 6.34*  |              | 2.97  | 130 | 5.97*  |              | 3.12  | 18 | 3.97* | 0 - 2.65     | 22 | 11.54* |               | 6.02  | 16 | 1.82* |             | 0.57  |
| Leukemia                              | 8  | 5.71*  | 3.92 - 9.69  | 1.11  | 14  | 1.46   | 4.99 - 7.09  | 0.13  | 6  | 3.22* | 2.35 - 6.27  | 5  | 5.99*  | 7.23 - 17.48  | 1.25  | 4  | 1.03  | 1.04 - 2.96 | 0.01  |
|                                       | 8  | 20.32* | 2.46 - 11.25 | 1.28  | 9   | 4.13*  | 0.8 - 2.45   | 0.2   | 1  | 1.84  | 1.18 - 7.01  | 4  | 17.35* | 1.95 - 13.98  | 1.13  | 2  | 2.53  | 0.28 - 2.64 | 0.1   |
| Acute Lymphocytic Leukemia            | 0  | 0      | 8.77 - 40.03 | -0.14 | 4   | 0.66   | 1.89 - 7.84  | -0.06 | 5  | 4.78* | 0.05 - 10.27 | 1  | 2.01   | 4.73 - 44.41  | 0.15  | 2  | 0.78  | 0.31 - 9.15 | -0.05 |
| Chronic Lymphocytic Leukemia          | 0  | 0      | 0 - 4.56     | -0.03 | 1   | 0.76   | 0.18 - 1.68  | -0.01 | 0  | 0     | 1.55 - 11.16 |    |        | 0.05 - 11.21  | -0.03 | 0  | 0     | 0.09 - 2.8  | -0.04 |
| Other Lymphocytic Leukemia            |    |        | 0 - 18.52    |       |     |        | 0.02 - 4.21  |       |    |       | 0 - 13.36    |    |        | 0 - 34.53     |       |    |       | 0 - 7.24    |       |
|                                       | 13 | 6.80*  |              | 1.86  | 116 | 9.52*  |              | 2.99  | 12 | 4.49* |              | 17 | 15.87* |               | 4.77  | 12 | 2.45* |             | 0.56  |
| Non-Lymphocytic Leukemia              |    |        | 3.62 - 11.63 |       |     |        | 7.87 - 11.42 |       |    |       | 2.32 - 7.84  |    |        | 9.24 - 25.41  |       |    |       | 1.26 - 4.27 |       |
|                                       | 11 | 9.35*  |              | 1.65  | 103 | 13.69* |              | 2.75  | 11 | 6.68* |              | 14 | 20.93* |               | 3.99  | 10 | 3.32* |             | 0.55  |
| Acute Non-Lymphocytic Leukemia (ANLL) |    |        | 4.67 - 16.73 |       |     |        | 11.17 - 16.6 |       |    |       | 3.33 - 11.95 |    |        | 11.44 - 35.12 |       |    |       | 1.59 - 6.1  |       |
|                                       | 13 | 7.30*  |              | 1.89  | 103 | 9.10*  |              | 2.64  | 11 | 4.42* |              | 16 | 16.05* |               | 4.49  | 12 | 2.64* |             | 0.59  |
| Myeloid and Monocytic Leukemia        |    |        | 3.89 - 12.49 |       |     |        | 7.42 - 11.03 |       |    |       | 2.21 - 7.9   |    |        | 9.17 - 26.06  |       |    |       | 1.37 - 4.62 |       |
|                                       | 11 | 10.60* |              | 1.67  | 84  | 12.67* |              | 2.23  | 10 | 6.90* |              | 13 | 22.03* |               | 3.72  | 9  | 3.38* |             | 0.5   |
| Acute Myeloid Leukemia                |    |        | 5.29 - 18.96 |       |     |        | 10.1 - 15.68 |       |    |       | 3.31 - 12.69 |    |        | 11.73 - 37.68 |       |    |       | 1.55 - 6.42 |       |
|                                       | 0  | 0      |              | -0.01 | 8   | 16.36* |              | 0.22  | 0  | 0     |              | 0  | 0      |               | -0.01 | 1  | 5.31  |             | 0.06  |
| Acute Monocytic Leukemia              |    |        | 0 - 48.64    |       |     |        | 7.06 - 32.24 |       |    |       | 0 - 34.45    |    |        | 0 - 84.81     |       |    |       | 0.13 - 29.6 |       |
|                                       | 0  | 0      |              | -0.11 | 8   | 2.03   |              | 0.12  | 1  | 1.14  |              | 2  | 5.86   |               | 0.5   | 2  | 1.26  |             | 0.03  |
| Chronic Myeloid Leukemia              |    |        | 0 - 5.9      |       |     |        | 0.88 - 4     |       |    |       | 0.03 - 6.36  |    |        | 0.71 - 21.18  |       |    |       | 0.15 - 4.54 |       |
|                                       | 1  | 7.51   |              | 0.15  | 3   | 2.96   |              | 0.06  | 0  | 0     |              | 0  | 0      |               | -0.03 | 0  | 0     |             | -0.03 |
| Mesothelioma                          |    |        | 0.19 - 41.85 |       |     |        | 0.61 - 8.65  |       |    |       | 0 - 21.17    |    |        | 0 - 43.32     |       |    |       | 0 - 8.94    |       |
|                                       | 0  | 0      |              | -0.29 | 73  | 6.37*  |              | 1.77  | 0  | 0     |              | 0  | 0      |               | -0.28 | 3  | 0.54  |             | -0.2  |
| Kaposi Sarcoma                        |    |        | 0 - 2.11     |       |     |        | 4.99 - 8     |       |    |       | 0 - 1.32     |    |        | 0 - 3.92      |       |    |       | 0.11 - 1.58 |       |
|                                       | 6  | 4.21*  |              | 0.77  | 33  | 3.23*  |              | 0.66  | 4  | 2.05  |              | 3  | 3.57   |               | 0.65  | 11 | 2.40* |             | 0.51  |
| Miscellaneous                         |    |        | 1.54 - 9.15  |       |     |        | 2.23 - 4.54  |       |    |       | 0.56 - 5.25  |    |        | 0.74 - 10.42  |       |    |       | 1.2 - 4.3   |       |
|                                       |    |        |              |       |     |        |              |       |    |       |              |    |        |               |       |    |       |             |       |

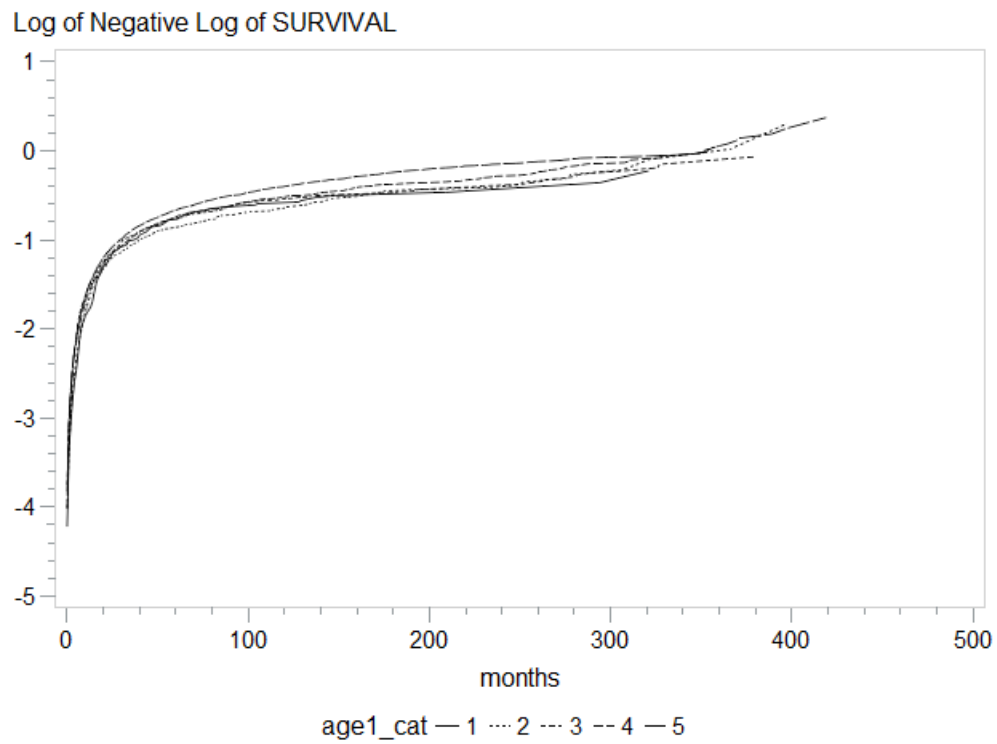
TABLE 8 – Risk of MPCs in Survivors of AYA Cancer by First Cancer Diagnosis, SEER 9 1973-2012 (Continued)

