NONCANCER MORTALITY AMONG ADOLESCENTS AND YOUNG ADULTS WITH CANCER

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ABSTRACT

Chelsea Anderson: Noncancer mortality among adolescents and young adults with cancer
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Background: As a result of cancer treatment-related exposures, cancer survivors may be at elevated risk for several noncancer conditions. We used data from the Surveillance, Epidemiology and End Results (SEER) program to examine patterns of noncancer mortality among adolescents and young adults (AYAs, ages 15-39 years) with cancer. **Methods:** In aim 1, we identified 235,542 patients diagnosed with cancer at ages 15-39 during 1973-2015 in the SEER 9 database. Rates of mortality from noncancer causes among AYAs with cancer were compared to rates in the general U.S. population using standardized mortality ratios (SMRs). In aim 2, we identified 242,940 women and 158,347 men diagnosed with AYA cancer during 1985-2015 in the SEER 18 database. Multivariable-adjusted hazard ratios (HR) were used to examine disparities in mortality from all noncancer causes, cardiovascular diseases (CVD) and infectious diseases (ID) according to race/ethnicity, geographic region, and county-level socioeconomic characteristics; analyses were stratified by sex. **Results:** *Aim 1:* A total of 12,948 deaths from noncancer causes occurred over 3.1 million total person-years. Overall, noncancer mortality was significantly increased among AYAs with cancer relative to the general population (SMR=1.84; 95% CI: 1.80-1.87). SMRs were particularly elevated for ID (SMR=5.13), CVD (SMR=1.55), and renal diseases (SMR=2.40). These associations persisted for more than 20 years after cancer diagnosis. Cancer types with the highest SMRs for all noncancer mortality included leukemias (SMR=5.26), Hodgkin lymphoma (SMR=3.12), non-Hodgkin lymphoma (SMR=6.33), central

nervous system tumors (SMR=3.38), head and neck cancers (SMR=2.09), and cervical/uterine cancers (SMR=2.03). *Aim 2:* All noncancer mortality was significantly increased among non-Hispanic Black AYAs (HR vs non-Hispanic White: HR_{Women}=2.31; $HR_{Men=}$2.17) and those in the South (HR vs. Northeast: HR_{Women}=1.18; HR_{Men}=1.42) or in rural counties (HR vs metro: HR_{Women}=1.74; HR_{Men}=1.57). Mortality from CVD (HR_{Women}=2.77; HR_{Men}=2.44) and ID (HR_{Women}=5.24; HR_{Men}=2.39) was also elevated among AYAs of Non-Hispanic Black race/ethnicity. **Conclusions:** AYAs with cancer have an elevated burden of mortality from noncancer causes that persists many years after cancer diagnosis, indicating the importance of comprehensive follow-up care for noncancer conditions throughout survivorship. Our analyses also highlight disparities among AYAs with cancer, and identify subgroups that may be targeted for increased medical surveillance.

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LIST OF ABBREVIATIONS

ACS	American Community Survey
AER	Absolute excess risk
ALiCCS	Adult Life after Childhood Cancer in Scandinavia
ALL	Acute lymphocytic leukemia
AYA	Adolescents and young adults
BRFSS	Behavioral Risk Factor Surveillance System
CCSS	Childhood Cancer Survivor Study
CHF	Congestive heart failure
CI	Confidence interval
CNS	Central nervous system
CVD	Cardiovascular disease
FIPS	Federal Information Processing Standards
GI	Gastrointestinal
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
ICD-O-3	International Classification of Diseases for Oncology, third edition
ID	Infectious disease
IRR	Incidence rate ratio
KPSC	Kaiser Permanente Southern California

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
RR	Rate ratio
SMR	Standardized mortality ratio
US	United States
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

Adolescents and young adults (AYAs) with cancer represent an understudied patient group in the United States (U.S.), falling between the childhood and older adult cancer patients who are more often the focus of cancer survivorship research. The National Cancer Institute defines AYAs with cancer as those diagnosed between the ages of 15 and 39 years.[1] Though a heterogenous group within themselves, AYAs with cancer are distinguished from childhood and older adult cancer patients in their cancer type distribution, disease and host biology, patterns of treatment, and psychosocial and other patient characteristics,[2] all of which may contribute to a unique risk profile for both short- and long-term health outcomes among AYA cancer patients and survivors.

A number of cancer treatments may increase risk of morbidity and mortality from noncancer causes among individuals with cancer relative to the general population. Perhaps most notoriously, many chemotherapeutic agents have immunosuppressive and/or cardiotoxic properties, predisposing patients to acute or chronic treatment-related complications from infection or heart disease. However, documented adverse effects of chemotherapy, as well as radiation and other anti-cancer therapies, are even more wide-ranging, with the potential to impact function of nearly all organ systems. While excess mortality from cardiovascular, infectious, and other noncancer causes has been well-studied in cancer patients diagnosed as children, there remains a paucity of evidence specific to those diagnosed as AYAs. For many AYAs, particularly those diagnosed at the older end of the age range, mortality estimates for

childhood cancer survivors are unlikely to adequately reflect their risk, making this a critical gap in the current evidence base.

The Surveillance, Epidemiology, and End Results (SEER) Program represents the largest source of population-based cancer information in the U.S. In addition to cancer incidence and cancer-specific mortality data, SEER registries also collect death certificate information to record noncancer causes of death among individuals with a cancer diagnosis. With active, long-term follow-up of patients diagnosed as early as 1973, the SEER database is the only existing data source in the U.S. with a sufficient sample size and length of follow-up to examine noncancer mortality among AYA cancer patients and survivors. This research utilized SEER data to compare mortality rates from noncancer causes between AYAs with cancer and the general population. Within the cohort of AYA cancer patients, we also estimated the cumulative incidence of noncancer mortality according to patient characteristics, with a focus on potential disparities related to race, sex, county-level socioeconomic indicators, rural-urban continuum, and geographic region. Ultimately this research may provide AYA-specific information on the risk of death from noncancer causes after a cancer diagnosis, and may aide patients and providers in developing appropriate plans for follow-up and survivorship care.

CHAPTER 2. REVIEW OF THE LITERATURE

2.1. Background

2.1.1. Descriptive epidemiology of cancer in AYAs

More than 70,000 AYAs are diagnosed with invasive cancer each year in the U.S., representing about 4% of all new cases,[2] and approximately seven times as many diagnoses as in children younger than 15 years.[3, 4] In recent decades, overall cancer incidence in AYAs in the U.S. has been slowly increasing, though patterns vary by cancer type, and the increase overall is largely driven by recent increases in thyroid cancer diagnoses.[5] The most common cancer types diagnosed across the AYA age range differ markedly from those most commonly diagnosed among children and older adults. In AYAs, thyroid cancers are most common overall,[6] though leukemia and lymphoma are most frequent among 15-24 year-olds, and breast cancer and melanoma occur most often in 25-39 year-olds.[7] Testicular cancer and bone sarcomas, including osteosarcoma and Ewing sarcoma, peak in incidence among AYAs,[5] and thyroid cancer in females also starts to become more common in this age group.[7] In total, the incidence of cancer in AYAs is slightly higher among females than males,[2] largely due to breast and thyroid cancers at the upper end of the AYA age spectrum. Across racial/ethnic groups, cancer incidence in AYAs is highest in non-Hispanic whites, and lowest in American Indians/Alaska Natives.[1]

Five-year relative survival among all AYAs diagnosed with cancer in the U.S. has been increasing steadily since the 1970s, from less than 70% among those diagnosed in 1975 to over 80% in those diagnosed in 2008.[5] However, recent reports have indicated that these survival

gains in AYAs have lagged behind those observed in childhood and older adult cancer patients.[8] Among AYAs, there are notable differences in five-year relative survival across the more common cancer sites, ranging from approximately 56% among those with carcinomas of the gastrointestinal (GI) tract (70% for colon and rectum; <40% for stomach, pancreas, and liver) and 64% among those diagnosed with leukemia, to nearly 100% among those diagnosed with thyroid cancer.[9] Thus even for cancers with the poorest prognosis on average, many AYA patients will go on to survive at least five years beyond their original diagnosis. Consequently, the long-term health of AYA cancer survivors, including late effects of cancer treatment on noncancer morbidity and associated mortality, has become a priority area for research.

2.1.2 Unique characteristics of the AYA cancer patient population

AYAs have been defined as a distinct cancer patient population due to well-recognized differences from children and older adults in disease and host biology, patient characteristics and psychosocial aspects, and patterns of treatment. All of these factors have the potential to impact survival from both cancer and noncancer causes, supporting the study of long-term health outcomes in AYA cancer survivors as a group separate from childhood or older adult survivors.

Disease and host biology

It has been suggested that the slower progress in improving survival among AYAs with cancer relative to that in other age groups is partially attributable to a lack of appreciation for unique aspects of cancer biology in AYAs.[10] In addition to differences in the cancer type distribution compared to children and older adults, there may also be distinct biological features of AYA cancer within individual cancer types and within the host,[10] leading to distinct patterns of treatment, and potentially, distinct long-term health outcomes in survivors.

Noteworthy examples of cancers types with a potentially unique biology in AYAs include breast cancer, colorectal cancer, and acute lymphocytic leukemia. Breast cancers diagnosed among younger women, including AYAs, tend to be less-hormone sensitive, of a higher grade, and with greater lymph nodal involvement than those diagnosed among older women. Tumors lacking receptors for estrogen, progesterone, and HER2, known as triple-negative tumors, are more common in younger women, and are associated with fewer treatment options and poorer prognosis than other tumor subtypes.[10-12] Other gene expression signatures, such as enriched growth factor signaling, are more common in younger women, when accounting for subtype distribution.[13, 14] Even within hormone-receptor positive tumor subtypes, younger women may have poorer survival than older women,[15] suggesting a more aggressive tumor biology. These differences contribute to the more aggressive treatment typically received by younger women, which may lead to different treatment-related sequelae and patterns of noncancer morbidity and mortality than those reported in older women.

While the incidence of colorectal cancer in older adults has decreased in the past 20 years, an increase in incidence has been observed in AYAs, with the obesity epidemic and lack of routine screening in younger adults likely contributing to this trend.[16] Distinguishing features of colorectal cancers in AYAs include microsatellite instability and a higher incidence of familial adenomatous polyposis and hereditary non-polyposis colon cancer, the heritable types of colorectal cancer. The non-inherited forms of sporadic colorectal cancer also tend to differ in AYAs, with a lower likelihood of KRAS mutations and other mutations more typically seen in older patients. The differences may affect the relative efficacy of specific anti-cancer therapies in younger patients compared to older adults.[10, 17] As described for breast cancer patients, the distinguishing characteristics of colorectal cancer biology in AYA patients may necessitate

different treatment strategies, which may in turn contribute to different long-term risk profiles for adverse late effects.

Acute lymphocytic leukemia (ALL) is most common in children and AYAs, but may present with different biological characteristics in the two groups. Characteristics which are more common in AYAs, and associated with poorer prognosis, include L2 morphology, pro-T cell immunophenotype, the t(9,22) BCR-ABL translocation, and the Hox^+ subtype. The TEL-AML1 chromosomal translocation, associated with favorable prognosis,[18] is significantly less common in AYAs.[5, 10] On the other hand, certain growth-regulating kinase tumor suppressor genes are more methylated in adult patients than in children,[19] and a potential target for anti-cancer drugs that act on hypermethylation sites. Newer therapies that are utilized more commonly in adults may have long-term health implications that differentiate AYA from childhood cancer patients.

Along with these distinguishing features of cancer biology, various aspects of host biology may also distinguish AYAs from younger and older patient groups. Physiological changes, particularly those related to hormonal changes, are an important consideration in the treatment and outcomes of AYAs, with the potential to affect drug metabolism and clearance, toxicities, and treatment efficacy.[10] Other host biological differences, such as a higher prevalence of obesity in AYAs compared with younger patients, and changes in body composition, can also contribute to worse outcomes in AYAs,[20] including higher treatment-related mortality.[21] In contrast, compared with older adults, AYAs have greater hematopoietic, renal, and hepatic capacity, and can therefore generally tolerate higher doses of therapies that may have associated late adverse effects.

Patterns of treatment

While children diagnosed with cancer in the U.S. are often treated in specialized pediatric cancer centers, AYAs are more likely to be treated in community-based settings than in academic centers, which can limit access to clinical trials and influence the treatment protocols used.[2, 22] For some cancers in AYAs, such as ALL and rhabdomyosarcoma, treatment with pediatric protocols has been associated with superior outcomes. For others, such as Hodgkin and non-Hodgkin lymphoma, the evidence does not suggest a benefit of pediatric over adult treatment protocols.[22] As noted previously, the distinctive biology of many cancers in AYAs may necessitate distinct treatment strategies from those used in other age groups. Consequently, it is critical that AYAs are seen by oncologists with specialized expertise and experience in treating cancers common in this age group. In general, AYAs have fewer comorbidities than older adult patients and can thus tolerate more intensive treatment regimens, and clinical guidelines from the National Comprehensive Cancer Network (NCCN) suggest that, though approaches will vary by diagnosis, most AYA without contraindications should be treated with aggressive therapy.[22] These aggressive treatment approaches may prove beneficial for improving survival from the original cancer diagnosis, but may also be associated with adverse early and late effects that contribute to mortality from noncancer causes.

Patient characteristics and psychosocial aspects

Individuals with cancer as AYAs may face special challenges related to insurance status and healthcare access, financial security before and after treatment, and the need for age-appropriate mental health and supportive care services. Historically, health insurance rates are at their lowest during young adulthood,[23] and a lack of coverage may be especially concerning for individuals with a cancer history who require long-term medical surveillance. Among younger cancer survivors, a lack of health insurance has been associated with a lower likelihood

of receiving the recommended follow-up and survivorship care,[24-27] which may be critical for early detection of recurrences, second malignancies, and late effects of treatment. Being uninsured has also been associated with higher all-cause mortality in cancer patients diagnosed as AYAs.[28] Furthermore, findings from the Behavioral Risk Factor Surveillance System (BRFSS), a nationally representative survey, have suggested that, although the proportion uninsured may be similar between survivors of cancer and controls, cancer survivors in the AYA age group may be more likely to forgo medical care due to costs, even for those with health insurance.[29] This is likely attributable to greater care needs and the associated costs for individuals with a cancer history. It is unclear how recent healthcare legislation changes will affect care among young people with medical conditions such as a cancer diagnosis. However, it remains likely that loss of health insurance coverage, either through loss of employment or aging out of parents' insurance, will be a critical issue for many young adults. For AYA cancer survivors, forgoing care due to costs, lack of insurance, or both, could negatively influence long-term survival from both cancer and noncancer causes.