| MPC Site                                                 | Germ Cell and Trophoblastic Neoplasms |        |              |       | Melanoma and Skin Carcinomas |       |              |       | Carcinomas |       |             |       | Miscellaneous Specified Neoplasms |        |              |       | Unspecified Malignant Neoplasms |        |              |       |
|----------------------------------------------------------|---------------------------------------|--------|--------------|-------|------------------------------|-------|--------------|-------|------------|-------|-------------|-------|-----------------------------------|--------|--------------|-------|---------------------------------|--------|--------------|-------|
|                                                          | O                                     | SIR    | 95% CI       | EAR   | O                            | SIR   | 95% CI       | EAR   | O          | SIR   | 95% CI      | EAR   | O                                 | SIR    | 95% CI       | EAR   | O                               | SIR    | 95% CI       | EAR   |
| All sites                                                | 1,306                                 | 1.65*  | 1.56 - 1.74  | 17.08 | 2,246                        | 1.63* | 1.57 - 1.7   | 22.35 | 9,382      | 1.79* | 1.75 - 1.83 | 30.53 | 132                               | 1.57*  | 1.32 - 1.86  | 17.84 | 67                              | 1.98*  | 1.53 - 2.51  | 31.2  |
| All sites (excluding non-Melanoma skin)                  | 1,300                                 | 1.65*  | 1.56 - 1.74  | 17.01 | 2,237                        | 1.63* | 1.57 - 1.7   | 22.26 | 9,339      | 1.79* | 1.75 - 1.82 | 30.35 | 132                               | 1.58*  | 1.32 - 1.87  | 17.96 | 65                              | 1.93*  | 1.49 - 2.46  | 29.45 |
| All Solid Tumors                                         | 1,150                                 | 1.67*  | 1.58 - 1.77  | 15.42 | 2,091                        | 1.69* | 1.62 - 1.76  | 21.85 | 8,705      | 1.82* | 1.78 - 1.86 | 28.9  | 115                               | 1.51*  | 1.25 - 1.82  | 14.5  | 57                              | 1.86*  | 1.41 - 2.41  | 24.84 |
| Oral Cavity and Pharynx                                  | 35                                    | 1.02   | 0.71 - 1.42  | 0.02  | 38                           | 1.06  | 0.75 - 1.45  | 0.06  | 306        | 2.90* | 2.59 - 3.25 | 1.48  | 4                                 | 2.11   | 0.58 - 5.41  | 0.78  | 1                               | 1.27   | 0.03 - 7.08  | 0.2   |
| Salivary Gland                                           | 7                                     | 2.46   | 0.99 - 5.07  | 0.14  | 9                            | 2.20* | 1.01 - 4.18  | 0.13  | 46         | 3.12* | 2.28 - 4.16 | 0.23  | 2                                 | 7.83   | 0.85 - 28.29 | 0.65  | 0                               | 0      | 0 - 35.72    | -0.1  |
| Digestive System                                         | 192                                   | 1.43*  | 1.23 - 1.64  | 1.92  | 154                          | 0.87  | 0.74 - 1.01  | -0.61 | 1,264      | 1.93* | 1.83 - 2.04 | 4.5   | 18                                | 1.66   | 0.98 - 2.62  | 2.66  | 12                              | 2.73*  | 1.41 - 4.76  | 7.16  |
| Esophagus                                                | 10                                    | 1.01   | 0.48 - 1.85  | 0     | 8                            | 0.83  | 0.36 - 1.64  | -0.04 | 46         | 1.80* | 1.32 - 2.14 | 0.15  | 2                                 | 4.43   | 0.54 - 15.99 | 0.58  | 0                               | 0      | 0 - 18.55    | -0.19 |
| Stomach                                                  | 15                                    | 1.26   | 0.71 - 2.08  | 0.1   | 10                           | 0.73  | 0.35 - 1.34  | -0.1  | 115        | 2.26* | 1.86 - 2.71 | 0.47  | 2                                 | 2.25   | 0.27 - 8.14  | 0.41  | 0                               | 0      | 0 - 10.24    | -0.34 |
| Small Intestine                                          | 4                                     | 0.96   | 0.26 - 2.46  | -0.01 | 9                            | 1.58  | 0.72 - 3     | 0.08  | 50         | 2.42* | 1.79 - 3.18 | 0.22  | 2                                 | 5.62   | 0.68 - 20.31 | 0.61  | 0                               | 0      | 0 - 25.82    | -0.13 |
| Colon, Rectum and Anus                                   | 88                                    | 1.22   | 0.98 - 1.51  | 0.54  | 86                           | 0.84  | 0.67 - 1.03  | -0.43 | 779        | 1.99* | 1.86 - 2.14 | 2.86  | 9                                 | 1.4    | 0.64 - 2.66  | 0.96  | 9                               | 3.50*  | 1.6 - 6.64   | 6.05  |
| Colon and Rectum                                         | 84                                    | 1.23   | 0.98 - 1.52  | 0.52  | 80                           | 0.83  | 0.66 - 1.03  | -0.43 | 732        | 1.99* | 1.85 - 2.14 | 2.69  | 9                                 | 1.49   | 0.68 - 2.84  | 1.11  | 7                               | 2.89*  | 1.16 - 5.96  | 4.31  |
| Liver, Gallbladder, Intrahep Bile Duct and Other Biliary | 18                                    | 0.94   | 0.56 - 1.49  | -0.04 | 15                           | 0.77  | 0.43 - 1.26  | -0.12 | 103        | 1.57* | 1.28 - 1.91 | 0.28  | 1                                 | 0.87   | 0.02 - 4.82  | -0.06 | 1                               | 2.03   | 0.05 - 11.3  | 0.48  |
| Liver                                                    | 12                                    | 0.79   | 0.41 - 1.38  | -0.11 | 9                            | 0.67  | 0.31 - 1.28  | -0.11 | 47         | 1.17  | 0.86 - 1.56 | 0.05  | 0                                 | 0      | 0 - 4.86     | -0.28 | 1                               | 2.99   | 0.08 - 16.66 | 0.63  |
| Gallbladder                                              | 2                                     | 2.63   | 0.32 - 9.5   | 0.04  | 1                            | 0.54  | 0.01 - 2.98  | -0.02 | 7          | 0.75  | 0.3 - 1.54  | -0.02 | 1                                 | 7.09   | 0.18 - 39.48 | 0.32  | 0                               | 0      | 0 - 66.26    | -0.05 |
| Pancreas                                                 | 50                                    | 3.23*  | 2.4 - 4.26   | 1.15  | 19                           | 0.86  | 0.52 - 1.35  | -0.08 | 134        | 1.63* | 1.37 - 1.93 | 0.38  | 1                                 | 0.77   | 0.02 - 4.29  | -0.11 | 2                               | 3.8    | 0.46 - 13.71 | 1.39  |
| Respiratory System                                       | 96                                    | 1.19   | 0.96 - 1.45  | 0.51  | 96                           | 0.76* | 0.61 - 0.92  | -0.79 | 810        | 1.65* | 1.54 - 1.77 | 2.36  | 17                                | 2.26*  | 1.32 - 3.62  | 3.52  | 8                               | 2.63*  | 1.13 - 5.18  | 4.67  |
| Nose, Nasal Cavity and Middle Ear                        | 2                                     | 1.18   | 0.14 - 4.26  | 0.01  | 5                            | 2.43  | 0.79 - 5.68  | 0.08  | 15         | 2.14* | 1.2 - 3.53  | 0.06  | 2                                 | 16.03* | 1.94 - 57.89 | 0.7   | 0                               | 0      | 0 - 74.07    | -0.05 |
| Lung, Bronchus, Trachea, Mediastinum and Other Resp Org  | 86                                    | 1.23   | 0.98 - 1.52  | 0.53  | 89                           | 0.77* | 0.62 - 0.95  | -0.68 | 749        | 1.64* | 1.53 - 1.76 | 2.16  | 15                                | 2.17*  | 1.21 - 3.57  | 3     | 6                               | 2.15   | 0.79 - 4.67  | 3.02  |
| Lung and Bronchus                                        | 85                                    | 1.23   | 0.98 - 1.52  | 0.52  | 88                           | 0.77* | 0.62 - 0.94  | -0.69 | 747        | 1.64* | 1.53 - 1.76 | 2.15  | 15                                | 2.18*  | 1.22 - 3.59  | 3.01  | 6                               | 2.16   | 0.79 - 4.7   | 3.03  |
| Bones and Joints                                         | 1                                     | 0.39   | 0.01 - 2.17  | -0.05 | 5                            | 1.58  | 0.51 - 3.69  | 0.05  | 23         | 2.30* | 1.46 - 3.45 | 0.1   | 0                                 | 0      | 0 - 18.72    | -0.07 | 0                               | 0      | 0 - 47.32    | -0.07 |
| Soft Tissue including Heart                              | 20                                    | 2.52*  | 1.54 - 3.89  | 0.4   | 18                           | 1.80* | 1.07 - 2.85  | 0.21  | 80         | 2.33* | 1.85 - 2.9  | 0.34  | 5                                 | 7.76*  | 2.52 - 18.11 | 1.62  | 0                               | 0      | 0 - 14.45    | -0.24 |
| Skin excluding Basal and Squamous                        | 72                                    | 1.02   | 0.8 - 1.28   | 0.04  | 1,011                        | 9.28* | 8.72 - 9.87  | 23.15 | 359        | 1.11  | 1 - 1.23    | 0.26  | 6                                 | 1.12   | 0.41 - 2.44  | 0.24  | 4                               | 1.8    | 0.49 - 4.61  | 1.67  |