In addition to insurance-related issues, AYAs with cancer may also experience greater concerns surrounding personal finances and employment. A cancer diagnosis and treatment can be an impediment in the transition to financial independence associated with young adulthood, presenting challenges in the pursuit of higher education and gainful employment. Those at the older end of the AYA age spectrum who have already established their career may face lost productivity if they become unable to work during or after cancer treatment, and cancer-related financial problems are reportedly more common among individuals diagnosed before age 40 than among those diagnosed at older ages.[30] Cancer-related financial problems have in turn been associated with a greater likelihood of delaying or forgoing medical care,[30] which may include

long-term surveillance for second cancer events and late effects of treatment. A 2012 online LIVESTRONG survey found that most AYA cancer patients had to take time off from work or school, switch to part-time work, or find a less demanding job, and many reported that their overall productivity at work was adversely affected by their cancer diagnosis.[3] Results from the 2009 BRFSS suggest that individuals with an AYA cancer history are more likely to be out of work or unable to work than their age-matched peers without a history of cancer.[31] Such interruptions or transitions in employment may strain personal finances, with the potential for long-lasting effects on health and well-being.

Finally, having cancer as an AYA can be a major life stressor in other aspects of life, bringing with it the need for age-appropriate psychological and social support. Late adolescence and early adulthood are critical periods for establishment of personal identity and independence, which may be disrupted by the need to rely on others during cancer treatment and recovery.[32] Other possible life disruptions may include those related to peer relations, family dynamics, and self-esteem, as well as future plans.[3] Furthermore, emotional development may not yet be complete in some AYAs,[33] who may benefit from psychological services to learn adequate coping strategies. AYAs with cancer may also have unique information and service needs related to fertility, body-image, financial issues, and mental health, which may require additional intervention. Prior reports have shown that as many as two-thirds of AYAs have unmet information needs related to their cancer,[34, 35] and that greater unmet information need may be associated with poorer mental and physical health-related quality of life.[34] The life disruptions and unmet information needs that accompany an AYA cancer diagnosis may be barriers to receipt of recommended follow-up care,[36] and may continue to exert an influence on psychological and physical health in the years following treatment.

2.1.3. Potential adverse effects of cancer treatment in AYAs

Established negative sequelae of cancer treatment include both short-term and long-term adverse effects, many of which may precipitate early death from noncancer causes. These effects include, among others, infectious, cardiovascular, pulmonary, renal, and gastrointestinal complications.[2] However, the preponderance of evidence to date on adverse effects has come from studies of cancer survivors diagnosed as children or older adults, rather than AYAs. For example, much of the evidence used to guide the assessment of long-term outcomes in AYAs comes from the reports from the Childhood Cancer Survivor Study (CCSS),[37] comprised of childhood and adolescent cancer survivors diagnosed before age 21. Given that age at treatment modifies the risk of several late effects,[22] there is a critical need to consider these outcomes among AYAs as a distinct group. A specific lack of evidence on long-term treatment-related effects in the AYA population has been noted in NCCN guidelines, particularly for cancers typically diagnosed at the upper end of the AYA age range.[22] The following sections describe possible adverse effects of cancer treatments on various organ systems that may be relevant for assessing noncancer mortality risk among AYAs with cancer.

Cardiovascular effects

Though the precise incidence of any cardiac injury following cancer therapy remains unknown,[38] a number of modern cancer treatments have been linked to acute and/or chronic cardiotoxicities (Table 1). These toxicities range from asymptomatic, temporary left ventricular ejection fraction decline and electrocardiographic changes, to more serious conditions such as congestive heart failure.[39] Notably, the likelihood and severity of cardiotoxic effects after certain cancer therapies may be modified by age,[40] though little research has investigated long-term cardiovascular outcomes specifically among AYA cancer survivors.

Systemic antineoplastic agents, including chemotherapeutic agents and molecular targeted therapies, can adversely impact cardiovascular function through either direct effects on the heart itself or peripheral effects on hemodynamics (i.e. hypertension or thrombotic events).[39] Metabolic abnormalities may also be an indirect effect of some systemic anticancer therapies, with a subsequent increase in risk for later cardiac events.[42] Anthracyclines, such as doxorubicin, epirubicin, and daunomycin, are the most common chemotherapeutic agents

Table 1.1 Cardiotoxicities associated with cancer therapies that may be used in AYA patients*

Class	Drugs	Cardiac toxicity	Associated cancer types common in AYAs
Radiation	--	Coronary artery disease, acute pericarditis, myocarditis, CHF, valvular disease, conduction disease	Breast, cervix, colorectal, thyroid, leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma
Chemotherapy			
Anthracyclines	Doxorubicin, epirubicin, idarubicin, Daunorubicin	Left ventricular dysfunction, CHF, pericarditis and/or myocarditis	Leukemia, breast, Hodgkin lymphoma, Non-Hodgkin lymphoma, thyroid, soft tissue and bone sarcomas
Taxanes	Paclitaxel, Docetaxel	Left ventricular dysfunction, cardiac ischemia, QT prolongation, bradycardia	Breast
Alkylating Agents	Cyclophosphamide, Ifosfamide, Cisplatin	Left ventricular dysfunction, CHF, thrombosis	Leukemia, breast, Hodgkin lymphoma, Non-Hodgkin lymphoma, testicular, osteosarcoma, cervical
Antimetabolites	Capecitabine, Fluorouracil, Cytarabine	Cardiac ischemia, pericarditis, CHF	Breast, colorectal, leukemia
Monoclonal Antibodies	Trastuzumab, Pertuzumab, Bevacizumab	Left ventricular dysfunction, CHF, arterial thrombosis, angina, myocardial infarction, hypertension	Breast, cervical, colorectal
Tyrosine kinase Inhibitors	Lapatinib, Imatinib, Dasatinib, Nilotinib, Sorafenib, Sunitinib, Ponatinib	Left ventricular dysfunction, CHF, QT prolongation, cardiac ischemia, hypertension	Breast, leukemia

CHF: congestive heart failure
*Adapted from refs [39-41]

associated with cardiotoxicity. These drugs are often used in the treatment of several AYA cancers, including breast cancer, sarcomas, lymphomas, and leukemias, and are thought to act through direct damage to cardiac myocytes, leading to possible left ventricular dysfunction,

congestive heart failure, pericarditis, or myocarditis.[42] Acute cardiotoxicity following anthracycline infusion is relatively rare (<1%) across age groups and is generally reversible.[39] Both early-onset (<1 year post-treatment) and late-onset (≥1 year post-treatment) chronic progressive anthracycline-induced cardiotoxicity are more common (~2-5% of patients) and are usually irreversible. Higher doses, co-administration with other cardiotoxic agents, pre-existing cardiovascular disease (CVD), and female sex are among the risk factors for cardiotoxicities caused by anthracyclines.[43, 44] Risk is also greater with increasing age, especially over 65 years,[42] suggesting that studies of long-term cardiovascular outcomes among older adult patients may not adequately reflect the risk profile for individuals treated with anthracyclines as AYAs.

Cyclophosphamide, an alkylating chemotherapeutic agent often used in the treatment of leukemia and breast cancer, has also been associated with acute toxicities such as left ventricular dysfunction[39] and congestive heart failure.[42] Cisplatin, another alkylating agent, has been linked to acute myocardial ischemia and diastolic heart failure in adults,[45] as well as in younger patients treated for testicular cancer,[46] a cancer type most common in AYAs. Other chemotherapy drugs which may be used in AYA patients and have been associated with cardiotoxicities include taxanes (e.g. paclitaxel), antimetabolites (e.g. 5-fluorouracil), and tyrosine kinase inhibitors (e.g. imatinib), with effects ranging from arrhythmias and left ventricular dysfunction to myocardial infarction, congestive heart failure, and sudden death.[39, 42, 45] Finally, trastuzumab, a biologic therapy used to treat breast tumors that overexpress the cell surface receptor HER2, has also been shown to increase risk of left ventricular dysfunction and congestive heart failure, particularly when used concurrently with anthracycline-based chemotherapy.[39]

In addition to cardiovascular risk from systemic therapies, toxicities from chest radiation, often used to treat breast cancer or Hodgkin's lymphoma, may include coronary artery disease, valvular disease, chronic pericardial disease, arrhythmias, cardiomyopathy, or carotid artery stenosis.[47, 48] Evidence also suggests a potential increased risk of stroke among those treated with radiation to the brain and/or neck.[48] Many of these effects may manifest long after treatment, with a latent period of up to 20 years until symptoms occur.[47] With modern radiation techniques, the incidence of cardiotoxicities is lower than that observed among patients treated in earlier eras.[47]

Infectious complications

Infections in cancer patients are a major cause of morbidity and mortality, often resulting from multiple complex factors which interact to cause disease. These factors may include treatment-induced immunosuppression, in addition to potential effects of the patient's underlying immunodeficiencies and/or effects of the malignancy itself.[49-51] In patients with hematologic malignancies, the neoplasm can directly interfere with immune function as a consequence of its location within the immune system.[51] Similarly, in patients with solid malignancies, the location of the tumor itself may impede normal immune function, or may disrupt barriers that normally act to help prevent infection.[52]

Cancer therapies that may increase risk of bacterial, fungal, parasitic, and/or viral infection include radiation, systemic therapies, and invasive procedures.[50] Extensive surgery, radiation therapy, and cytotoxic chemotherapies such as anthracyclines and 5-fluorouracil, for example, can weaken innate immunity by compromising anatomical barriers that are protective against most infectious agents. Chemotherapy, in particular, is also associated with bone marrow suppression and neutropenia, predisposing patients to potentially life-threatening infections.[50,

53, 54] For patients with solid tumors receiving conventional chemotherapies, the risk of serious infectious complications is fairly low. However, hematologic cancer patients are generally considered to be at higher risk, due to treatment protocols which tend to induce more extreme and protracted neutropenia.[55] While immune system function recovers in most patients by 6-12 months after therapy, some may have infectious complications years later.[56-60] Those receiving allogenic hematopoietic stem cell transplantation are particularly at risk for infectious disease associated with chronic graft-versus-host disease and impaired immune reconstitution.[61] However, some evidence suggests that other therapies, such as total body irradiation, may also be associated with late morbidity and mortality from infectious causes.[62]

Renal effects

Several cancer therapies have been associated with renal impairment, increasing the risk of both acute toxicities and long-term dysfunction, and contributing to morbidity, reduced quality of life, and potentially even mortality. Adverse effects may include declines in glomerular filtration rate, tubular dysfunction, albuminuria, and hypertension.[63] Renal failure, though rare, may also result from exposure to cancer treatments. Among the more common causes of nephrotoxicity is treatment with alkylating agents such as ifosphamide and cisplatin, which may cause both glomerular and tubular damage.[64] While acute, subclinical manifestations of renal toxicities are often reversible, they may lead to more serious, persistent impairments in cases of more severe damage. In a study of children, adolescents, and young adult sarcoma patients treated with ifosphamide, more than one-fourth of all patients were found to have clinically significant nephrotoxicity up to 4 years after completing treatment.[65] Other studies have shown toxicities persisting up to 10 years after treatment with ifosphamide or platinum-based agents.[63, 66] In addition to these alkylating agents, other cancer treatments that may lead to acute and/or chronic nephrotoxicities include nitrosoureas, hematopoietic stem cell

transplantation, methotrexate, anti-infective drugs, immunosuppressive drugs, radiation to the kidneys, or nephrectomy.[64]

Pulmonary effects

A number of studies have reported abnormal pulmonary function in children and adults with cancer, with effects observed acutely or several years after treatment completion. Lung injury following cancer treatment may involve the lung parenchyma, conducting airways, pleura, or pulmonary circulation,[64] depending on the treatment received. The most well-studied pulmonary effects are those induced by bleomycin, a chemotherapeutic agent, and mediastinal radiation. Bleomycin is often used to treat germ cell tumors and Hodgkin lymphoma, cancer types common in AYAs, and, depending on the patient population studied, the estimated incidence of bleomycin-induced pneumonitis is as high as 46%.[47] A minority of patients (<5%) may also develop pulmonary fibrosis following receipt of bleomycin, which may prove fatal in a small proportion of cases.[64] Mediastinal radiation may result in pneumonitis in patients treated for Hodgkin lymphoma or breast cancer, though it is less common in these patients than in those with lung cancer. Radiation-related pneumonitis usually occurs 1-3 months after completing therapy and is soon completely resolved, but in some cases it may develop into progressive pulmonary fibrosis at 6-24 months after treatment.[47] Patients with hematologic malignancies may also be subject to pulmonary complications following hematopoietic stem cell transplantation, with chronic dysfunction in the form of restrictive or obstructive lung disease.[64]

Gastrointestinal and liver effects

Gastrointestinal toxicities are among the most common side effects reported by patients actively receiving antineoplastic therapy.[67] Some short-term effects, such as nausea and vomiting, are generally not life-threatening in themselves, and typically resolve soon after

treatment completion. However, others, such as diarrhea, can be severe enough to require hospitalization and, in some cases, may prove fatal.[67] In addition to acute effects, some therapies, particularly abdominal surgery and radiation, are also thought to have possible long-term consequences for the gastrointestinal tract and the liver,[67] ranging from constipation, which may adversely impact quality of life,[68] to more severe conditions such as liver cirrhosis, which may contribute to mortality.[69] These late effects, and the potential for excess mortality from gastrointestinal and liver diseases, have not been well-studied among cancer survivors diagnosed as AYAs.

2.2. Critical review of the literature

The following sections summarize studies that have investigated excess morbidity and/or mortality from noncancer conditions among AYA cancer survivors, highlighting gaps in the current evidence base on noncancer mortality risk in this population.

2.2.1. Cardiovascular outcomes

Previous studies in the U.S., Canada, and Europe have reported an increased risk of CVD and its major risk factors among AYA cancer survivors compared to individuals without cancer, which is likely due, at least in part, to late effects of cardiotoxic cancer therapies. Self-reported data from the 2009 BRFSS suggested that, compared to age-matched respondents without a cancer history, those with a cancer diagnosis at ages 15-29 years had a higher prevalence of cardiovascular disease (14% vs 7%), hypertension (35% vs 29%), and diabetes (12% vs 9%).[31] Similarly, in a study of 5,673 two-year survivors of AYA cancer diagnosed between 1998 and 2009 at Kaiser Permanente Southern California (KPSC), Chao et al. reported a greater than two-fold risk of developing CVD relative to a comparison cohort of age-matched patients without cancer (incidence rate ratio [IRR]: 2.37; 95% CI: 1.93, 2.93).[70] For their study, CVD was

defined exclusively by clinical events, including myocardial infarction, congestive heart failure, and stroke. The excess risk was greatest among survivors of leukemia (IRR: 4.23; 95% CI: 1.73, 10.31) and breast cancer (IRR: 3.63; 95% CI: 2.41, 5.47). AYA cancer survivors also had a higher incidence of diabetes (IRR: 1.48; 95% CI: 1.31, 1.66) and dyslipidemia (IRR: 1.17; 95% CI: 1.08, 1.27), but not hypertension, than the comparison group. The number of events was insufficient to report cancer site-specific estimates for sites other than breast, lymphoma, leukemia, melanoma, and thyroid, and relative risks for CVD-specific mortality for AYA cancer survivors versus the comparison group were not investigated.

Recent studies from Denmark have similarly documented higher rates of hospitalization for cardiovascular disease among AYA cancer survivors identified from the national cancer registry compared to age-matched controls selected from a national population registry.[71, 72] Rugbjerg et al. reported a rate ratio (RR) of 1.30 (95% CI: 1.28, 1.33) for first hospitalization for cardiovascular disease for AYA cancer survivors versus comparisons, which corresponded to an absolute excess risk (AER) of 400 and 350 extra cases per 100,000 person-years among survivors for those with an age at discharge of 20 to 59 and 60 to 79 years, respectively.[72] In a separate report from Denmark, the hospitalization rate ratio for all diseases of the circulatory system, comparing five-year AYA cancer survivors to age-matched comparisons, was 1.28 (95% CI: 1.25, 1.31), and was of slightly greater magnitude among men (RR=1.34; 95% CI: 1.29, 1.39) than among women (RR= 1.24; 95% CI: 1.21, 1.28). Subgroup analyses suggested that the rate ratio was greatest for AYAs diagnosed with Hodgkin lymphoma (RR=2.3; 95% CI: 2.1, 2.5), corresponding to an AER of 1079 cases per 100,000 person-years.[71] As in the KPSC study,[70] these studies did not include estimates of cause-specific mortality, though they

suggest that the risk of life-threatening cardiovascular conditions, such as those requiring hospitalization, is elevated among AYA cancer survivors relative to individuals without cancer.

In a study from Finland, Kero et al. compared rates of hospitalization for cardiovascular morbidities in five-year survivors of childhood and young adult cancers (diagnosed at ages 0-34 years) with those of siblings.[73] In general, magnitudes of association were greater for those diagnosed at ages 0-19 years than for those diagnosed at ages 20-34 years. However, hazard ratios in the 20-34 year age group for survivors compared to siblings were significantly elevated for cardiomyopathy/cardiac insufficiency (HR=3.6; 95% CI: 2.8-4.6), atherosclerosis/brain vascular thrombosis (HR=1.7; 95% CI: 1.4-2.0), myocardial infarction/cardiac ischemia (HR=1.8; 95% CI: 1.5-2.1), and cardiac arrhythmia (HR=1.4; 95% CI: 1.2, 1.7). Though numbers were small within categories of cancer type, the excess of these outcomes seemed most pronounced among survivors of Hodgkin lymphoma, non-Hodgkin lymphoma, and testicular cancer. The differences in relative risk for those diagnosed at younger versus older ages in this study suggest the importance of quantifying long-term morbidity and mortality outcomes in AYA cancer survivors as a group distinct from childhood cancer survivors.

A recent study from British Columbia focused on hospitalization rates for various morbidities among five-year AYA cancer survivors diagnosed between the ages of 20 and 24 years from 1981 to 1999.[74] The most common cancer type in their sample was lymphoma, followed by carcinomas, melanoma, and germ cell tumors. Overall, the rate of hospitalization for diseases of the circulatory system among survivors was nearly twice that among age-matched controls (IRR= 1.90; 95% CI: 1.33, 2.72), with 4.1 and 2.1 events per 1000 person-years in survivors and controls, respectively.

Though lacking general population rates for comparison, Keegan et al. recently reported rates of CVD, defined as hospitalization or death from cardiovascular conditions, among 2-year AYA cancer survivors in California.[75] Cancer types with the highest cumulative incidence of CVD at 10 years post-diagnosis included central nervous system tumors (7.30%), acute lymphoid leukemia (6.85%), acute myeloid leukemia (6.84%), and non-Hodgkin lymphoma (4.12%). Other characteristics associated with higher CVD incidence included distant stage disease, receipt of chemotherapy or stem cell transplant, black race, low neighborhood socioeconomic status, and having either public or no health insurance, suggesting disparities in CVD outcomes among patients with an AYA cancer history.

Studies of mortality from cardiovascular causes among AYA cancer survivors are more limited, and most have focused exclusively on deaths occurring at least 5 years after the initial cancer diagnosis. In the largest study to date, based in England and Wales, Henson et al. examined mortality from cardiac diseases among 200,945 five-year AYA cancer survivors diagnosed from 1971 to 2006 and followed through 2014.[76] For all cancer types and ages combined, the standardized mortality ratio (SMR) for all cardiac disease was 1.4 (95% CI: 1.3, 1.4), corresponding to an absolute excess risk of 1.9 deaths per 10,000 person-years. The SMR was greatest for survivors diagnosed at ages 15 to 19 years, and for those diagnosed with Hodgkin lymphoma, acute myeloid leukemia, and genitourinary cancers other than bladder cancer. In a smaller study of 9,245 childhood and AYA cancer survivors in Finland, an excess of death from any circulatory disease was identified among survivors overall (SMR= 1.9; 95% CI: 1.5-2.3), with a higher SMR for those diagnosed at ages 15 to 19 years (SMR=3.5; 95% CI: 2.0-5.7) than at ages 0 to 14 (SMR= 2.7) or 20 to 34 years (SMR=1.6).[77] As in the study by Henson et al.,[76] the excess in circulatory disease deaths was greatest among patients with

Hodgkin lymphoma (SMR=6.6; 95% CI: 4.8-8.9), though the number of observed deaths was too small to produce stable estimates within strata of most other cancer types.[77] Kero et al. reported similar findings for excess cardiovascular disease deaths in another study of five-year childhood and AYA cancer survivors in Finland.[78] To our knowledge, no prior U.S.-based study has quantified the excess incidence of cardiovascular mortality among AYA survivors of all cancer types compared to the general population.

2.2.2. Infectious disease outcomes

Elevated rates of hospitalization for infectious and parasitic diseases among AYAs with cancer relative to age-matched noncancer controls have been reported in population-based studies from Denmark (RR=1.69; 95% CI: 1.61-1.77) and British Columbia (RR=1.98; 95% CI: 1.14-3.43). However, studies of mortality from infectious causes in AYA cancer survivors are more limited. Among five-year cancer survivors in Finland, Kero et al. reported an SMR of 4.0 (95% CI: 2.1-5.8) for infectious disease death for those diagnosed with cancer at ages 20-34 years.[78] Though the number of deaths was small in each group, this estimate appeared to be of smaller magnitude than that observed among survivors diagnosed at ages 0-19 (SMR=10; 95% CI: 2.6-17.4), but similar to that reported in the U.S.-based Childhood Cancer Survivor Study for survivors diagnosed before age 21 (SMR=4.2; 95% CI: 3.2-5.4).[62] It is unclear how the SMR for infectious diseases for AYA cancer survivors in the U.S. would compare to estimates reported for U.S. childhood cancer survivors. To date, the only AYA-focused analysis of noncancer mortality using U.S. SEER data was restricted to survivors of bone and soft tissue sarcoma, and reported an SMR of 4.01 (95% CI: 2.57-5.96) for infectious disease death in this group.[79] Estimates specific to AYAs with other cancer types have not been reported in a U.S.-based study.

2.2.3. Renal outcomes

A number of reports have documented renal effects in childhood cancer patients,[80-84] including an excess incidence of acute renal failure, chronic kidney disease, and other renal diseases.[82, 85] Studies investigating renal outcomes specifically among AYA cancer patients are less common, though patients ages 15-19 are often included in studies of late effects in childhood cancer. A study of renal and urinary outcomes in childhood cancer survivors in Nordic countries, which included patients with a maximum age at diagnosis of 19 years, found an elevated rate of first hospitalization for any glomerular diseases, renal tubule-interstitial diseases, acute renal failure, and chronic kidney disease in one-year survivors relative to a matched comparison group.[82] The magnitude of the rate ratio for any renal or urinary tract disease was the lowest, though still statistically significant, in the subgroup of patients aged 15 to 19 years at diagnosis (RR=2.1; 95% CI: 1.9-2.2). Cancer types associated with the greatest excess of hospitalizations for acute renal failure and/or chronic kidney disease included leukemia, lymphomas, malignant bone tumors, soft tissue sarcomas, and germ cell neoplasms, all cancers common in AYAs. Similarly, in a study using data from the Kaiser Permanente Southern California health plan, Chao et al. found a higher incidence of renal failure among childhood cancer survivors, with a maximum age at diagnosis of 18 years, than among age-matched controls (IRR=13.7; 95% CI: 3.3-57.6).[85] However, renal failure was a relatively rare outcome overall, with an incidence of only 1.3 per 1000 person-years in the cancer survivor group. The most common cancer types among patients included in this study were leukemia and lymphomas.

Rates of hospitalization for any disease of the genitourinary system among AYA cancer survivors have been investigated in studies from Denmark[71] and Canada.[74] Rugbjerg et al.

reported a modestly elevated rate among five-year survivors in Denmark compared to matched controls (RR=1.28; 95% CI: 1.25-1.31), which was somewhat higher among men than among women. Among five-year AYA survivors diagnosed at ages 20-24 years in British Columbia, Zhang et al. also found an excess of hospitalization for genitourinary diseases relative to a matched comparison group (RR=1.34; 95% CI: 1.09-1.63).[74] The extent to which these estimates reflect hospitalization for kidney diseases, as opposed to other urinary tract conditions, is unclear, as is the extent to which estimates may have been influenced by bias due to increased surveillance among cancer survivors. However, taken together with reports from studies of childhood cancer survivors, these findings suggest that renal late effects severe enough to require hospitalization may be an important contributor to excess morbidity and mortality among AYA cancer survivors.

2.2.4. Pulmonary outcomes

In the study by Rugbjerg et al. from Denmark, rates of hospitalization for diseases of the respiratory system were significantly elevated among five-year AYA cancer survivors compared to a matched comparison group (RR=1.47; 95% CI: 1.43, 1.52).[71] The excess of hospitalizations for respiratory causes was most pronounced among survivors diagnosed with leukemia (RR=4.9; 95% CI: 4.0-6.0). Likewise, Zhang et al. reported a rate ratio of 1.71 (95% CI: 1.26, 2.31) for hospitalization for respiratory diseases for AYAs diagnosed at ages 20-24 in British Columbia relative to a matched noncancer cohort.[74]

Few studies have evaluated respiratory mortality among AYA cancer survivors compared to individuals without a cancer history, though those that have are consistent with the findings for hospitalization noted above. In a study from Finland, a total of 15 deaths from respiratory causes were observed among 9,245 childhood and AYA cancer survivors over 147,446 person-

years of follow-up, with 13 of these occurring among patients diagnosed at ages 20-34.[77] This corresponded to an SMR of 2.3 (95% CI: 1.3-3.8) overall, and 2.4 (95% CI: 1.3-4.1) in the 20-34 year age group. The number of deaths was insufficient to produce stable estimates within strata defined by cancer type. A second report from Finland, with more recent years of follow-up, also found excess mortality from respiratory diseases among AYAs diagnosed at ages 20-34 (SMR=1.7; 95% CI: 1.1-2.4).[78] Site-specific analyses were performed for central nervous system (CNS) tumors (SMR=5.5), Hodgkin lymphoma (SMR=6.6), and Non-Hodgkin lymphoma (SMR=5.0), though the numbers of observed deaths in each group were only 6, 10, and 4, respectively, and estimates were imprecise.

Though limited by small sample sizes, these studies from Finland suggest that the excess of deaths from respiratory causes may be smaller in AYA cancer survivors than in childhood cancer survivors. In the U.S.-based Childhood Cancer Survivor Study, for example, Mertens et al. reported an SMR of 8.8 (95% CI: 6.8, 11.2) for deaths from pulmonary causes.[86] For those with diagnoses of Hodgkin or Non-Hodgkin lymphoma, SMRs were 10.8 and 9.1, respectively. To our knowledge, no study has evaluated SMRs for respiratory causes among AYA cancer survivors in the U.S., which may differ from Finland in background cause-specific mortality rates. Differences in respiratory mortality according to factors such as time since diagnosis have also not been examined.

2.2.5. Gastrointestinal and liver outcomes

Studies of childhood cancer survivors, with patients as old as 19 or 20 years at diagnosis, have demonstrated an increased occurrence of gastrointestinal and liver conditions, or hospitalization for these conditions, among survivors compared to either siblings or the general population.[87, 88] In a report from the Childhood Cancer Survivor Study, Goldsby et al.

examined self-reported conditions of the liver and upper and lower gastrointestinal tract, and found that more than 40% of childhood cancer survivors had experienced one or more of these complications by 20 years after cancer treatment.[87] Though relatively uncommon overall, the rate of liver cirrhosis, beginning at 5 years post-diagnosis, was nearly 9 times as high in survivors as in cancer-free siblings (RR=8.9; 95% CI: 2.0-40.0). Rates of ulcers, esophageal disease, gallstones, intestinal polyps/diverticular disease, and colostomy/ileostomy were also significantly elevated among survivors. Abdominal radiation and surgery were associated with late-onset complications, as were high-dose alkylating agents and anthracyclines. Unexpectedly, older age at diagnosis (10+ years) was also a significant predictor of complications.

Similarly, a registry-based study of childhood cancer survivors in Scandinavian countries, known as the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study, found an increased rate of hospitalization for any gastrointestinal or liver disease among one-year survivors of childhood and adolescent cancers compared to expected rates in the general population (RR=1.6; 95% CI: 1.6, 1.7).[88] The excess of hospitalizations was greatest in the 1 to 4 years after cancer diagnosis, but remained significantly elevated at 20 years or more. Analyses of specific gastrointestinal and liver diseases suggested that hospitalizations for many of those with the greatest potential to affect mortality, including liver cirrhosis, viral hepatitis, intestinal obstruction, and ulcers, were all in excess among childhood and adolescent cancer survivors. However, neither ALiCCS or the U.S.-based Childhood Cancer Survivor Study have investigated whether mortality from gastrointestinal or liver conditions is also elevated among survivors compared to individuals without cancer, likely due to an insufficient number of deaths from these relatively rare causes.

Morbidity and mortality from gastrointestinal and liver diseases have not been well-characterized among young adults with cancer. Rugbjerg et al. reported an increased rate of hospitalization for diseases of the digestive organs (RR=1.39; 95% CI: 1.35, 1.42) in five-year AYA cancer survivors compared to sex- and age-matched controls in Denmark.[71] Likewise, Zhang et al. found a modestly elevated rate of hospitalization for any digestive conditions among five-year AYAs survivors (diagnosed at ages 20-24) in British Columbia relative to a matched comparison group (RR=1.29; 95% CI: 1.07-1.56).[74] To date, mortality from gastrointestinal conditions such as liver disease and cirrhosis or ulcers has not been specifically examined in AYA cancer survivors compared to the general population.