| Melanoma of the Skin                                     | 66                                    | 0.99   | 0.76 - 1.26  | -0.03 | 1,002                        | 9.68* | 9.09 - 10.29 | 23.06 | 316        | 1.03  | 0.92 - 1.15 | 0.08  | 6                                 | 1.2    | 0.44 - 2.61  | 0.37  | 2                               | 0.96   | 0.12 - 3.46  | -0.08 |
| Breast                                                   | 29                                    | 0.97   | 0.65 - 1.39  | -0.03 | 283                          | 0.86* | 0.76 - 0.97  | -1.17 | 3,685      | 2.16* | 2.09 - 2.23 | 14.58 | 25                                | 0.98   | 0.64 - 1.45  | -0.16 | 13                              | 1.33   | 0.71 - 2.27  | 3.01  |
| Female Breast                                            | 29                                    | 1.02   | 0.68 - 1.46  | 0.02  | 281                          | 0.86* | 0.76 - 0.96  | -1.19 | 3,683      | 2.16* | 2.09 - 2.23 | 14.58 | 25                                | 0.98   | 0.64 - 1.45  | -0.15 | 13                              | 1.33   | 0.71 - 2.27  | 3.03  |
| Female Genital System                                    | 8                                     | 0.71   | 0.31 - 1.41  | -0.11 | 107                          | 0.86  | 0.71 - 1.04  | -0.43 | 980        | 1.54* | 1.44 - 1.63 | 2.52  | 14                                | 1.48   | 0.81 - 2.48  | 1.69  | 7                               | 1.91   | 0.77 - 3.94  | 3.14  |
| Cervix Uteri                                             | 1                                     | 0.32   | 0.01 - 1.81  | -0.07 | 18                           | 0.64  | 0.38 - 1.01  | -0.26 | 111        | 0.78* | 0.64 - 0.94 | -0.23 | 3                                 | 1.31   | 0.27 - 3.83  | 0.26  | 1                               | 1.09   | 0.03 - 6.05  | 0.07  |
| Corpus and Uterus, NOS                                   | 3                                     | 0.63   | 0.13 - 1.85  | -0.06 | 52                           | 0.91  | 0.68 - 1.19  | -0.13 | 373        | 1.24* | 1.12 - 1.38 | 0.54  | 3                                 | 0.7    | 0.14 - 2.05  | -0.47 | 4                               | 2.46   | 0.67 - 8.29  | 2.23  |
| Corpus Uteri                                             | 3                                     | 0.65   | 0.13 - 1.89  | -0.05 | 49                           | 0.87  | 0.64 - 1.15  | -0.19 | 365        | 1.24* | 1.12 - 1.37 | 0.52  | 3                                 | 0.72   | 0.15 - 2.09  | -0.44 | 4                               | 2.51   | 0.68 - 6.43  | 2.27  |
| Uterus, NOS                                              | 0                                     | 0      | 0 - 37.28    | 0     | 3                            | 3.09  | 0.64 - 9.02  | 0.05  | 8          | 1.42  | 0.62 - 2.81 | 0.02  | 0                                 | 0      | 0 - 41.89    | -0.03 | 0                               | 0      | 0 - 108.84   | -0.03 |
| Ovary                                                    | 3                                     | 1.12   | 0.23 - 3.29  | 0.01  | 34                           | 1.11  | 0.77 - 1.55  | 0.09  | 382        | 2.44* | 2.2 - 2.7   | 1.66  | 5                                 | 2.19   | 0.71 - 5.1   | 1.01  | 2                               | 2.27   | 0.27 - 8.19  | 1.05  |
| Vagina                                                   | 0                                     | 0      | 0 - 32.57    | 0     | 1                            | 0.82  | 0.02 - 4.58  | -0.01 | 46         | 6.90* | 5.05 - 9.2  | 0.29  | 2                                 | 19.84* | 2.4 - 71.68  | 0.71  | 0                               | 0      | 0 - 93.93    | -0.04 |
|                                                          | 484                                   | 2.58*  |              | 9.87  | 162                          | 1.1   |              | 0.39  | 223        | 0.92  |             | -0.15 | 3                                 | 0.63   |              | -0.65 | 2                               | 0.86   |              | -0.3  |
| Male Genital System                                      | 158                                   | 1      | 2.36 - 2.82  | 0.02  | 152                          | 1.16  | 0.94 - 1.29  | 0.55  | 196        | 0.88  | 0.8 - 1.04  | -0.19 | 2                                 | 0.51   | 0.13 - 1.85  | -0.73 | 0                               | 0      | 0.1 - 3.11   | -1.9  |
| Prostate                                                 | 322                                   | 11.20* | 0.85 - 1.17  | 9.76  | 10                           | 0.67  | 0.99 - 1.36  | -0.13 | 26         | 1.27  | 0.77 - 1.02 | 0.04  | 1                                 | 1.32   | 0.06 - 1.83  | 0.09  | 2                               | 7.02   | 0 - 1.83     | 1.62  |
| Testis                                                   | 2                                     | 2.03   | 10.01 - 12.5 | 0.03  | 0                            | 0     | 0.32 - 1.23  | -0.02 | 1          | 0.82  | 0.83 - 1.87 | 0     | 0                                 | 0      | 0.03 - 7.37  | -0.01 | 0                               | 0      | 0.85 - 25.35 | -0.01 |
| Penis                                                    | 132                                   | 1.94*  | 0.25 - 7.34  | 2.13  | 79                           | 1     | 0 - 5.02     | 0     | 484        | 2.09* | 0.02 - 4.56 | 1.86  | 6                                 | 1.58   | 0 - 135.24   | 0.81  | 2                               | 1.25   | 0 - 301.83   | 0.37  |
| Urinary System                                           | 62                                    | 1.82*  | 1.62 - 2.3   | 0.93  | 30                           | 0.79  | 0.79 - 1.25  | -0.21 | 179        | 1.77* | 1.91 - 2.29 | 0.57  | 2                                 | 1.28   | 0.58 - 3.43  | 0.16  | 0                               | 0      | 0.15 - 4.5   | -0.65 |
| Urinary Bladder                                          | 64                                    | 1.93*  | 1.4 - 2.34   | 1.03  | 47                           | 1.18  | 0.53 - 1.12  | 0.19  | 268        | 2.12* | 1.52 - 2.05 | 1.05  | 4                                 | 1.83   | 0.16 - 4.64  | 0.67  | 2                               | 2.24   | 0 - 5.37     | 1.04  |
| Kidney and Renal Pelvis                                  | 11                                    | 5.30*  | 1.49 - 2.47  | 0.3   | 3                            | 1.12  | 0.87 - 1.58  | 0.01  | 51         | 5.71* | 1.88 - 2.39 | 0.31  | 0                                 | 0      | 0.5 - 4.69   | -0.05 | 0                               | 0      | 0.27 - 8.11  | -0.05 |
| Kidney                                                   | 59                                    | 1.84*  | 2.64 - 9.47  | 0.9   | 46                           | 1.2   | 0.23 - 3.26  | 0.2   | 254        | 2.09* | 4.25 - 7.51 | 0.98  | 4                                 | 1.89   | 0 - 27.47    | 0.7   | 2                               | 2.32   | 0 - 65.48    | 1.07  |
| Renal Pelvis                                             | 5                                     | 4.66*  | 1.4 - 2.37   | 0.13  | 1                            | 0.71  | 0.88 - 1.6   | -0.01 | 14         | 3.02* | 1.84 - 2.36 | 0.07  | 0                                 | 0      | 0.52 - 4.84  | -0.03 | 0                               | 0      | 0.28 - 8.38  | -0.03 |
| Eye and Orbit                                            | 2                                     | 0.98   | 1.51 - 10.87 | 0     | 10                           | 3.39* | 0.02 - 3.94  | 0.18  | 12         | 1.33  | 1.65 - 5.07 | 0.02  | 0                                 | 0      | 0 - 53.48    | -0.05 | 0                               | 0      | 0 - 127.71   | -0.06 |
| Brain and Other Nervous System                           | 23                                    | 1.19   | 0.12 - 3.53  | 0.12  | 20                           | 0.82  | 1.62 - 6.23  | -0.11 | 109        | 1.45* | 0.69 - 2.32 | 0.25  | 4                                 | 2.99   | 0 - 25.52    | 0.99  | 6                               | 11.08* | 0 - 62.07    | 5.14  |
| Brain                                                    | 48                                    | 1.95*  | 0.76 - 1.79  | 0.78  | 101                          | 1.52* | 0.5 - 1.27   | 0.89  | 391        | 1.51* | 1.19 - 1.75 | 0.97  | 11                                | 2.52*  | 0.81 - 7.64  | 2.46  | 3                               | 1.72   | 4.06 - 24.11 | 1.19  |
| Endocrine System                                         | 47                                    | 2.04*  | 1.44 - 2.58  | 0.8   | 100                          | 1.56* | 1.24 - 1.85  | 0.92  | 371        | 1.48* | 1.36 - 1.66 | 0.88  | 10                                | 2.37*  | 1.26 - 4.51  | 2.15  | 3                               | 1.78   | 0.36 - 5.04  | 1.24  |
| Thyroid                                                  |                                       |        | 1.5 - 2.72   |       |                              |       | 1.27 - 1.9   |       |            |       | 1.33 - 1.63 |       |                                   |        | 1.14 - 4.36  |       |                                 |        | 0.37 - 5.21  |       |

|                                          |     |        |              |       |     |      |             |       |     |       |             |       |    |       |              |       |   |       |              |       |
|------------------------------------------|-----|--------|--------------|-------|-----|------|-------------|-------|-----|-------|-------------|-------|----|-------|--------------|-------|---|-------|--------------|-------|
|                                          | 0   | 0      |              | -0.02 | 0   | 0    |             | -0.02 | 8   | 2.72* |             | 0.04  | 0  | 0     |              | -0.02 | 0 | 0     |              | -0.02 |
| Adrenal Gland                            | 135 | 1.48*  | 0 - 7.66     | 1.45  | 135 | 1.18 | 0 - 4.76    | 0.53  | 510 | 1.34* | 1.18 - 5.37 | 0.96  | 17 | 2.53* | 0 - 73.3     | 3.82  | 6 | 2.21  | 0 - 183.24   | 3.1   |
| All Lymphatic and Hematopoietic Diseases | 64  | 1.09   | 1.24 - 1.75  | 0.17  | 85  | 1.18 | 0.99 - 1.4  | 0.34  | 276 | 1.20* | 1.23 - 1.47 | 0.33  | 6  | 1.43  | 1.47 - 4.05  | 0.67  | 3 | 1.77  | 0.81 - 4.81  | 1.23  |
| Lymphoma                                 | 9   | 0.77   | 0.84 - 1.39  | -0.09 | 16  | 1.24 | 0.95 - 1.46 | 0.08  | 39  | 1.04  | 1.06 - 1.35 | 0.01  | 1  | 1.2   | 0.52 - 3.11  | 0.06  | 1 | 2.97  | 0.36 - 5.17  | 0.62  |
| Hodgkin Lymphoma                         | 55  | 1.17   | 0.35 - 1.46  | 0.26  | 69  | 1.17 | 0.71 - 2.01 | 0.26  | 237 | 1.23* | 0.74 - 1.42 | 0.32  | 5  | 1.49  | 0.03 - 6.71  | 0.61  | 2 | 1.47  | 0.08 - 16.56 | 0.6   |
| Non-Hodgkin Lymphoma                     | 14  | 1.64   | 0.88 - 1.52  | 0.18  | 8   | 0.69 | 0.91 - 1.48 | -0.09 | 45  | 0.96  | 1.07 - 1.39 | -0.01 | 4  | 5.05* | 0.48 - 3.47  | 1.19  | 2 | 6.33  | 0.18 - 5.31  | 1.59  |
| Myeloma                                  | 57  | 2.38*  | 0.9 - 2.75   | 1.1   | 42  | 1.35 | 0.3 - 1.35  | 0.28  | 189 | 1.86* | 0.7 - 1.29  | 0.64  | 7  | 4.04* | 1.38 - 12.92 | 1.96  | 1 | 1.43  | 0.77 - 22.88 | 0.28  |
| Leukemia                                 | 10  | 0.85   | 1.8 - 3.08   | -0.06 | 19  | 1.3  | 0.98 - 1.83 | 0.11  | 40  | 0.91  | 1.6 - 2.14  | -0.03 | 1  | 1.4   | 1.63 - 8.33  | 0.11  | 1 | 3.38  | 0.04 - 7.95  | 0.66  |
| Lymphocytic Leukemia                     | 0   | 0      | 0.41 - 1.57  | -0.07 | 2   | 0.81 | 0.78 - 2.03 | -0.01 | 8   | 1.02  | 0.65 - 1.23 | 0     | 0  | 0     | 0.04 - 7.8   | -0.06 | 1 | 16.37 | 0.09 - 18.8  | 0.88  |
| Acute Lymphocytic Leukemia               | 9   | 1.15   | 0 - 1.74     | 0.04  | 13  | 1.25 | 0.1 - 2.94  | 0.07  | 30  | 0.94  | 0.44 - 2.01 | -0.01 | 1  | 2.09  | 0 - 23.81    | 0.19  | 0 | 0     | 0.41 - 91.23 | -0.19 |
| Chronic Lymphocytic Leukemia             | 1   | 0.55   | 0.53 - 2.19  | -0.03 | 4   | 2.27 | 0.66 - 2.13 | 0.06  | 2   | 0.46  | 0.63 - 1.34 | -0.02 | 0  | 0     | 0.05 - 11.64 | -0.03 | 0 | 0     | 0 - 18.26    | -0.03 |
| Other Lymphocytic Leukemia               | 47  | 3.84*  | 0.01 - 3.06  | 1.16  | 23  | 1.4  | 0.62 - 5.81 | 0.17  | 149 | 2.59* | 0.06 - 1.66 | 0.67  | 6  | 5.90* | 0 - 45.61    | 1.85  | 0 | 0     | 0 - 111.07   | -0.38 |
| Non-Lymphocytic Leukemia                 | 39  | 5.26*  | 2.82 - 5.11  | 1.05  | 16  | 1.53 | 0.89 - 2.11 | 0.14  | 108 | 2.91* | 2.19 - 3.04 | 0.52  | 5  | 7.83* | 2.17 - 12.85 | 1.62  | 0 | 0     | 0 - 9.12     | -0.24 |
| Acute Non-Lymphocytic Leukemia (ANLL)    | 45  | 3.94*  | 3.74 - 7.19  | 1.12  | 20  | 1.31 | 0.88 - 2.49 | 0.12  | 140 | 2.63* | 2.39 - 3.51 | 0.64  | 6  | 6.38* | 2.54 - 18.28 | 1.88  | 0 | 0     | 0 - 14.51    | -0.35 |
| Myeloid and Monocytic Leukemia           | 33  | 5.05*  | 2.87 - 5.27  | 0.88  | 15  | 1.63 | 0.8 - 2.02  | 0.15  | 91  | 2.78* | 2.21 - 3.1  | 0.43  | 5  | 8.85* | 2.34 - 13.88 | 1.65  | 0 | 0     | 0 - 9.86     | -0.21 |
| Acute Myeloid Leukemia                   | 5   | 10.23* | 3.47 - 7.09  | 0.15  | 0   | 0    | 0.91 - 2.69 | -0.02 | 10  | 4.22* | 2.23 - 3.41 | 0.06  | 0  | 0     | 2.87 - 20.66 | -0.02 | 0 | 0     | 0 - 16.39    | -0.02 |
| Acute Monocytic Leukemia                 | 6   | 1.44   | 3.32 - 23.87 | 0.06  | 3   | 0.6  | 0 - 5.37    | -0.05 | 35  | 2.08* | 2.03 - 7.77 | 0.13  | 1  | 3.2   | 0 - 90.84    | 0.26  | 0 | 0     | 0 - 229.49   | -0.12 |
| Chronic Myeloid Leukemia                 | 1   | 0.79   | 0.53 - 3.14  | -0.01 | 3   | 1.79 | 0.12 - 1.75 | 0.03  | 8   | 1.62  | 1.45 - 2.89 | 0.02  | 0  | 0     | 0.08 - 17.82 | -0.03 | 0 | 0     | 0 - 29.79    | -0.03 |
| Mesothelioma                             | 13  | 0.82   | 0.02 - 4.41  | -0.1  | 13  | 1.35 | 0.37 - 5.23 | 0.09  | 14  | 0.91  | 0.7 - 3.19  | -0.01 | 2  | 4.05  | 0 - 50.64    | 0.56  | 1 | 4.96  | 0 - 115.61   | 0.75  |
| Kaposi Sarcoma                           | 15  | 1.38   | 0.44 - 1.4   | 0.14  | 11  | 0.71 | 0.72 - 2.32 | -0.12 | 124 | 2.09* | 0.5 - 1.53  | 0.48  | 0  | 0     | 0.49 - 14.62 | -0.36 | 2 | 5.11  | 0.13 - 27.66 | 1.51  |
| Miscellaneous                            |     |        | 0.77 - 2.27  |       |     |      | 0.35 - 1.26 |       |     |       | 1.74 - 2.49 |       |    |       | 0 - 3.8      |       |   |       | 0.62 - 18.46 |       |