2.2.6. Mortality disparities among AYAs with cancer by race and socioeconomic status

Studies of potential disparities among AYA cancer patients have generally restricted their analyses to cancer-specific and overall survival, with little investigation into deaths from specific noncancer causes. Notably, almost all prior AYA-specific studies of race- and socioeconomic status-related disparities have exclusively used data on patients diagnosed in California. In a report using data from the California Cancer Registry, DeRouen et al. examined overall survival among all AYAs diagnosed with a first invasive cancer from 2001-2011.[89] Independent of age, neighborhood socioeconomic status, and insurance status, Black AYAs with breast cancer, testicular cancer, Hodgkin lymphoma, leukemia, and cervical cancer experienced poorer overall survival than white AYAs with the same cancer type. Being in the lowest quintile of neighborhood socioeconomic status was also associated with shorter survival for AYAs with several cancer types, including breast cancer, lymphomas, and leukemia. The extent to which estimates were driven by deaths from cancer, relative to noncancer deaths, was not indicated.

Others have investigated survival disparities in studies focused on specific cancer types. Among AYAs diagnosed with Hodgkin lymphoma in California from 1988-2011, Keegan et al. reported significantly lower overall survival for Black patients compared to white patients (HR=1.40; 95% CI: 1.14-1.71), with slightly greater than half of all deaths in both groups due to Hodgkin lymphoma.[90] Likewise, AYAs in the lowest, compared to the highest, quintile of neighborhood socioeconomic status, had an HR or 1.88 (95% CI: 1.53-2.30) for death from all causes. These associations largely persisted in analyses stratified by disease stage. In a separate report, Keegan et al. examined disparities in survival among AYAs diagnosed with differentiated (papillary or follicular) thyroid cancer in California between 1988 and 2010.[91] While race/ethnicity was not strongly associated with overall survival, those in the two lowest quintiles of neighborhood socioeconomic status had significantly poorer survival than those in the highest three quintiles (HR=1.85; 95% CI: 1.48-2.31). Male gender was also strongly associated with poorer overall survival (HR=2.68; 95% CI: 2.14-3.34). The authors indicated that patterns were similar in analyses of noncancer-specific survival, though associations with specific causes of noncancer deaths were not reported. Elevated all-cause mortality among Black compared to White AYAs identified in the California Cancer Registry has also been reported in studies specific to testicular cancer patients (HR=1.41; 95% CI: 1.01-1.97)[92] and female breast cancer patients (HR=1.45; 95% CI: 1.31-1.61).[93] In contrast, Chao et al. did not find significant differences in all-cause mortality for Black versus White race among AYAs with Non-Hodgkin lymphoma diagnosed at Kaiser Permanente Southern California during 1990-2010, though results suggested an increase in mortality for Asians/Pacific Islanders and individuals with the lowest neighborhood incomes.[94]

Despite the overall paucity of research addressing disparities in noncancer mortality among AYAs, there is some evidence to suggest that, among U.S. childhood and AYA cancer survivors, mortality from cardiovascular disease may differ significantly according to race. Berkman et al. identified cases diagnosed from 1973 to 2011 at ages 0-34 years in the SEER registries, and estimated hazard ratios (HR) for death from cardiovascular causes for blacks compared to whites.[95] For all cancers types combined, the HR for cardiovascular disease death was 2.13 (95% CI: 1.85, 2.46), though this varied somewhat by cancer type. In the subgroup of those aged 15-34 years at diagnosis, the magnitude of this association was smaller and non-significant, though imprecise (HR=1.33; 95% CI: 0.60, 2.95). Individuals diagnosed at ages 35-39 were not included, and estimates of race-specific incidence of cardiovascular disease mortality were not reported.

2.3. Summary of literature review

Though numerous studies have examined noncancer health outcomes among long-term survivors of childhood cancers, little research has evaluated such outcomes among patients diagnosed as AYAs. To date, the few AYA-specific investigations of mortality from noncancer causes after cancer have been based almost exclusively in Northern European countries, with sample sizes too small to adequately examine mortality from noncancer causes other than cardiovascular disease, or to consider variability according to cancer type and other patients characteristics. Additionally, limited research has investigated potential disparities in noncancer outcomes after AYA cancer, an important consideration for the diverse patient population diagnosed and treated in the U.S. Thus for patients and physicians planning follow up care after initial treatment, and for AYAs across various phases of survivorship, there remains a need for AYA-specific research that examines long-term patterns of mortality from causes other than

cancer, especially from causes other than cardiovascular disease, and that investigates potential disparities in noncancer outcomes in this population.

CHAPTER 3. AIMS

Each year, more than 70,000 adolescents and young adults (AYAs) ages 15-39 are diagnosed with cancer in the United States. Over the past three decades, 5-year relative survival among AYAs has steadily increased, and currently stands at over 80% for all sites combined.[2] These gains are largely attributable to advances in cancer treatments, which, while extending survival from the original cancer diagnosis, may also contribute to future morbidity and mortality from noncancer causes.

Previous population-based studies have documented higher mortality from infectious diseases, cardiovascular diseases, and suicide among individuals with a cancer diagnosis compared with the general population.[96, 97] However, most investigations of noncancer mortality have focused on individuals diagnosed as children or older adults. To date, little research has investigated long-term mortality, including noncancer causes of death, specifically in the AYA cancer population, despite increasingly widespread recognition of the unique characteristics and needs of AYAs with cancer.[22] AYA patients are known to differ from childhood and adult cancer patients with respect to cancer type distribution, underlying disease biology, treatment setting, treatment protocols and dose intensity, and personal characteristics such as psychosocial development, insurance status and healthcare access,[2, 5, 22] all factors which may contribute to subsequent risk of mortality from causes other than the original cancer diagnosis. Clinical practice guidelines from the National Comprehensive Cancer Network have specifically acknowledged a lack of evidence on long-term adverse effects following AYA

cancers, particularly for those typically diagnosed at the upper end of the AYA age range (e.g. breast cancer).[22]

This research investigated mortality from noncancer causes among AYA cancer patients diagnosed during 1973-2015 and included in the Surveillance, Epidemiology, and End Results (SEER) database. Noncancer causes of deaths in SEER were ascertained from death certificates and categorized into 25 groups, which included, among others, diseases of the heart, cerebrovascular disease, suicide and self-inflicted injury, pneumonia and influenza, and other infectious and parasitic diseases. The specific aims were:

Aim 1: To examine mortality from noncancer causes among AYA cancer patients compared to the general population. We estimated SMRs for all noncancer causes combined and for cause-specific categories, both overall and in subgroups defined by cancer type, stage, age at diagnosis and time since diagnosis.

We hypothesized that noncancer mortality would be significantly elevated among AYA patients, particularly for infectious disease mortality and cardiovascular disease mortality.

Aim 2: To examine characteristics associated with noncancer mortality within the AYA cancer patient population. Using competing risk methods, we estimated the 5-, 10-, and 20-year cumulative incidence of all noncancer mortality, cardiovascular disease mortality, and infectious disease mortality, both overall and according to cancer type and other patient characteristics. We also estimated hazard ratios for all noncancer mortality, cardiovascular mortality, and infectious disease mortality among AYA cancer patients, with a focus on disparities related to race/ethnicity, county-level socioeconomic status indicators, rural-urban continuum, and geographic region.

We hypothesized that greater noncancer mortality would be associated with non-Hispanic Black race/ethnicity, male gender, and living in a lower SES-area.

CHAPTER 4. METHODS

4.1. Data source

The Surveillance, Epidemiology, and End Results (SEER) program, funded by the National Cancer Institute (NCI) since 1973, is a system of population-based cancer registries that collects and publishes data on cancer incidence and survival in the U.S. Since the 1970's, the SEER program has expanded from its original 9 registries (SEER 9) to the 20 registries included today (SEER 18). These registries are located strategically across the country and cover approximately 35% of the total U.S. population. SEER areas are demographically representative of the entire U.S., and include 32% of whites, 30% of African Americans, 44% of Hispanics, 49% of American Indian/Alaska Natives, 57% of Asians, and 69% of Native Hawaiian/Pacific Islanders.[98]

Patient information collected by SEER registries includes patient demographic information, primary tumor site and morphology, stage at diagnosis, and first course of treatment. SEER also conducts follow-up for patient vital status, and reports survival and mortality data, including cause of death. Quality control activities are conducted on a continual basis by staff from NCI and each the SEER registries and by external contractors to standardize the coding of patient data, evaluate the accuracy and consistency of data coding, and other activities to maintain high data quality.[99]

4.2. Aim 1

4.2.1. Study population

For Aim 1 analyses, we used SEER*Stat (version 8.3.5)[100] to identify all patients in the SEER 9 database with a first primary malignancy diagnosed at ages 15 to 39 years between January 1, 1973 and December 31, 2015. We selected only cases with a known patient age and a neoplasm with malignant behavior. Death certificate and autopsy only cases were excluded, as were those for whom the state death certificate was not available, or was available but did not have cause of death information. We also excluded patients with Kaposi sarcoma because high rates of infectious disease mortality associated with this cancer type were expected to inflate overall estimates of noncancer mortality among AYAs with cancer relative to the general population. Because general population mortality rates are not produced for individuals of unknown race, AYA cancer patients with unknown race (~1% of all patients[101]) were excluded for analyses in Aim 1.

4.2.2. Key variables

SEER defines variables for the major cancer site groups using the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) primary site and histology codes submitted by the registries. A variable adapted specifically for cancers in AYAs is also available in the SEER database, with cancer sites recoded based on a classification scheme from Barr et al. (AYA Site Recode/WHO 2008; Appendix 1).[102] We utilized this classification scheme to define all cancer types, with the exception of those that do not have their own AYA-specific recode (e.g. testicular cancer), which were defined according to the regular site recode ICD-O-3/WHO 2008.

Table 4.1 Noncancer causes of death in SEER		
Category	Causes of Death	ICD-10 codes
Infectious diseases	Tuberculosis, syphilis, HIV, septicemia, pneumonia and influenza, other infectious and parasitic diseases	A15-A19, A50-A53, B20-B24, A40-A41, J09-J18, A00-A08, A20-A33, A35-A39, A42-A49, A54-B19, B25-B99
Cardiovascular diseases	Diseases of heart, hypertension without heart disease, cerebrovascular disease, atherosclerosis, aortic aneurysm and dissection, other diseases of arteries, arterioles, capillaries	I00-I09, I11, I13, I20-I51, I10, I12, I60-I69, I70, I71, I72-I78
Respiratory	Chronic obstructive pulmonary disease and allied conditions	J40-J47
Gastrointestinal and liver	Stomach and duodenal ulcers, chronic liver disease and cirrhosis	K25-K28, K70, K73-K74
Renal	Nephritis, nephrotic syndrome, and nephrosis	N00-N07, N17-N19, N25-N27
External causes	Accidents and adverse effects, suicide and self-inflicted injury, homicide and legal intervention	V01-X59, Y85-Y86, U03, X60-X84, Y87.0, U01-U02, X85-Y09, Y35, Y87.1, Y89.0
Other	All other noncancer causes of death	--
*In situ, benign or unknown behavior neoplasm		D00-D48
*Was not included in our definition of noncancer mortality Table adapted from ref [103]		

Cause of death information in SEER is ascertained from death certificates. Using ICD versions 8-10 (depending on the year of death), SEER defines noncancer causes of death using 25 categories (Table 4.1; Appendix 2).[103] These categories have been consistently defined over time and include, 'Diseases of the Heart,' 'Septicemia,' 'Pneumonia and Influenza,' and 'Suicide and Self-Inflicted Injury,' and other noncancer causes listed among the leading causes of death in the U.S.[104] SEER also defines deaths from in situ, benign, or unknown behavior neoplasms as a separate category of noncancer deaths.[103] However, for our analyses in Aims 1 and 2, we did not include these deaths in our definition of 'all noncancer deaths.'

4.2.3. Statistical analysis

All analyses in Aim 1 were conducted using SEER*Stat.[100] For noncancer causes of death available in SEER, we estimated standardized mortality ratios (SMR) comparing the number of observed deaths among AYAs with cancer to that expected in the general population with the same distribution of age, sex, and race over the same time period. General population mortality rates available in SEER were obtained from the Centers for Disease Control and Prevention's National Center for Health Statistics. Within SEER*Stat, the number of expected deaths was calculated as the product of the general population mortality rate for each cause of death and the person-time at risk in the AYA cancer patient sample. For all calculations, we allowed a 2-month latency exclusion period. This was the default setting in SEER*Stat and represented the number of months after cancer diagnosis during which person-time at-risk and potential events of interest were ignored. Thus person-time was accrued from two months after the date of cancer diagnosis until death, the date of last contact, or December 2015, whichever occurred first. The 95% confidence intervals for SMRs were estimated using exact methods. We also reported absolute excess risks (AER), calculated as the difference between the observed and expected deaths, divided by the total person-years of observation. These were multiplied by 10,000 to yield the number of excess deaths per 10,000 person-years. SMRs and AERs were estimated for all noncancer causes of death combined, for each of the 25 individual noncancer causes of death, and for cause-specific categories defined as infectious, cardiovascular, respiratory, gastrointestinal and liver, renal, external, and other causes, as shown in abbreviated form in Table 4.1, and in full in Appendix 2.

In subgroup analyses, we estimated SMRs and AERs according to cancer site, age at diagnosis (15-19, 20-24, 25-29, 30-34, 35-39) and time since diagnosis (< 1 year, 1- <5 years, 5-

<10 years, 10-<20 years, 20+ years). For the 12 most common cancer types (Table 4.2), we also conducted site-specific analyses, according to age at diagnosis, cancer stage, and time since diagnosis. Stage was categorized using Ann Arbor staging (I, II, III, IV; diagnosis years 1983+) for lymphomas and SEER Historic Stage A (localized, regional, distant) for most other malignancies. Analyses according to stage could not be performed for leukemias and central nervous system tumors due to lack of a consistently defined stage variable over the entirety of the study period.

In sensitivity analyses, we considered latency exclusion periods of 0 months (i.e. person-time begins at diagnosis) or 6 months, to assess the sensitivity of results to varying the start of follow-up for noncancer deaths. We also conducted sensitivity analyses to assess the potential influence of varying degrees of cause of death misclassification on SMR estimates. For example, for all noncancer deaths combined, we re-estimated SMRs assuming that 10% (or 20% or 30%) of observed deaths were actually attributable to cancer, but were misclassified as noncancer deaths.

Table 4.2 Cancers examined in site-specific analyses, defined using AYA Site Recode/WHO 2008

Leukemias
Non-Hodgkin lymphoma
Hodgkin lymphoma
Central nervous system tumors
Soft tissue sarcomas*
Melanoma
Thyroid carcinoma
Other head and neck carcinomas
Breast carcinoma
Cervical/uterine carcinomas
Colorectal carcinomas
Testicular cancer**

*Excludes Kaposi sarcoma
**Defined using Site recode ICD-O-3/WHO 2008

4.3. Aim 2

4.3.1. Study population

In Aim 2, we used SEER*Stat to identify all patients in the SEER 18 registries with a first primary cancer at ages 15-39 years during 1985-2015, selecting only those with a known

patient age and a neoplasm with malignant behavior. Patients diagnosed prior to 1985 were excluded to facilitate analyses of county-level socioeconomic characteristics, which were only reported for selected years (see section 4.3.2). As in Aim 1, we excluded patients with Kaposi sarcoma, unknown race, death certificate and autopsy only cases, and those for whom the state death certificate was not available, or was available but did not have cause of death information.