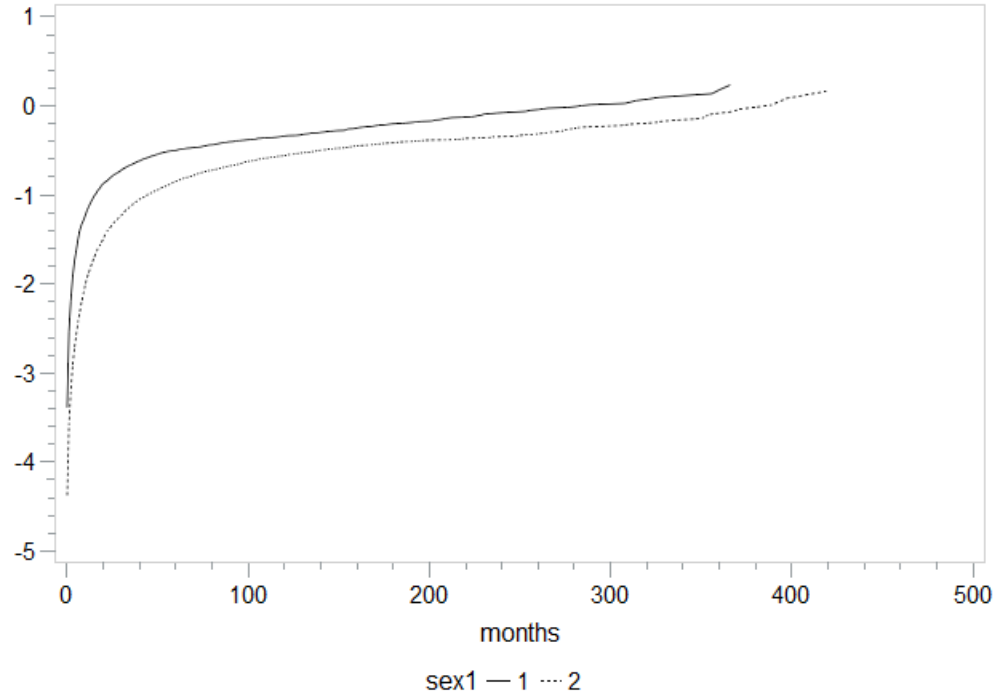
### log[-log S(t)] plots – Aim 3

#### log[-log S(t)] plot of Age at 1<sup>st</sup> Cancer Diagnosis



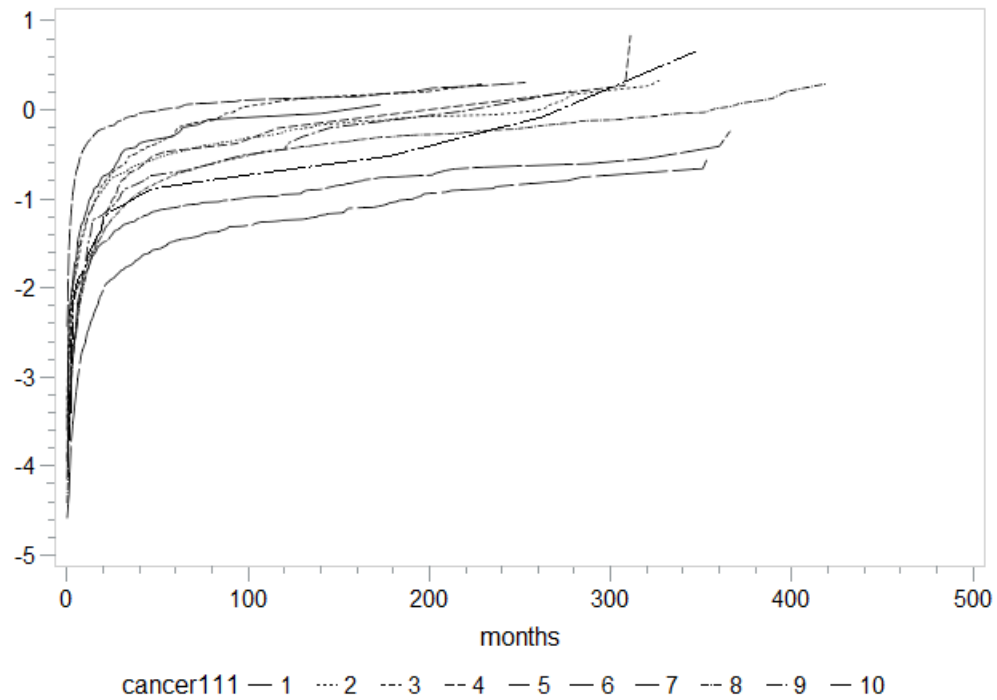
### log[-log S(t)] plot of Sex

Log of Negative Log of SURVIVAL

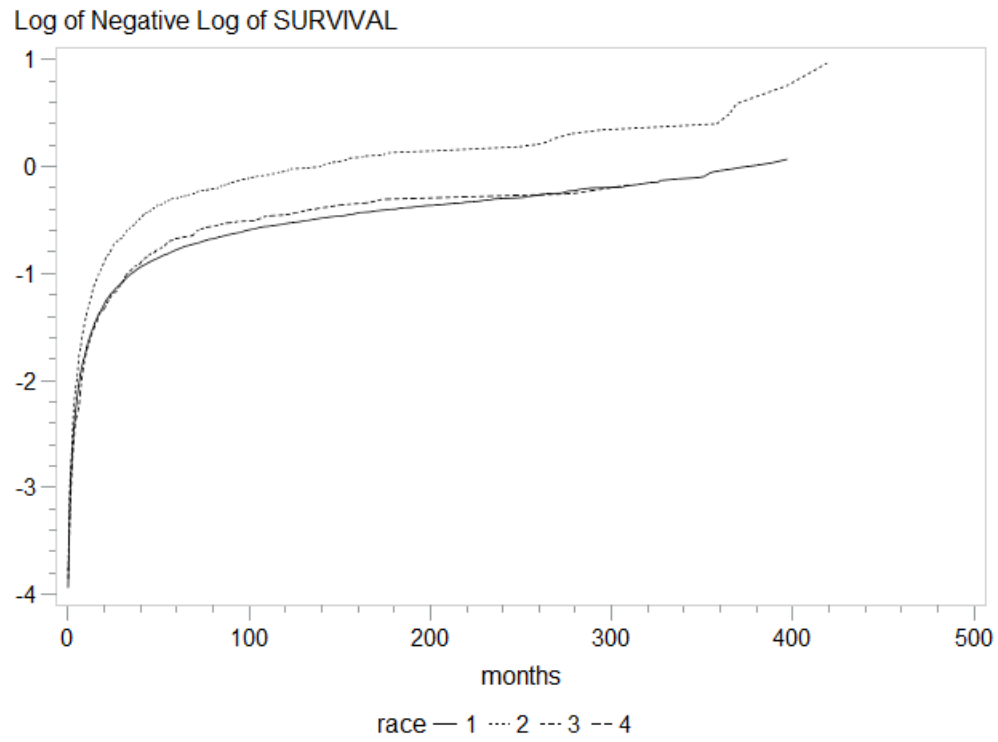


### log[-log S(t)] plot of Type of 1<sup>st</sup> Cancer

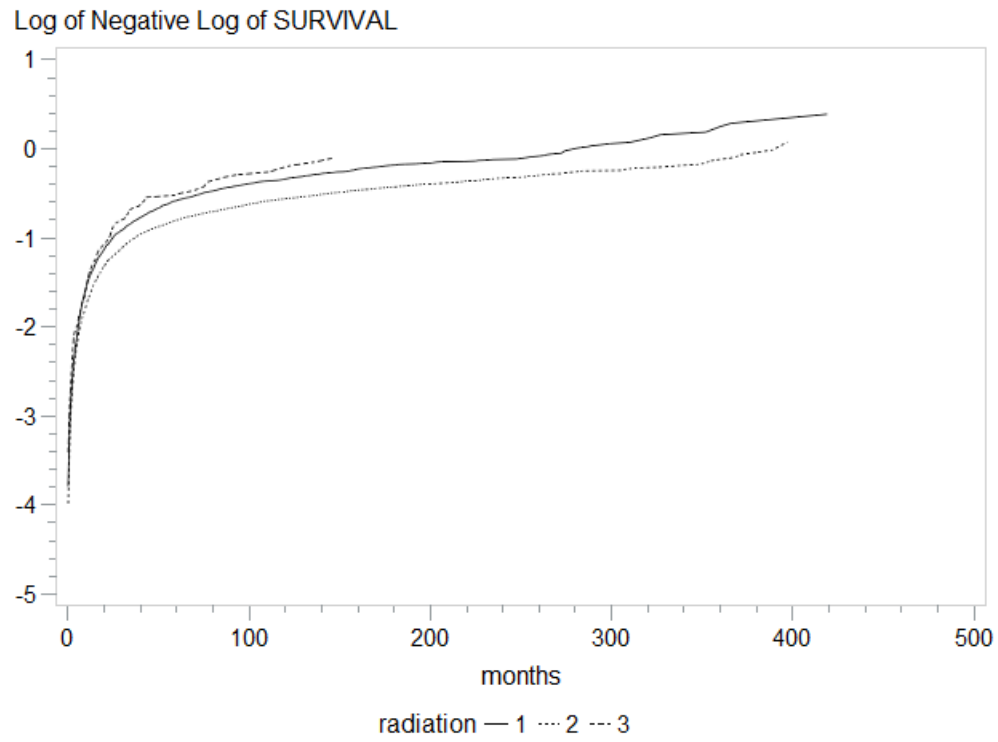