4.3.2. Key variables

Person-time of follow-up for each patient was calculated from the date of diagnosis to either the date of last contact or the date of death in the SEER database. This variable is recorded in SEER in months, rather than days, due to confidentiality issues regarding the reporting of days in some U.S. registries.

SEER registries do not collect individual-level information on education, income, or other socioeconomic characteristics. However, county-level information, based on data from the U.S. Census Bureau,[105, 106] is linked to patient data by state-county Federal Information Processing Standards (FIPS) codes and is available in the SEER database. For our analyses, we focused on two county attributes: percent of persons below poverty and percent of persons with less than a high school education. In SEER, these variables are currently defined from the decennial census for the years 1990 and 2000,[106] and from the American Community Survey (ACS) for the years 2007-2015.[107] The ACS is conducted each year by U.S. Census Bureau, and five-year estimates for demographic and social characteristics for U.S. counties are published and accessible through SEER.[107] Within SEER*Stat, we accessed census data on percent of persons below poverty and percent of persons with less than a high school education for all U.S. counties for 1990 (decennial census), 2000 (decennial census), and 2008-2012 (ACS) to create quartile cut points. We then assigned quartile values for each county attribute variable

using 1990 cut points for patients diagnosed during 1985-1994, using 2000 cut points for patients diagnosed during 1995-2004, and using 2008-2012 cut points for patients diagnosed during 2005-2015.

We also performed analyses according to the county's rural-urban continuum code, a classification scheme which was developed by the U.S. Department of Agriculture[108] and is also linked to patient data within the SEER database. These variables have been defined for each county for the years 1974, 1983, 1993, 2003, and 2013. For our analyses, we used rural-urban designations for the years 2003 and 2013. Although coding schemes are available for earlier years, as listed above, they are not fully comparable with those of 2003 and 2013, due to changes in the definitions of metro vs nonmetro areas,[108] and cannot be used together in the same analysis. Therefore analyses according to rural-urban continuum were restricted to patients diagnosed in 1998 and later, so that a maximum of 5 years was allowed between cancer diagnosis and the year for which the rural-urban continuum code was defined. We used the rural-urban continuum variable from 2003 for patients diagnosed during 1998-2007, and from 2013 for patients diagnosed during 2008-2015. The 2003 and 2013 coding schemes assign counties to one of nine categories, which range from metro counties with a

Table 4.3 Rural-Urban Continuum Code Definitions for 2003 and 2013

Code	Description	Category for analysis
1	Counties in metro areas of 1 million or more	Metro
2	Counties in metro areas of 250,000 to 1 million	
3	Counties in metro areas of fewer than 250,000	
4	Urban population of 20,000 or more, adjacent to metro area	Urban
5	Urban population of 20,000 or more, not adjacent to metro area	
6	Urban population of 2,500 to 19,999, adjacent to metro area	
7	Urban population of 2,500 to 19,999, not adjacent to metro area	Rural
8	Completely rural or less than 2,500 urban population, adjacent to metro area	
9	Completely rural or less than 2,500 urban population, not adjacent to metro area	
88,99	Unknown	

population of one million or more, to nonmetro counties that are not adjacent to a metro area and have a population of less than 2,500.[108] We redefined categories as metro, urban, and rural, a recategorization scheme which has been used in previous SEER analyses (Table 4.3).[109]

Disparities were also evaluated according to geographic region. We categorized SEER registries into West, South, Northeast, and Midwest, as shown in Table 4.4.[110] Due to small numbers of patients in the Alaska Native and Hawaii registries, we excluded these registries from analyses according to region.

Table 4.4. Geographic regions defined using SEER registries

Region	**SEER registries**
West	San-Francisco-Oakland; San-Jose Monterey; Los Angeles; Greater California; New Mexico; Seattle/Puget Sound; Utah
South	Atlanta; Rural Georgia; Greater Georgia; Kentucky; Louisiana
Northeast	Connecticut; New Jersey
Midwest	Detroit; Iowa

4.3.3. Statistical analysis

All analyses in Aim 2 were stratified by sex to accommodate adjustment for cancer type, including male-only and female-only cancers as separate categories, in statistical models. Cause-specific hazard ratios for all noncancer deaths, cardiovascular disease deaths, and infectious disease deaths (see Appendix 2) according to race, county-level socioeconomic characteristics, rural-urban continuum, and geographic region were estimated using Cox proportional hazards regression models. For individuals with 0 months of survival, we assigned a survival time of 0.5 months for consistency with previous literature.[111] The proportional hazards assumption was assessed through visual inspection of plots of the survival function versus time, and the log(-log(survival)) versus log(time). Multivariable models accounted for age at diagnosis, cancer type, year of diagnosis, and race, covariates that were determined *a priori* and are available

through SEER. We also estimated the cumulative incidence of deaths from all noncancer causes, cardiovascular diseases, and infectious diseases at 5, 10, and 20 years using nonparametric methods to account for death from other causes as a competing risk,[112] among all AYA patients and according to cancer type, race, and other patient characteristics. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC)

CHAPTER 5. NONCANCER MORTALITY AMONG ADOLESCENTS AND YOUNG ADULTS WITH CANCER

5.1 Background

Each year, more than 70,000 adolescents and young adults (AYAs, ages 15-39 years) are diagnosed with cancer in the U.S.[113] Though a heterogeneous group, AYAs with cancer have been increasingly recognized as a distinct patient subpopulation, differing from childhood and older adult cancer patients in cancer type distribution, underlying disease biology, and treatment protocols.[5] Despite the unique characteristics associated with cancers in this age group, few studies have examined long-term health outcomes among patients diagnosed as AYAs.

Five-year relative survival among AYAs with cancer has steadily increased over the past few decades, and currently stands at >80% for all invasive cancers combined.[8] Among patients diagnosed at young ages, improvements in survival are largely attributable to recent advances in cancer treatments, which, while preventing death from the primary cancer, may increase risk of future morbidity and mortality from noncancer causes. The cardiotoxic and/or immunosuppressive effects of many chemotherapeutic agents are perhaps most well-known, and may predispose patients to treatment-related complications from heart disease or infection. However, documented adverse effects of anti-cancer therapies are even more wide-ranging, with the potential to impact short- and/or long-term function of nearly all organ systems.[4] Recent evidence suggests that AYAs with cancer continue to have a small, but statistically significant excess of all-cause mortality relative to the general population even after surviving 20 years

beyond diagnosis,[114] but the extent to which deaths from causes other than cancer may contribute has rarely been examined.[76-78]

The objective of this study was to compare rates of mortality from noncancer causes among AYA cancer patients with those in the general U.S. population using nationally representative cancer registry data.

5.2 Methods

5.2.1 Data source

We identified AYA patients using data from the Surveillance, Epidemiology, and End Results (SEER) program,[98] a system of population-based cancer registries that collects and reports data on cancer incidence and survival in the U.S. Patient information collected by SEER includes demographic information, primary tumor site and morphology, stage, and first course of treatment. SEER also conducts active follow-up for patient vital status and reports the number of months survived since cancer diagnosis and the cause of death as ascertained from death certificates. U.S. general population mortality rates from the National Center for Health Statistics are accessible through the SEER program.

5.2.2 Study population

For this study, we used data from the original SEER 9 registries,[115] and included patients with a first malignant primary diagnosed at ages 15 to 39 years between 1973 and 2015 (N=249,021). Because general population mortality rates for comparison are not available for individuals without a known race, we excluded patients with unknown race (N=3,053). Death certificate and autopsy only cases were excluded (N=3), as were patients for whom the death certificate was either not available or was available without cause of death information (N=2,693). We further excluded patients with Kaposi sarcoma (N=7,631) due to its strong

association with HIV infection,[116] and the likelihood of high infectious disease mortality rates within this group. We categorized cancer type using an AYA-specific recode of International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) primary site and histology codes.[117]

5.2.3 Noncancer causes of death

SEER recodes ICD 8-10 codes from death certificates and categorizes deaths from noncancer causes in 26 major groups.[103] These groups have been defined consistently over time and include many of the leading causes of death in the U.S., such as 'Diseases of the Heart,' 'Pneumonia and Influenza,' and 'Suicide and Self-Inflicted Injury." We further consolidated these groups into 7 broad categories of infectious diseases, cardiovascular diseases (CVD), respiratory diseases, gastrointestinal and liver diseases, renal diseases, external causes, and other causes, as shown in Appendix 2. Although SEER also includes deaths from 'In situ, benign or unknown behavior neoplasm' among its 26 groups of noncancer deaths,[103] we did not consider these deaths as noncancer deaths for our analyses.

5.2.4 Statistical analysis

We estimated standardized mortality ratios (SMRs) as the number of observed deaths from noncancer causes among AYAs with cancer divided by the number expected in the general population with the same distribution of age, sex, race, and calendar year. The number of expected deaths was calculated as the product of the general population mortality rate for each cause of noncancer death and the person-time at risk in the AYA cancer patient cohort. For all SMR calculations, we allowed a 2-month latency exclusion period, during which person-time at risk and deaths were ignored. Thus person-time among AYAs with cancer was accrued from two months after the date of cancer diagnosis until death, date of last contact, or December 2015,

whichever occurred first. Exact methods were used to calculate 95% confidence intervals (CI) for all SMRs. We also estimated absolute excess risks (AER), calculated as the difference between observed and expected noncancer deaths, divided by the total person-years of observation, and reported as the number of excess deaths per 10,000 person-years.

In subgroup analyses, SMRs were estimated according to cancer type, age at diagnosis, and time since diagnosis. For selected cancers, we also performed cancer type-specific analyses, and estimated SMRs according to age at diagnosis, time since diagnosis and disease stage. Ann Arbor staging was used for lymphomas (diagnosed in 1983 and later), and SEER Historic Stage A, a summary staging measure, was used for most other cancer types.[118] We did not conduct analyses according to stage for central nervous system (CNS) tumors or leukemias, due to lack of a consistently defined stage variable across the study period in SEER. We also re-estimated SMRs excluding patients with non-Hodgkin lymphoma (NHL), to further reduce the influence of HIV-related deaths on estimates among all AYAs with cancer combined. All analyses were performed using SEER*Stat, version 8.3.5.[119]

In sensitivity analyses, we considered latency exclusion periods of 0 and 6 months, rather than 2 months, for estimation of SMRs among AYAs of all cancer types combined. We also conducted a sensitivity analysis to assess the potential influence of cause of death misclassification on SMR estimates. This was done by re-estimating SMRs under the assumption that a specified proportion (10%, 20%, or 30%) of observed noncancer deaths from a particular cause had been misattributed.

5.3 Results

Among 235,641 AYAs with cancer included in these analyses, a total of 12,948 deaths from noncancer causes were observed over approximately 3.1 million total person-years of

follow-up (Table 5.1). The majority of included AYAs were female (60%), diagnosed at ages 30-39 years (65%), and diagnosed between 1993 and 2015 (60%). Overall, noncancer mortality among AYA cancer survivors was 1.84 (95% CI: 1.80-1.87) times that in the general U.S. population, reflecting an excess of approximately 19 noncancer deaths per 10,000 person-years among survivors (Table 5.2). SMRs were particularly elevated for the cause-specific categories of infectious diseases (SMR=5.13; 95% CI: 4.95-5.32), cardiovascular diseases (SMR=1.55; 95% CI: 1.50-1.60), renal diseases (SMR=2.40; 95% CI: 2.12-2.71), and other causes (SMR=2.06; 95% CI: 2.00-2.13), but were also weakly elevated for respiratory diseases (SMR= 1.16; 95% CI: 1.05-1.28) and external causes (SMR= 1.08; 95% CI: 1.03-1.13). When AYAs with NHL (N=14,209 patients, N=2,212 noncancer deaths) were excluded, SMRs for all noncancer deaths (SMR=1.60) and infectious disease deaths (SMR=2.74) were attenuated but still elevated among AYA cancer survivors. SMRs for other broad cause of death categories were not substantially changed when NHL patients were excluded (*data not shown*).

5.3.1 All noncancer mortality

For all noncancer causes combined, mortality was significantly increased relative to the general population for AYAs with every cancer type we evaluated, other than thyroid cancer and melanoma, with the highest SMRs among those with NHL (SMR=6.33), leukemias (SMR=5.26), CNS tumors (SMR=3.38), and Hodgkin lymphoma (HL) (SMR=3.12) (Table 5.3). AYAs with thyroid cancer (SMR=0.81) and melanoma (SMR=0.65) had significantly lower noncancer mortality than the general population. Among AYAs of all cancer types combined, SMRs for all noncancer mortality decreased with increasing age at diagnosis, from 2.63 among those aged 15-19 to 1.67 among those aged 35-39, and with increasing time since diagnosis, from 10.30 within the first year to 1.34 at 20+ years post-diagnosis. SMRs for all noncancer mortality also tended to

be higher among AYAs with a more advanced disease stage, but were significantly elevated even for those with localized disease for soft tissue sarcomas, head and neck cancers, cervical/uterine cancers, and colon and rectal cancers, and for those with stage I HL or NHL (Table 5.5).

5.3.2 Cardiovascular disease mortality

The highest SMRs for cardiovascular disease mortality were observed for AYAs with HL (SMR=4.44), CNS tumors (SMR=3.32), and leukemias (SMR=3.06), followed by those with NHL (SMR=2.05), cervical/uterine cancers (SMR=1.83), and head and neck cancers (SMR=1.80). SMRs were also significantly elevated for those with breast cancer (SMR=1.38) and colon and rectal cancers (SMR=1.35) (Table 5.3). There was a clear trend of decreasing SMRs with increasing age at diagnosis overall (Table 5.3), and among AYAs with NHL, HL, and breast cancer (Table 5.9). SMRs for cardiovascular diseases also decreased with increasing time since diagnosis for most cancer types, although an increase at 10+ years post-diagnosis was apparent for AYAs with HL and CNS tumors (Table 5.7).

5.3.3 Infectious disease mortality

Mortality from infectious diseases was significantly elevated among AYAs with all cancer types examined other than melanoma and thyroid cancer (Table 5.3). SMRs were highest among those with NHL (SMR=47.71) and leukemias (SMR=16.06). There was little evidence of a trend in SMRs according to age at diagnosis, except for a suggested decrease with increasing age among patients with leukemias (Table 5.9). Overall, SMRs declined sharply with time since diagnosis, from 67.49 within the first year of diagnosis, to 1.61 at 20+ years post-diagnosis (Table 5.3), but remained significantly elevated at 20+ years overall and for patients with leukemias, NHL, HL, CNS tumors, and cervical/uterine cancers (Table 5.7).

5.3.4 Mortality from other noncancer causes

Though the number of observed deaths was small, AYAs with leukemias had the highest SMRs among all cancer types examined for respiratory diseases (SMR=4.69), gastrointestinal and liver diseases (SMR=4.06), renal diseases (SMR=10.25), and other causes of death (SMR=9.89) (Tables 5.3, 5.4). SMRs for respiratory diseases were also substantially elevated for those with HL (SMR=2.08), head and neck cancers (SMR=3.32), and cervical/uterine cancers (SMR=1.83), while those for gastrointestinal and liver diseases only appeared elevated for AYAs with head and neck cancers (SMR=1.65), cervical/uterine cancers (SMR=1.57), and colon and rectal cancers (SMR=1.52) (Table 5.3). For renal diseases, SMRs ranged from ~3 to 5 for AYAs with head and neck cancers, cervical/uterine cancers, colon/rectal cancers, HL, NHL, and CNS tumors, and were also significantly elevated for AYAs with testicular cancer (SMR=1.78) (Table 5.4). Patterns for respiratory diseases, gastrointestinal and liver diseases, and renal diseases, suggested a decrease in SMRs with increases in age at diagnosis and time since diagnosis (Tables 5.7-5.10). In cancer type-specific analyses, SMRs were elevated at 20 or more years post-diagnosis for renal disease among AYAs with leukemias, HL, and cervical/uterine cancers, for respiratory disease among those with HL, head and neck cancers, and cervical/uterine cancers, for gastrointestinal and liver diseases among those with leukemias, and for external causes among those with CNS tumors, soft tissue sarcomas, head and neck cancers, and cervical/uterine cancers (Tables 5.7-5.8).

5.3.5 Sensitivity analyses

Using a latency exclusion period of 0 months, rather than 2 months, a total of 13,792 deaths from all noncancer causes were observed among AYAs of all cancer types combined, with corresponding SMR of 1.94 (95% CI: 1.91, 1.98) (Table 5.11). SMRs for cause-specific

categories also tended to be slightly elevated compared to those estimated in primary analyses using a 2-month latency exclusion period. In contrast, when a 6-month latency exclusion period was used, the SMR for all noncancer mortality among AYAs of all cancer types combined was 1.70 (95% CI: 1.67, 1.73), reflecting a total of 11,854 observed deaths. SMRs for cause-specific categories tended to be slightly attenuated compared to the primary analysis, but remained significantly elevated for infectious diseases, cardiovascular diseases, respiratory diseases, renal diseases, external causes, and other causes.

In sensitivity analyses examining the potential influence of cause of death misclassification, the SMR for all noncancer mortality among AYAs of all cancer types combined remained significantly elevated even when 30% of observed noncancer deaths were assumed to have been misclassified (SMR=1.29; 95% CI: 1.26, 1.31) (Table 5.12). SMRs for infectious diseases, cardiovascular diseases, renal diseases, and other causes also remained significantly elevated under the assumption of 30% misclassification.

5.4 Discussion

This study represents one of the largest to date, and one of the first among U.S. patients, to examine noncancer mortality rates among AYAs with cancer. In our analyses, mortality from all noncancer causes among AYA cancer survivors was approximately 1.8 times that of the general population, with the highest SMRs among those with hematologic malignancies and CNS tumors, cancers more predominant among the patients diagnosed as adolescents. SMRs tended to be lower for AYAs diagnosed with breast cancer, colorectal cancer, and other cancers more commonly diagnosed in older adults. For all cancers types combined, SMRs were generally greatest within the first year of cancer diagnosis, but remained significantly elevated at 20+ years post-diagnosis for all noncancer mortality, and specifically for infectious diseases, cardiovascular

diseases, and renal diseases, underscoring the importance of comprehensive long-term follow-up care for patients with a history of AYA cancer.

Many modern cancer therapies, including anthracycline-based chemotherapies, alkylating chemotherapies, and chest radiation, have been associated with acute and/or chronic cardiotoxicities,[41] potentially contributing to increases in mortality from heart disease among cancer patients and survivors. In contrast to the extensive literature on long-term cardiovascular outcomes among childhood cancer survivors,[86, 120, 121] there exists relatively little research to date specific to young adults with cancer, particularly for those with cancer types other than HL.[122-124] The SMR for heart diseases in our overall analyses (1.58) is similar to that in a recent study of five-year AYA cancer survivors in England and Wales (SMR=1.4),[76] but considerably smaller than that among five-year survivors of childhood cancers in the U.S.-based Childhood Cancer Survivor Study (SMR=7.0).[86] The lower SMRs for heart disease among AYA patients compared to childhood cancer patients may be a reflection of both higher rates of mortality from heart disease in the general population with increasing age, and differences in cancer type distribution between children and AYAs. Lymphomas, leukemias, and CNS tumors, all cancers which span both the childhood and AYA age range, were among the cancer types with the highest SMRs for CVD in the current study. However, though SMRs were of smaller magnitude, our findings also suggest that some cancer types diagnosed almost exclusively among older AYAs, and therefore not included in most childhood cancer studies, such as breast, cervical/uterine, colon/rectal, and head and neck cancers, are also associated with an increased risk of CVD mortality compared to the general population. Notably, SMRs remained significantly elevated at more than 20 years post-diagnosis for AYAs with breast, cervical/uterine, and head and neck cancers, highlighting priority groups for long-term

cardiovascular surveillance and disease management additional to those identified in previous childhood cancer studies.

Infections are a significant cause of morbidity and treatment-related complications among cancer patients, and may develop as a consequence of neutropenia from aggressive chemotherapeutic regimens, exposure to invasive procedures or medical devices, hematopoietic stem cell transplantation (HSCT), malnutrition, and/or effects of the malignancy itself on immune function.[50, 51] The exceptionally high SMR for infectious disease mortality associated with NHL in our analyses is undoubtedly a reflection of its relationship with HIV infection, particularly given the time period spanned by our study. However, even when NHL patients were excluded, SMRs remained significantly elevated among all other AYAs with cancer combined. Other cancer types with noticeably high SMRs for infectious diseases included leukemia and HL, consistent with the potential for hematologic malignancies to directly compromise bone marrow, and with a greater likelihood of exposure to immunosuppressive chemotherapies and HSCT in these patients than in those with non-hematologic cancers.[55, 61] However, with the exception of melanoma and thyroid cancer, SMRs for infectious diseases were also significantly elevated for AYAs with all other cancer types we examined, likely reflecting a combination of treatment- and host-related risk factors. For some cancer types, including hematologic malignancies, CNS tumors, and cervical/uterine cancers, the increase persisted at more than 20 years post-diagnosis, and further research may be needed to investigate cancer treatment-related and other contributors to the long-term excess risk in these groups.

Though rare relative to deaths from cardiovascular and infectious diseases, deaths from renal diseases, defined in our analysis as nephritis, nephrotic syndrome, and nephrosis, were also increased among AYAs with cancer. Across cancer types that we evaluated, only soft tissue

sarcomas, thyroid cancer, melanoma, and breast cancer were not associated with an excess of renal disease mortality. Alkylating chemotherapies, such as ifosfamide and cisplatin, have been linked to nephrotoxicity in prior clinical studies, and are thought to be among the more common causes of kidney damage following cancer treatment.[64] However, other cancer therapies, including nitrosoureas, methotrexate, HSCT, anti-infective drugs, immunosuppressive drugs, and radiation to the kidneys (including from total body irradiation) may also be associated with acute and/or chronic nephrotoxicities,[64, 125] and may be at least partially responsible for the observed increases in deaths from renal diseases among AYAs with hematologic malignancies and other cancer types.

Our results suggest that mortality from suicide is significantly increased among AYA cancer survivors relative to the age-matched general population, potentially reflecting the psychological distress and reduced quality of life that may be associated with a cancer diagnosis and treatment. However, the SMR observed in the current study (1.23) is smaller than SMRs reported by most previous studies of suicide among predominately older adult cancer patients.[126-128] Though based on a small number of deaths, mortality from pregnancy-related complications was also elevated among AYA cancer survivors. This is consistent with a prior study reporting an increased risk of serious pregnancy complications, such as pre-eclampsia and post-partum hemorrhage, among women with an AYA cancer history.[129]

In our analyses, AYAs with melanoma and thyroid cancer had significantly lower noncancer mortality than the general population. Relative to many of the other cancer types that we examined, particularly those such as hematologic malignancies and CNS tumors, melanoma and thyroid cancer are more often treated with lower intensity regimens that would be less likely to increase risk of mortality from noncancer causes. Other factors specific to these cancer types

may also contribute to reduced mortality. Given the relationship between skin malignancies and sun exposure, patients with melanoma may be more physically active, on average, than the general population, potentially contributing to lower mortality from CVD and many other noncancer conditions. Higher socioeconomic status and greater access to healthcare may explain much of the reduction in noncancer mortality among AYAs with thyroid cancer, as these factors have been associated with a higher thyroid cancer incidence in the U.S.,[130] a relationship thought to be largely attributable to overdiagnosis.

Strengths of this study include the large population-based cohort and the more 3 million person-years of follow-up, which allowed us to examine noncancer mortality according to characteristics such as cancer type and time since diagnosis. A limitation of our analyses is the potential for cause of death misclassification due to inaccurate coding of death certificates. However, for several noncancer causes of death, including suicide[131] and coronary heart disease,[132] prior studies have suggested reasonable validity (sensitivity and specificity >70%) for cause of death codes abstracted from death certificates compared to the gold standard measure of cause of death determination by a physician review panel.[132, 133] In our sensitivity analyses, we found that the SMR for all noncancer mortality among AYAs of all cancer types combined remained significantly elevated even under the assumption that 30% of observed noncancer deaths had been misclassified. SMRs for cause-specific categories (e.g. “Diseases of the Heart”) represent weighted averages of the component conditions, potentially obscuring variation across finer subcategorizations. It will important to investigate more precisely defined outcomes in future etiological studies designed to better understand the pathophysiology of these conditions and pinpoint prevention efforts. Due to concerns over patient confidentiality, HIV deaths and deaths due to ‘other infectious and parasitic diseases’ are

combined into a single code in SEER data.[103] Therefore we could not directly evaluate the contribution of HIV-related deaths to elevated SMRs among AYAs with cancer. Also, we were unable to consider the impact of cancer relapse on our findings, as this information is not captured in SEER data. Lastly, elevated SMRs for cardiovascular disease and other noncancer causes may be largely attributable to acute complications or late effects of specific therapies received by AYAs with cancer. However, detailed cancer treatment information is not available in SEER, precluding analyses of noncancer mortality according to receipt of specific chemotherapeutic agents or chemo- or radiotherapy doses in this study.

Results of the current study suggest that AYAs with cancer face an elevated burden of mortality from noncancer causes relative to the general population that persists many years after cancer diagnosis, suggesting the importance of comprehensive, coordinated follow-up care throughout survivorship. Examining long-term patterns of noncancer health outcomes according to receipt of specific cancer therapies is an area for future research among AYA cancer survivors, particularly those diagnosed at ages 21-39 years who are not represented in studies of childhood cancer survivors.

5.5 Tables

Table 5.1. Characteristics of AYAs diagnosed with cancer, SEER 9, 1973-2015

	N Persons	% Persons	N Person-years	% Person-years
Total	235,641	100%	3,124,255.19	100%
Cancer type				
Leukemias	9,624	4%	70,566.31	2%
Non-Hodgkin lymphoma	14,209	6%	146,911.65	5%
Hodgkin lymphoma	15,974	7%	252,654.37	8%
CNS tumors	10,561	4%	98,698.03	3%
Soft tissue sarcomas [a]	8,345	4%	114,612.32	4%
Melanoma	27,923	12%	441,883.48	14%
Thyroid	26,406	11%	398,556.76	13%
Head and neck	5,923	3%	82,284.00	3%
Breast	36,225	15%	463,375.21	15%
Cervix/uterus	16,814	7%	275,709.66	9%
Colon and rectum	10,582	4%	104,123.26	3%
Testicular	18,957	8%	307,808.68	10%
Other	34,098	14%	367,071.46	12%
Sex				
Male	93,090	40%	1,169,179.46	37%
Female	142,551	60%	1,955,075.73	63%
Race				
White	192,774	82%	2,675,111.67	86%
Black	23,413	10%	242,498.40	8%
Other	19,454	8%	206,645.12	7%
Age at diagnosis				
15-19	15,357	7%	214,346.07	7%
20-24	25,518	11%	366,981.39	12%
25-29	41,679	18%	595,550.00	19%
30-34	62,308	26%	829,385.36	27%
35-39	90,779	39%	1,117,992.37	36%
Diagnosis year				
1973-1982	39,397	17%	876,954.72	28%
1983-1992	54,393	23%	1,012,284.10	32%
1993-2002	59,519	25%	797,044.47	26%
2003-2015	82,332	35%	437,971.91	14%

Abbreviations: AYAs, adolescents and young adults; CNS, central nervous system

[a] Excludes Kaposi sarcoma

Table 5.2. Rates of mortality from noncancer causes among AYAs with cancer compared to the general population

	Observed	Expected	SMR (95% CI)	Excess Risk [a]	Deaths per 100,000 PY among AYAs with cancer
All noncancer	12948	7053.34	1.84 (1.80-1.87)	18.87	414.43
Infectious	3068	597.58	5.13 (4.95-5.32)	7.91	98.20
Tuberculosis	9	5.11	1.76 (0.81-3.35)	0.01	0.29
Syphilis	0	0.22	0 (0-16.58)	0.00	0.00
Septicemia	319	121.14	2.63 (2.35-2.94)	0.63	10.21
Other Infectious and Parasitic Diseases including HIV	2,292	338.27	6.78 (6.50-7.06)	6.25	73.36
Pneumonia and Influenza	448	132.83	3.37 (3.07-3.70)	1.01	14.34
Cardiovascular	3,573	2311.77	1.55 (1.50-1.60)	4.04	114.36
Diseases of Heart	2,906	1841.72	1.58 (1.52-1.64)	3.41	93.01
Hypertension without Heart Disease	75	56.89	1.32 (1.04-1.65)	0.06	2.40
Cerebrovascular Diseases	489	340.24	1.44 (1.31-1.57)	0.48	15.65
Atherosclerosis	20	10.26	1.95 (1.19-3.01)	0.03	0.64
Aortic Aneurysm and Dissection	37	36.72	1.01 (0.71-1.39)	0.00	1.18
Other Diseases of Arteries, Arterioles, Capillaries	46	25.93	1.77 (1.30-2.37)	0.06	1.47
Respiratory					
Chronic Obstructive Pulmonary Disease and Allied Conditions	408	351.95	1.16 (1.05-1.28)	0.18	13.06
Gastrointestinal and liver	370	336.63	1.10 (0.99-1.22)	0.11	11.84
Stomach and Duodenal Ulcers	33	13.68	2.41 (1.66-3.39)	0.06	1.06
Chronic Liver Disease and Cirrhosis	337	322.95	1.04 (0.94-1.16)	0.04	10.79
Renal					
Nephritis, Nephrotic Syndrome and Nephrosis	270	112.39	2.40 (2.12-2.71)	0.50	8.64
External	1,802	1668.25	1.08 (1.03-1.13)	0.43	57.68
Accidents and Adverse Effects	1,120	1042.17	1.07 (1.01-1.14)	0.25	35.85
Suicide and Self-Inflicted Injury	540	437.42	1.23 (1.13-1.34)	0.33	17.28