Log of Negative Log of SURVIVAL



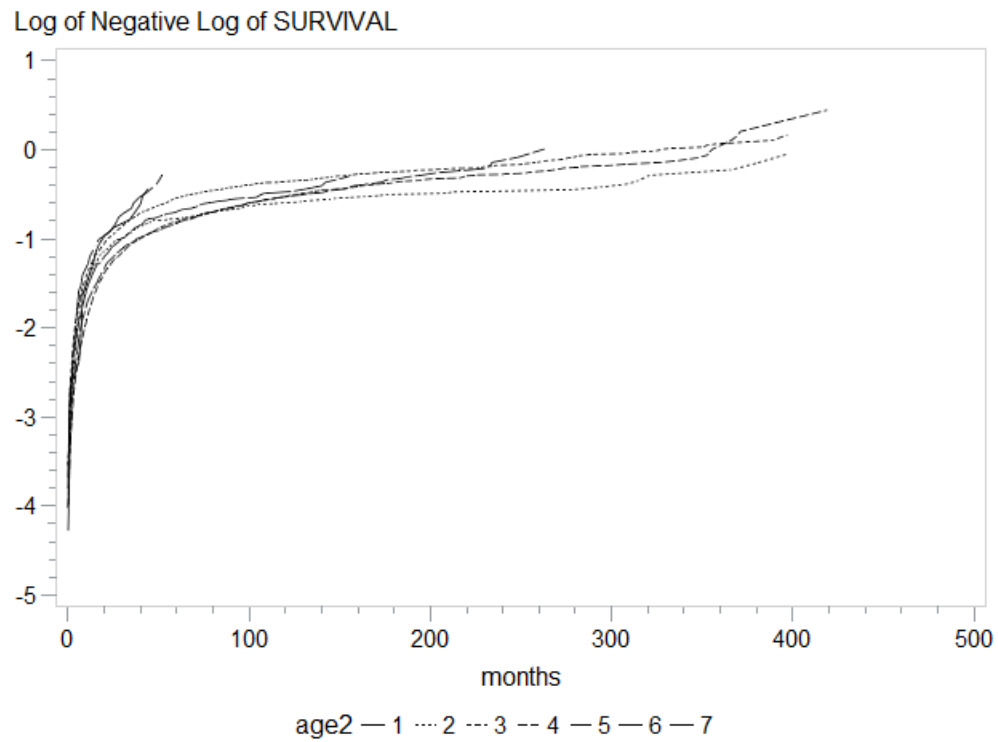
### log[-log S(t)] plot of Race



### log[-log S(t)] plot of Radiation

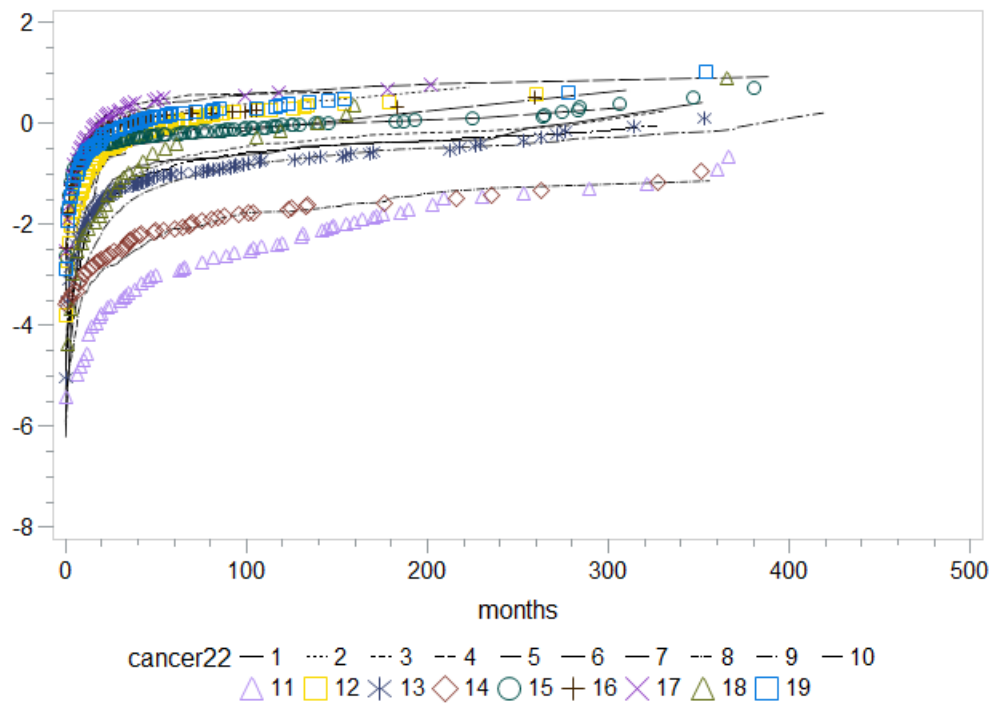


### log[-log S(t)] plot of Age at 2<sup>nd</sup> Cancer Diagnosis



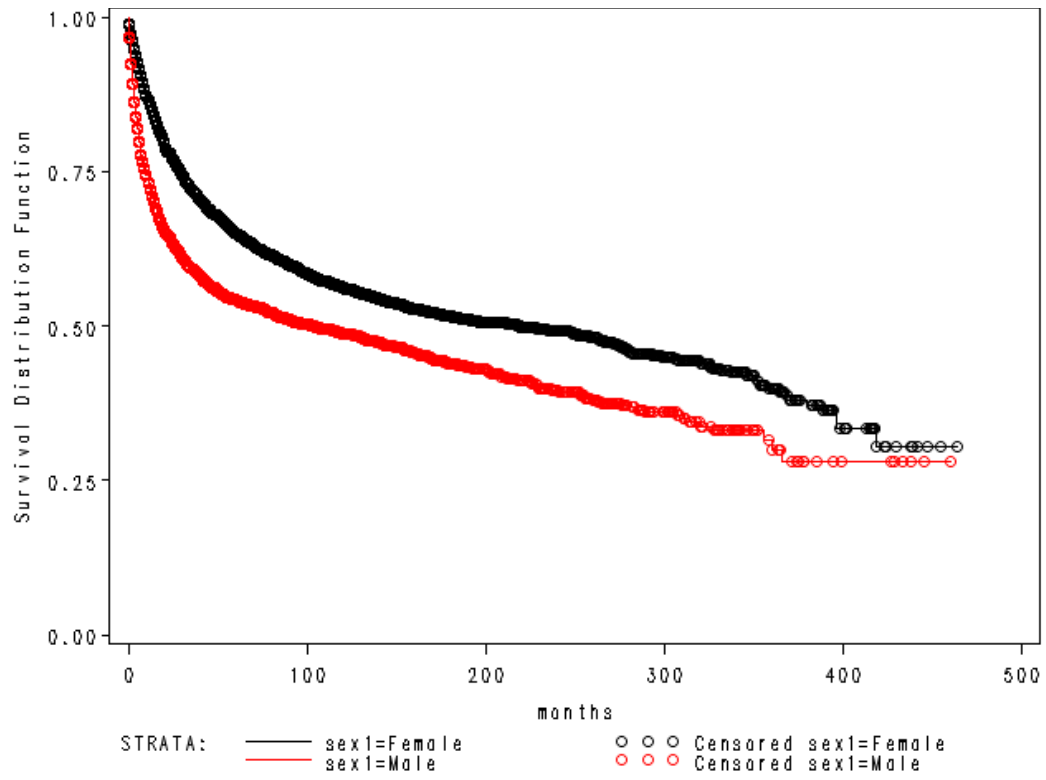
## log[-log S(t)] plot of Type of 2<sup>nd</sup> Cancer