Homicide and Legal Intervention	142	188.67	0.75 (0.63-0.89)	-0.15	4.55
Other	3457	1674.78	2.06 (2.00-2.13)	5.70	110.65
Diabetes Mellitus	373	304.65	1.22 (1.10-1.36)	0.22	11.94
Alzheimers disease (ICD-9 and 10 only)	28	28.93	0.97 (0.64-1.40)	0.00	0.90
Complications of Pregnancy, Childbirth, Puerperium	66	8.73	7.56 (5.84-9.61)	0.18	2.11
Congenital Anomalies	95	42.61	2.23 (1.80-2.73)	0.17	3.04
Certain Conditions Originating in Perinatal Period	4	0.33	12.04 (3.28-30.83)	0.01	0.13
Symptoms, Signs and Ill-Defined Conditions	258	142.55	1.81 (1.60-2.04)	0.37	8.26
Other Causes of Death	2,633	1146.98	2.30 (2.21-2.38)	4.76	84.28

Abbreviations: AYAs, adolescents and young adults; PY, person-years; SMR, standardized mortality ratio; HIV, human immunodeficiency virus

[a] Deaths per 10,000 person-years

Table 5.3. SMRs for mortality from all noncancer causes, infectious diseases, cardiovascular diseases, and respiratory diseases among AYAs with cancer according to patient characteristics

	All noncancer		Infectious		Cardiovascular		Respiratory	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Cancer type								
Leukemias	703	5.26 (4.87-5.66)	187	16.06 (13.84-18.53)	111	3.06 (2.52-3.69)	18	4.69 (2.78-7.42)
Non-Hodgkin lymphoma	2212	6.33 (6.07-6.60)	1521	47.71 (45.35-50.17)	224	2.05 (1.79-2.34)	20	1.55 (0.95-2.40)
Hodgkin lymphoma	1551	3.12 (2.96-3.28)	308	6.80 (6.07-7.61)	625	4.44 (4.10-4.81)	33	2.08 (1.43-2.93)
CNS tumors	593	3.37 (3.11-3.66)	91	5.71 (4.59-7.01)	150	3.32 (2.81-3.90)	8	1.70 (0.73-3.35)
Soft tissue sarcomas [a]	391	1.38 (1.25-1.52)	51	1.93 (1.43-2.53)	108	1.16 (0.95-1.40)	14	1.13 (0.62-1.90)
Melanoma	662	0.65 (0.60-0.70)	82	1.03 (0.82-1.27)	185	0.54 (0.47-0.63)	18	0.33 (0.19-0.51)
Thyroid	606	0.81 (0.75-0.88)	42	0.70 (0.51-0.95)	204	0.84 (0.73-0.96)	24	0.58 (0.37-0.86)
Other head and neck	489	2.09 (1.91-2.29)	64	3.15 (2.42-4.02)	151	1.80 (1.53-2.11)	36	3.32 (2.33-4.60)
Breast	1197	1.25 (1.18-1.32)	116	1.47 (1.22-1.77)	457	1.38 (1.25-1.51)	49	0.72 (0.53-0.95)
Cervix/uterus	1145	2.03 (1.91-2.15)	112	2.45 (2.02-2.95)	361	1.83 (1.65-2.03)	75	1.83 (1.44-2.29)
Colon and rectum	513	1.76 (1.61-1.91)	109	4.20 (3.45-5.06)	140	1.35 (1.14-1.59)	12	0.84 (0.43-1.47)
Testicular	998	1.10 (1.03-1.17)	133	1.70 (1.42-2.01)	295	1.03 (0.91-1.15)	19	0.66 (0.40-1.04)
Sex								
Male	7108	1.94 (1.90-1.99)	2293	7.08 (6.79-7.37)	1787	1.49 (1.42-1.56)	136	1.12 (0.94-1.32)
Female	5840	1.72 (1.68-1.77)	775	2.83 (2.64-3.04)	1786	1.61 (1.54-1.69)	272	1.18 (1.05-1.33)
Age at diagnosis								
15-19	666	2.63 (2.44-2.84)	108	5.77 (4.73-6.97)	164	4.04 (3.45-4.71)	11	3.00 (1.50-5.37)
20-24	1235	2.28 (2.15-2.41)	216	4.52 (3.94-5.17)	328	2.77 (2.48-3.09)	23	1.91 (1.21-2.87)
25-29	2075	1.94 (1.86-2.03)	525	5.34 (4.89-5.82)	542	1.83 (1.68-1.99)	55	1.50 (1.13-1.96)
30-34	3449	1.83 (1.77-1.89)	960	5.78 (5.42-6.16)	884	1.42 (1.33-1.52)	102	1.11 (0.91-1.35)
35-39	5523	1.67 (1.63-1.72)	1259	4.72 (4.46-4.99)	1655	1.34 (1.28-1.41)	217	1.07 (0.91-1.19)
Time since diagnosis (years)								
2 mo - <1	2017	10.30 (9.85-10.76)	1274	67.49 (63.84-71.30)	157	5.47 (4.65-6.40)	4	2.44 (0.66-6.24)
1- <5	2416	2.92 (2.81-3.04)	785	9.56 (8.91-10.26)	373	2.52 (2.28-2.79)	20	2.37 (1.45-3.66)

5-<10	1625	1.65 (1.57-1.73)	314	3.15 (2.81-3.52)	381	1.61 (1.45-1.78)	18	1.19 (0.70-1.88)
10-<20	2857	1.41 (1.36-1.46)	351	1.92 (1.72-2.13)	972	1.44 (1.36-1.54)	83	1.24 (0.99-1.54)
20+	4033	1.34 (1.29-1.38)	344	1.61 (1.44-1.79)	1690	1.38 (1.31-1.45)	283	1.09 (0.97-1.22)

Abbreviations: SMR-standardized mortality ratio; AYAs-adolescents and young adults; CNS-central nervous system

[a] Excludes Kaposi sarcoma

Table 5.4. SMRs for mortality from gastrointestinal (GI) and liver diseases, renal diseases, external causes, and other causes among AYAs with cancer according to patient characteristics

	GI and liver		Renal		External		Other	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Cancer type								
Leukemias	25	4.06 (2.63-5.99)	16	10.25 (5.86-16.65)	71	1.53 (1.19-1.92)	275	9.89 (8.76-11.13)
Non-Hodgkin lymphoma	18	1.07 (0.63-1.68)	23	4.81 (3.05-7.22)	125	1.27 (1.06-1.51)	281	3.73 (3.31-4.19)
Hodgkin lymphoma	25	1.07 (0.69-1.58)	24	3.97 (2.55-5.91)	189	1.18 (1.02-1.36)	347	3.28 (2.94-3.64)
CNS tumors	9	1.11 (0.51-2.11)	10	5.25 (2.52-9.65)	114	1.80 (1.48-2.16)	211	5.77 (5.02-6.61)
Soft tissue sarcomas [a]	12	0.93 (0.48-1.63)	4	0.86 (0.24-2.21)	84	1.21 (0.96-1.50)	118	1.83 (1.52-2.19)
Melanoma	20	0.38 (0.23-0.59)	5	0.34 (0.11-0.79)	156	0.65 (0.55-0.76)	196	0.81 (0.70-0.93)
Thyroid	21	0.58 (0.36-0.89)	19	1.51 (0.91-2.36)	112	0.67 (0.55-0.80)	184	0.97 (0.83-1.12)
Other head and neck	19	1.65 (0.99-2.58)	11	2.98 (1.49-5.33)	93	1.81 (1.46-2.22)	115	2.22 (1.83-2.66)
Breast	40	0.96 (0.69-1.31)	21	1.02 (0.63-1.55)	136	0.94 (0.79-1.11)	378	1.40 (1.26-1.55)
Cervix/uterus	38	1.57 (1.11-2.16)	42	3.40 (2.45-4.60)	135	1.58 (1.33-1.87)	382	2.40 (2.16-2.65)
Colon and rectum	21	1.52 (0.94-2.33)	18	3.58 (2.12-5.66)	74	1.19 (0.94-1.50)	139	2.06 (1.73-2.43)
Testicular	49	1.01 (0.75-1.34)	18	1.78 (1.06-2.82)	249	0.90 (0.79-1.02)	235	1.32 (1.16-1.50)
Sex								
Male	199	1.06 (0.92-1.22)	126	2.85 (2.37-3.39)	1084	1.02 (0.96-1.09)	1483	2.06 (1.96-2.17)
Female	171	1.15 (0.98-1.33)	144	2.11 (1.78-2.49)	718	1.18 (1.10-1.27)	1974	2.06 (1.97-2.16)
Age at diagnosis								
15-19	15	1.95 (1.09-3.22)	13	6.77 (3.60-11.57)	144	1.08 (0.91-1.28)	211	4.44 (3.86-5.08)
20-24	31	1.38 (0.93-1.95)	27	4.99 (3.29-7.25)	261	1.17 (1.03-1.32)	349	3.10 (2.79-3.45)
25-29	52	1.01 (0.75-1.32)	40	2.91 (2.08-3.96)	337	1.02 (0.92-1.14)	524	2.16 (1.98-2.36)
30-34	105	1.11 (0.91-1.34)	59	1.96 (1.49-2.53)	445	1.04 (0.94-1.14)	894	1.98 (1.85-2.11)
35-39	167	1.04 (0.89-1.21)	131	2.14 (1.79-2.54)	615	1.11 (1.03-1.20)	1479	1.80 (1.71-1.90)
Time since diagnosis (years)								
2 mo - <1	25	3.99 (2.58-5.89)	27	19.47 (12.83-28.33)	133	1.32 (1.10-1.56)	397	10.42 (9.42-11.49)
1- <5	49	1.53 (1.13-2.03)	41	6.40 (4.59-8.68)	427	1.12 (1.01-1.23)	721	4.31 (4.00-4.64)

5-<10	61	1.25 (0.96-1.61)	20	2.19 (1.34-3.38)	381	1.05 (0.94-1.16)	450	2.14 (1.94-2.34)
10-<20	110	0.94 (0.77-1.13)	59	2.24 (1.70-2.89)	516	1.05 (0.96-1.14)	766	1.64 (1.53-1.76)
20+	125	0.94 (0.79-1.13)	123	1.78 (1.48-2.12)	345	1.05 (0.95-1.17)	1123	1.42 (1.34-1.50)

Abbreviations: SMR-standardized mortality ratio; AYAs-adolescents and young adults; GI-gastrointestinal; CNS-central nervous system

[a] Excludes Kaposi sarcoma

Table 5.5. SMRs for mortality from all noncancer causes, infectious diseases, cardiovascular diseases and respiratory diseases among AYAs with cancer according to stage, stratified by cancer type

	All noncancer		Infectious		Cardiovascular		Respiratory	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Non-Hodgkin lymphoma [a]								
I	650	8.03 (7.43-8.68)	503	66.47 (60.79, 72.54)	51	2.25 (1.70, 2.99)	3	1.39 (0.29, 4.07)
II	193	4.88 (4.21-5.61)	120	33.93 (28.13, 40.57)	19	1.75 (1.06, 2.74)	0	0 (0, 3.35)
III	221	9.88 (8.62-11.27)	143	54.52 (45.95, 64.22)	26	3.61 (2.36, 5.29)	3	4.48 (0.92, 13.09)
IV	758	12.36 (11.49-13.27)	592	98.13 (90.38, 106.40)	38	2.27 (1.61, 3.12)	6	3.75 (1.37, 8.15)
Hodgkin lymphoma [a]								
I	157	2.02 (1.71-2.36)	19	2.58 (1.56, 4.04)	65	3.17 (2.45, 4.04)	1	0.49 (0.01, 2.70)
II	300	2.56 (2.28-2.86)	60	5.86 (4.47, 7.55)	117	4.18 (3.46, 5.01)	3	1.04 (0.21, 3.03)
III	183	3.11 (2.67-3.59)	48	8.68 (6.40, 11.51)	52	3.61 (2.69, 4.73)	3	2.25 (0.46, 6.58)
IV	168	4.27 (3.65-4.97)	70	18.01 (14.04, 22.76)	34	3.29 (2.28, 4.59)	3	3.09 (0.64, 9.02)
Soft tissue sarcomas [b]								
Localized	234	1.24 (1.09-1.41)	24	1.39 (0.89, 2.07)	72	1.14 (0.89, 1.43)	8	0.92 (0.40, 1.81)
Regional	82	1.44 (1.14-1.78)	8	1.44 (0.62, 2.83)	22	1.22 (0.76, 1.84)	3	1.41 (0.29, 4.11)
Distant	28	5.71 (379-8.25)	7	15.48 (6.22, 31.89)	6	5.22 (1.91, 11.35)	0	0 (0, 37.69)
Melanoma								
Localized	545	0.60 (0.55-0.66)	63	0.90 (0.69, 1.15)	156	0.52 (0.44, 0.61)	16	0.33 (0.19, 0.53)
Regional	49	0.96 (0.71-1.27)	7	1.74 (0.70, 3.59)	10	0.63 (0.30, 1.15)	1	0.44 (0.01, 2.44)
Distant	15	2.47 (1.38-4.07)	5	9.81 (3.19, 22.90)	4	2.53 (0.82, 5.90)	0	0 (0, 14.59)
Thyroid								
Localized	334	0.77 (0.69-0.85)	24	0.70 (0.45, 1.04)	120	0.84 (0.70, 1.00)	13	0.51 (0.27, 0.88)
Regional	226	0.85 (0.74-0.97)	18	0.85 (0.50, 1.34)	65	0.77 (0.60, 0.98)	8	0.58 (0.25, 1.15)
Distant	27	1.14 (0.75-1.65)	0	0 (0, 1.87)	10	1.33 (0.64, 2.45)	2	1.74 (0.21, 6.30)
Other head and neck								
Localized	231	1.65 (1.44-1.88)	25	2.11 (1.36, 3.11)	74	1.44 (1.13, 1.81)	16	2.30 (1.31, 3.73)
Regional	139	2.26 (1.90-2.66)	26	4.53 (2.96, 6.63)	56	2.65 (2.00, 3.44)	12	2.36 (2.62, 8.87)
Distant	36	4.42 (3.09-6.12)	8	9.67 (4.17, 19.05)	6	2.30 (0.84, 5.00)	2	7.24 (0.88, 26.16)