Log of Negative Log of SURVIVAL

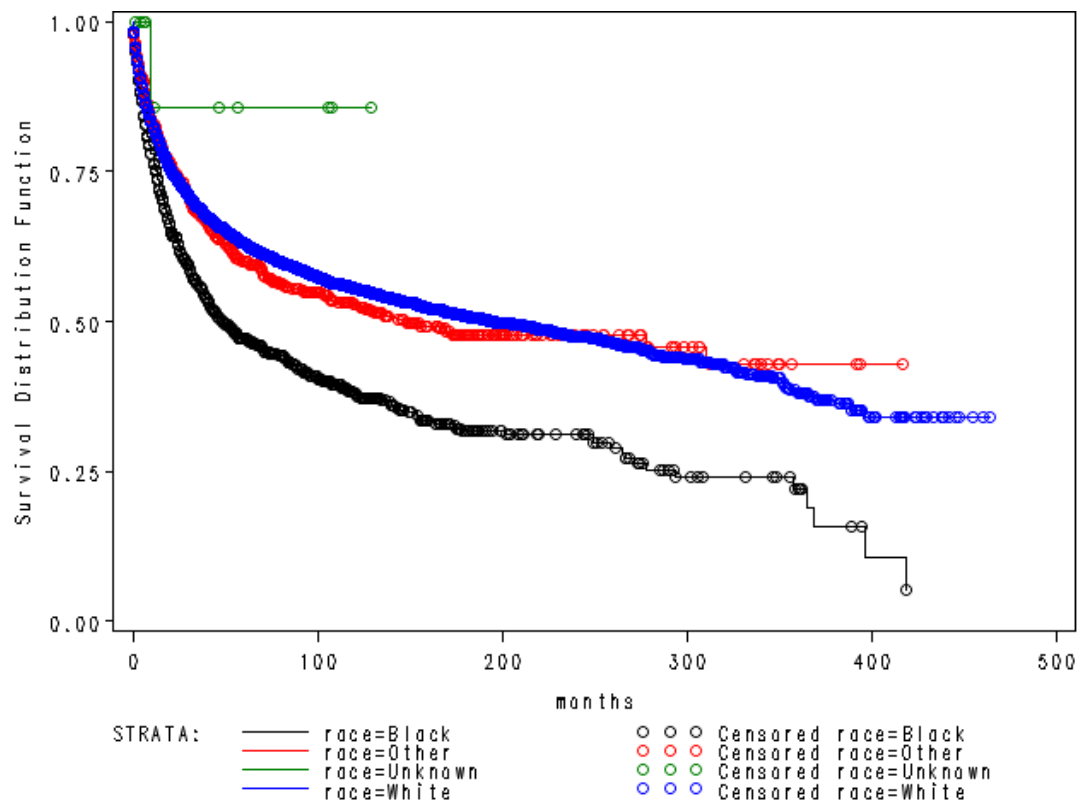


### Kaplan Meier Survival Curves – Aim 3

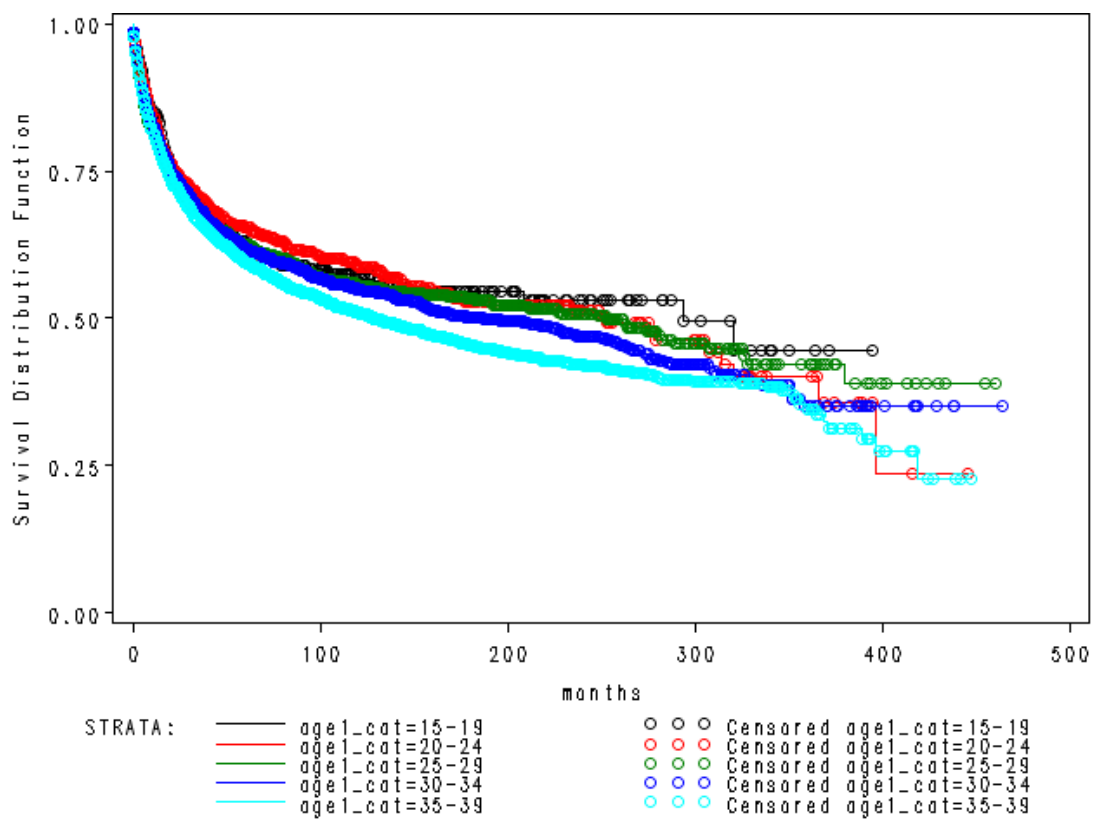
Survival by Sex



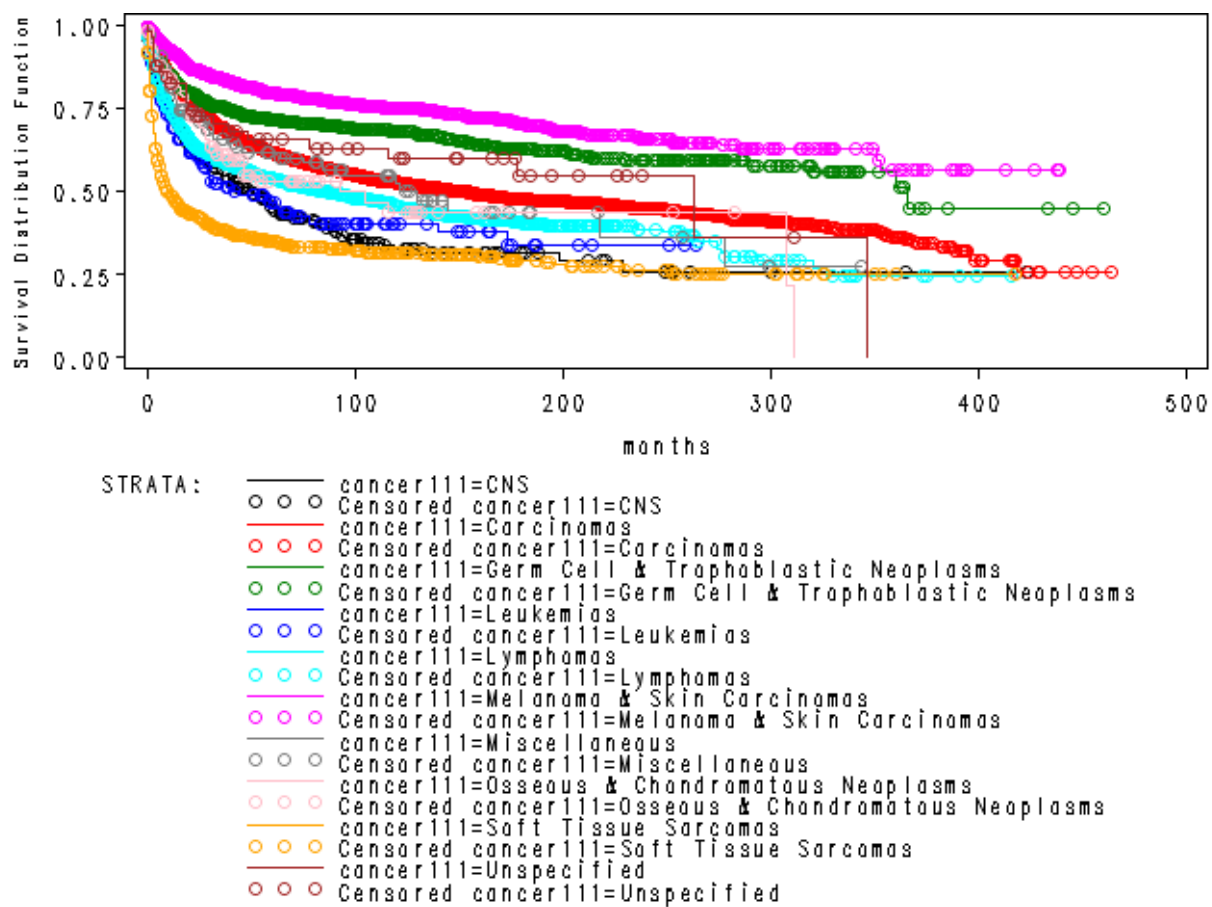
## Survival by Race



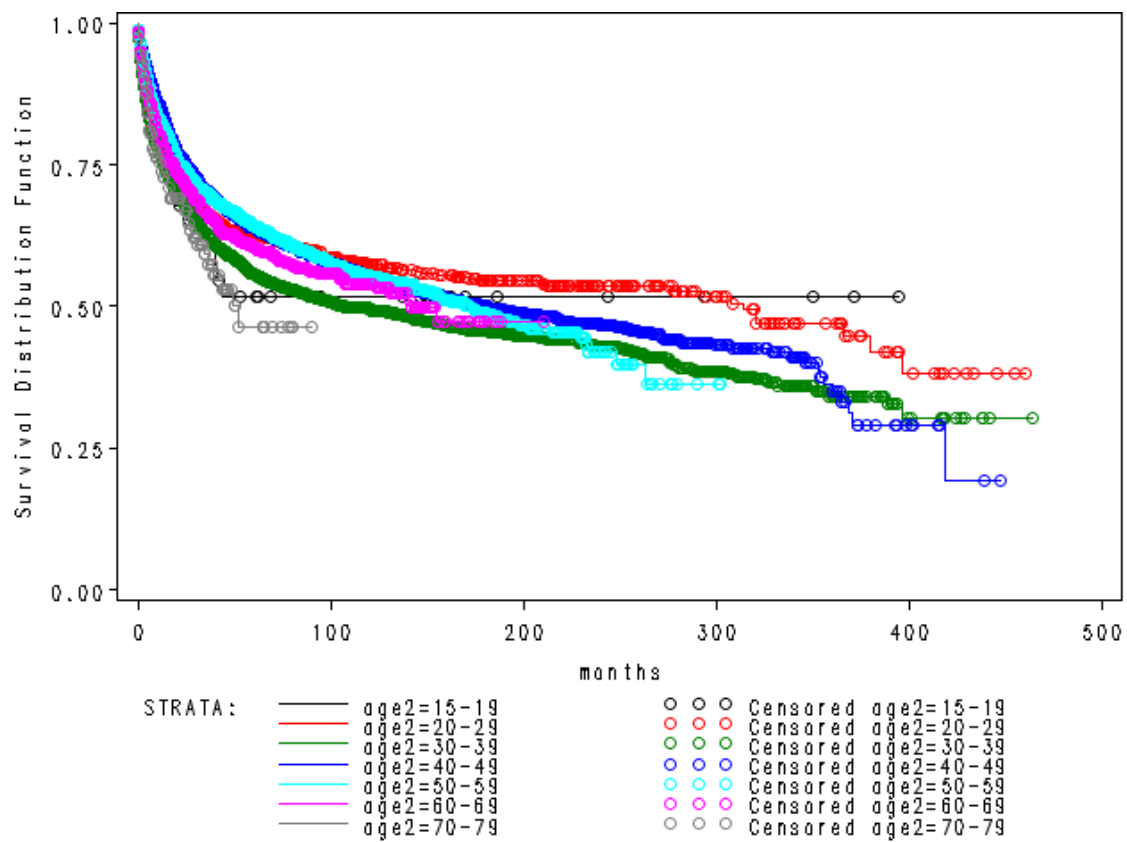
## Survival by Age at 1<sup>st</sup> Cancer Diagnosis



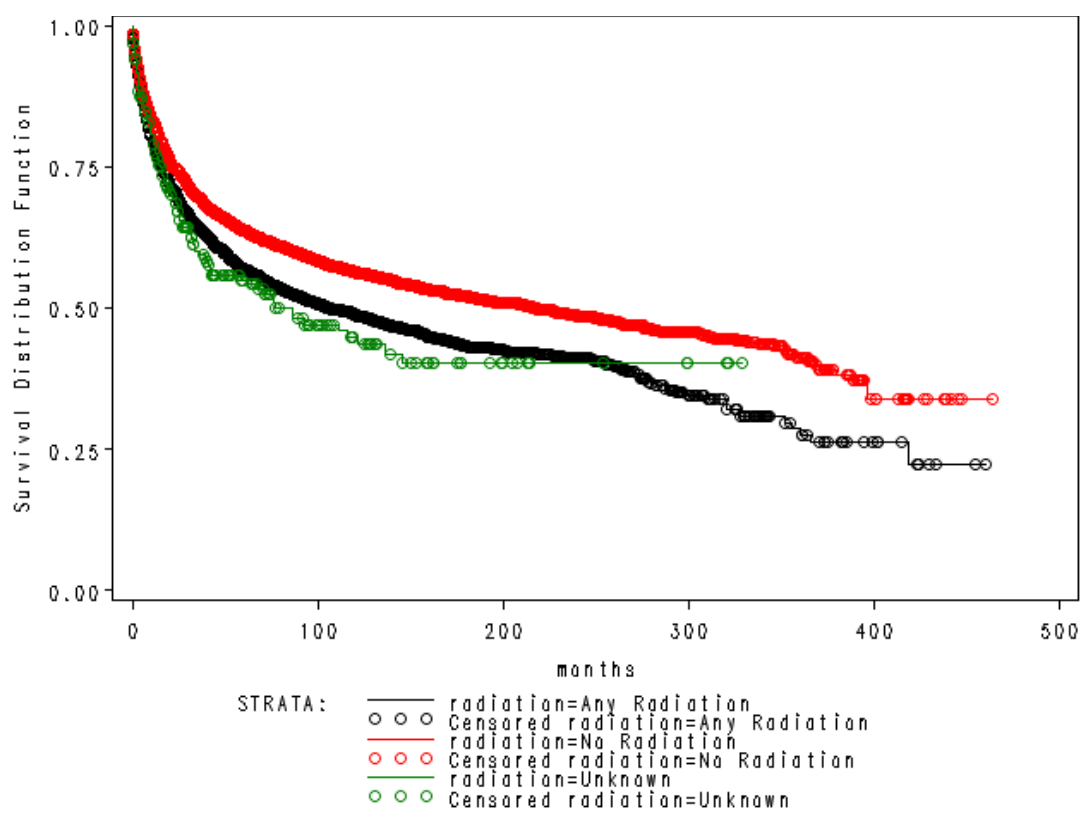
## Survival by Type of 1<sup>st</sup> Cancer



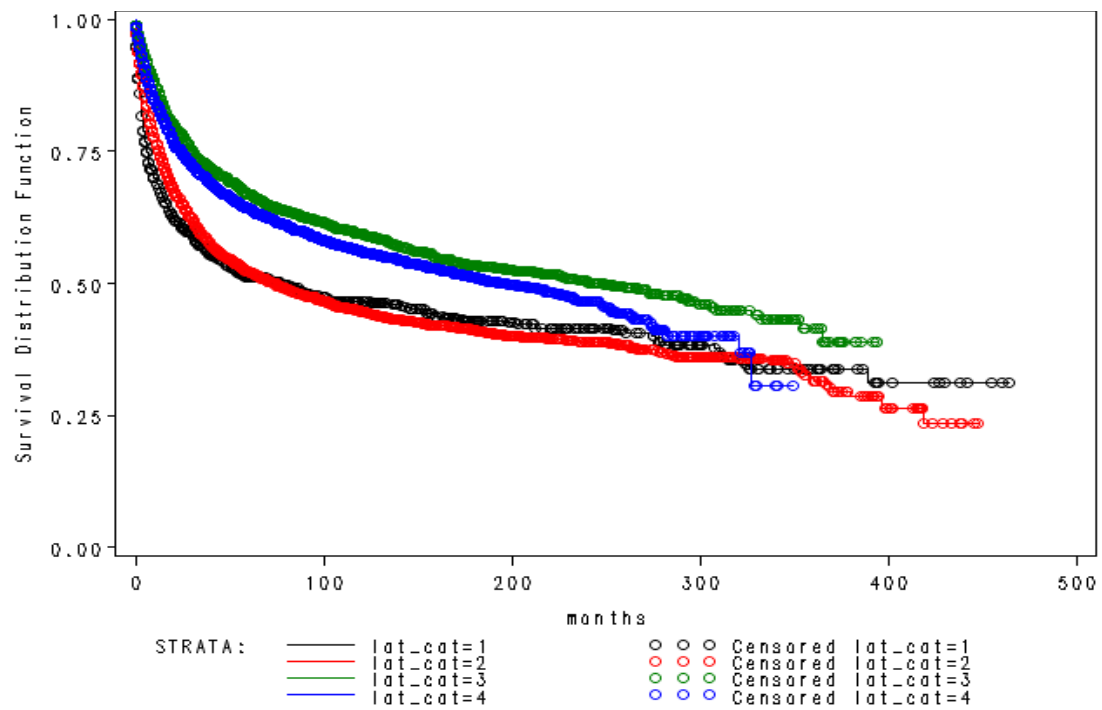
## Survival by Age at 2<sup>nd</sup> Cancer Diagnosis



## Survival by Radiation Treatment Status



# Survival by Time from 1<sup>st</sup> to 2<sup>nd</sup> Cancer Diagnosis



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