Breast								
Localized	588	0.99 (0.91-1.08)	46	0.96 (0.70, 1.28)	207	0.99 (0.86, 1.13)	32	0.73 (0.50, 1.03)
Regional	519	1.58 (1.44-1.72)	56	2.02 (1.53, 2.62)	212	1.90 (1.66, 2.18)	18	0.81 (0.48, 1.29)
Distant	47	4.00 (2.94-5.32)	10	9.33 (4.48, 17.16)	21	6.30 (3.90, 9.63)	0	0 (0, 6.98)
Cervix/uterus								
Localized	854	1.81 (1.70-1.94)	76	2.02 (1.59, 2.52)	277	1.68 (1.49, 1.89)	60	1.73 (1.32, 2.23)
Regional	174	2.95 (2.53-3.42)	25	5.07 (3.28, 7.49)	43	2.16 (1.56, 2.90)	10	2.53 (1.21, 4.65)
Distant	28	4.84 (3.22-7.00)	4	8.37 (2.28, 21.43)	11	5.72 (2.86, 10.24)	1	2.78 (0.07, 15.50)
Colon and rectum								
Localized	204	1.38 (1.19-1.58)	39	3.01 (2.14, 4.11)	68	1.27 (0.99, 1.61)	6	0.79 (0.29, 1.73)
Regional	213	1.84 (1.60-2.10)	42	4.08 (2.94, 5.51)	51	1.24 (0.92, 1.62)	5	0.90 (0.29, 2.10)
Distant	59	4.44 (3.38-5.73)	15	12.04 (6.74, 19.85)	12	3.11 (1.61, 5.43)	0	0 (0, 7.84)
Testicular								
Localized	570	0.91 (0.84-0.99)	66	1.24 (0.96, 1.57)	171	0.86 (0.73, 1.00)	10	0.50 (0.24, 0.92)
Regional	243	1.30 (1.14-1.47)	34	2.06 (1.43, 2.88)	74	1.26 (0.99, 1.58)	4	0.69 (0.19, 1.78)
Distant	162	2.19 (1.86-2.55)	30	4.58 (3.09, 6.54)	40	1.82 (1.30, 2.47)	3	1.49 (0.31, 4.34)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Ann Arbor staging classification, includes patients diagnosed in 1983 and later only

[b] Excludes Kaposi sarcoma

Table 5.6. SMRs for mortality from gastrointestinal (GI) and liver diseases, renal diseases, external causes, and other causes among AYAs with cancer according to stage, stratified by cancer type

	GI and liver		Renal		External		Other	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Non-Hodgkin lymphoma [a]								
I	1	0.25 (0.01, 1.38)	7	7.04 (2.83, 14.49)	26	0.98 (0.64, 1.44)	59	3.43 (2.61, 4.42)
II	1	0.51 (0.01, 2.85)	4	8.45 (2.30, 21.64)	15	1.14 (0.64, 1.88)	34	4.01 (2.77, 5.60)
III	3	2.31 (0.48, 6.74)	0	0 (0, 11.74)	18	2.10 (1.25, 3.32)	28	5.06 (3.36, 7.32)
IV	5	1.67 (0.54, 3.90)	9	12.39 (5.67, 23.52)	30	1.47 (0.99, 2.10)	78	6.07 (4.80, 7.58)
Hodgkin lymphoma [a]								
I	6	1.64 (0.60, 3.56)	0	0 (0, 4.05)	26	0.97 (0.63, 1.42)	40	2.42 (1.73, 3.29)
II	5	0.95 (0.31, 2.23)	1	0.77 (0.02, 4.31)	50	1.13 (0.84, 1.49)	64	2.51 (1.93, 3.20)
III	3	1.12 (0.23, 3.28)	5	7.95 (2.58, 18.56)	33	1.49 (1.02, 2.09)	39	3.21 (2.29, 4.39)
IV	1	0.57 (0.01, 3.15)	4	8.58 (2.34, 21.96)	16	1.16 (0.66, 1.89)	40	4.90 (3.50, 6.67)
Soft tissue sarcomas [b]								
Localized	7	0.82 (0.33, 1.69)	3	0.96 (0.33, 1.69)	54	1.22 (0.92, 1.59)	66	1.53 (1.18, 1.95)
Regional	3	1.15 (0.24, 3.35)	0	0 (0, 4.03)	18	1.20 (0.71, 1.90)	28	2.18 (1.45, 3.15)
Distant	0	0 (0, 19.78)	0	0 (0, 67.37)	4	2.02 (0.55, 5.17)	11	11.16 (5.57, 19.97)
Melanoma								
Localized	15	0.33 (0.18, 0.54)	3	0.23 (0.05, 0.67)	130	0.62 (0.52, 0.73)	162	0.76 (0.64, 0.88)
Regional	2	0.78 (0.09, 2.82)	0	0 (0, 5.60)	15	1.07 (0.60, 1.76)	14	1.23 (0.67, 2.06)
Distant	0	0 (0, 11.87)	0	0 (0, 47.41)	1	0.61 (0.02, 3.39)	5	3.84 (1.25, 8.96)
Thyroid								
Localized	8	0.39 (0.17, 0.76)	9	1.19 (0.54, 2.25)	58	0.63 (0.47, 0.81)	102	0.91 (0.74, 1.10)
Regional	12	0.93 (0.48, 1.62)	9	2.14 (0.98, 4.06)	44	0.69 (0.50, 0.92)	70	1.06 (0.83, 1.34)
Distant	1	0.87 (0.02, 4.82)	1	2.73 (0.07, 15.19)	5	0.85 (0.28, 1.98)	8	1.40 (0.61, 2.77)
Other head and neck								
Localized	10	1.46 (0.70, 2.68)	6	2.68 (0.98, 5.83)	49	1.67 (1.24, 2.21)	51	1.62 (1.21, 2.13)
Regional	5	1.58 (0.51, 3.69)	2	2.13 (0.26, 7.69)	29	1.94 (1.30, 2.79)	41	3.06 (2.20, 4.15)
Distant	2	5.00 (0.61, 18.05)	2	15.71 (1.90, 56.74)	6	2.82 (1.03, 6.13)	10	5.64 (2.71, 10.38)

Breast								
Localized	21	0.82 (0.51, 1.26)	9	0.69 (0.31, 1.30)	83	0.97 (0.78, 1.21)	190	1.13 (0.98, 1.31)
Regional	16	1.09 (0.62, 1.77)	8	1.17 (0.50, 2.30)	41	0.76 (0.51, 1.03)	168	1.81 (1.55, 2.11)
Distant	1	1.85 (0.05, 10.33)	2	9.93 (1.20, 35.88)	3	1.07 (0.22, 3.14)	10	3.04 (1.46, 5.60)
Cervix/uterus								
Localized	29	1.45 (0.97, 2.08)	34	3.29 (2.28, 4.60)	102	1.46 (1.19, 1.77)	276	2.08 (1.84, 2.34)
Regional	4	1.53 (0.42, 3.91)	4	3.26 (0.89, 8.36)	20	2.06 (1.26, 3.18)	68	4.10 (3.18, 5.20)
Distant	0	0 (0, 14.49)	2	16.91 (2.05, 61.07)	2	1.93 (0.23, 6.96)	8	4.97 (2.15, 9.79)
Colon and rectum								
Localized	6	0.86 (0.32, 1.88)	5	1.91 (0.62, 4.45)	23	0.76 (0.48, 1.15)	57	1.65 (1.25, 2.14)
Regional	13	2.36 (1.25, 4.03)	7	3.54 (1.42, 7.29)	41	1.66 (1.19, 2.25)	54	2.03 (1.53, 2.65)
Distant	0	0 (0, 5.96)	6	33.20 (12.18, 72.26)	5	1.26 (0.41, 2.94)	21	7.12 (4.41, 10.89)
Testicular								
Localized	34	1.02 (0.71, 1.42)	7	0.99 (0.40, 2.05)	158	0.84 (0.72, 0.98)	124	1.01 (0.84, 1.20)
Regional	6	0.60 (0.22, 1.31)	7	3.46 (1.39, 7.13)	56	0.96 (0.73, 1.25)	62	1.70 (1.30, 2.18)
Distant	7	1.85 (0.74, 3.81)	4	5.19 (1.41, 13.29)	32	1.29 (0.88, 1.82)	46	3.26 (2.39, 4.35)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Ann Arbor staging classification, includes patients diagnosed in 1983 and later only

[b] Excludes Kaposi sarcoma

Table 5.7 SMRs for mortality from all noncancer causes, infectious diseases, cardiovascular diseases, and respiratory diseases among AYAs with cancer according to time since diagnosis, stratified by cancer type

	All noncancer		Infectious		Cardiovascular		Respiratory	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Leukemias								
2 mo- <1 year	165	19.75 (16.85, 23.00)	53	70.96 (53.13, 92.82)	17	16.40 (9.55, 26.26)	0	0 (0, 66.41)
1 - <5 years	281	10.57 (9.37, 11.88)	85	33.78 (26.98, 41.77)	29	6.98 (4.68, 10.03)	4	19.07 (5.20, 48.82)
5- <10 years	92	3.71 (2.99, 4.54)	18	7.50 (4.45, 11.86)	20	3.68 (2.25, 5.68)	6	20.45 (7.51, 44.52)
10-<20 years	95	2.37 (1.92, 2.90)	20	5.64 (3.45, 8.71	22	1.77 (1.11, 2.68)	3	2.94 (0.61, 8.59)
20+ years	70	2.06 (1.61, 2.61)	11	4.51 (2.25, 8.07)	23	1.75 (1.11, 2.62)	5	2.22 (0.72, 5.18)
Non-Hodgkin lymphoma								
2 mo- <1 year	1125	81.40 (76.71, 86.30)	1007	624.07 (586.13, 663.83)	31	16.03 (10.89, 22.76)	0	0 (0, 37.57)
1 - <5 years	505	9.50 (8.69, 10.37)	339	57.50 (51.54, 63.96)	36	3.85 (2.69, 5.32)	3	6.55 (1.35, 19.15)
5- <10 years	186	3.12 (2.69, 3.60)	90	14.13 (11.37, 17.37)	27	1.89 (1.24, 2.74)	0	0 (0, 4.83)
10-<20 years	218	2.03 (1.77, 2.31)	63	6.36 (4.88, 8.13)	54	1.50 (1.13, 1.96)	9	3.05 (1.40, 5.79)
20+ years	178	1.55 (1.33, 1.79)	22	2.72 (1.71, 4.12)	76	1.59 (1.25, 1.99)	8	0.93 (0.40, 1.83)
Hodgkin lymphoma								
2 mo- <1 year	85	6.03 (4.81, 57.85)	50	43.88 (32.57, 57.85)	6	4.12 (1.51, 8.96)	0	0 (0, 42.82)
1 - <5 years	235	3.68 (3.22, 4.18)	90	15.31 (12.31, 15.21)	42	5.06 (3.64, 6.84)	0	0 (0, 8.12)
5- <10 years	204	2.68 (2.32, 3.07)	51	6.24 (4.64, 8.20)	49	3.42 (2.53, 4.52)	0	0 (0, 4.77)
10-<20 years	393	2.58 (2.33, 2.85)	54	3.41 (2.56, 4.45)	184	4.24 (3.65, 4.89)	4	1.23 (0.34, 3.16)
20+ years	634	3.32 (3.07, 3.59)	63	4.42 (3.40, 5.66)	344	4.71 (4.22, 5.23)	29	2.57 (1.72, 3.69)
CNS tumors								
2 mo- <1 year	62	6.60 (5.06, 8.46)	22	26.47 (16.59, 40.07)	12	10.47 (5.41, 18.29)	0	0 (0, 62.03)
1 - <5 years	140	4.06 (3.41, 4.79)	27	8.25 (5.44, 12.00)	22	4.35 (2.73, 6.59)	1	3.86 (0.10, 21.52)
5- <10 years	78	2.37 (1.88, 2.96)	10	2.99 (1.43, 5.50)	12	1.82 (0.94, 3.19)	0	0 (0, 10.04)
10-<20 years	145	2.80 (2.37, 3.30)	17	3.43 (2.00, 5.49)	38	2.56 (1.81, 3.51)	1	0.82 (0.02, 4.56)
20+ years	168	3.56 (3.04, 4.14)	15	4.23 (2.37, 6.98)	66	3.77 (2.91, 4.79)	6	2.15 (0.79, 4.67)

Soft tissue sarcomas [a]								
2 mo- <1 year	34	4.37 (3.03, 6.11)	9	11.54 (5.28, 21.91)	2	1.94 (0.24, 7.02)	0	0 (63.01)
1 - <5 years	64	1.99 (1.53, 2.54)	17	4.86 (2.83, 7.78)	9	1.68 (0.77, 3.20)	0	0 (0, 12.87)
5- <10 years	59	1.55 (1.18, 2.00)	8	1.81 (0.78, 3.56)	14	1.59 (0.87, 2.68)	1	2.03 (0.05, 11.33)
10-<20 years	89	1.11 (0.89, 1.36)	5	0.59 (0.19, 1.39)	35	1.32 (0.92, 1.83)	2	0.91 (0.11, 3.30)
20+ years	145	1.16 (0.98, 1.36)	12	1.28 (0.66, 2.24)	48	0.93 (0.69, 1.23)	11	1.18 (0.59, 2.10)
Melanoma								
2 mo- <1 year	27	1.20 (0.79, 1.74)	6	3.01 (1.11, 6.56)	6	1.88 (0.69, 4.09)	0	0 (0, 22.21)
1 - <5 years	90	0.84 (0.68, 1.04)	19	1.92 (1.16, 3.00)	12	0.64 (0.33, 1.11)	3	3.04 (0.63, 8.87)
5- <10 years	101	0.74 (0.60, 0.90)	14	1.10 (0.60, 1.85)	24	0.73 (0.47, 1.09)	0	0 (0, 1.82)
10-<20 years	176	0.59 (0.51, 0.68)	18	0.74 (0.44, 1.17)	54	0.54 (0.41, 0.71)	2	0.20 (0.02, 0.71)
20+ years	268	0.58 (0.51, 0.65)	25	0.81 (0.52, 1.19)	89	0.48 (0.38, 0.58)	13	0.31 (0.17, 0.53)
Thyroid								
2 mo- <1 year	17	1.02 (0.59, 1.63)	1	0.75 (0.02, 4.17)	2	0.84 (0.10, 3.03)	0	0 (0, 22.99)
1 - <5 years	67	0.85 (0.66, 1.08)	4	0.60 (0.16, 1.52)	15	1.09 (0.61, 1.80)	0	0 (0, 4.03)
5- <10 years	79	0.80 (0.64, 1.00)	7	0.79 (0.32, 1.63)	20	0.88 (0.54, 1.36)	0	0 (0, 2.18)
10-<20 years	163	0.80 (0.68, 0.93)	10	0.57 (0.27, 1.04)	55	0.85 (0.64, 1.11)	6	0.84 (0.31, 1.83)
20+ years	280	0.80 (0.70, 0.89)	20	0.80 (0.49, 1.23)	112	0.81 (0.66, 0.97)	18	0.57 (0.34, 0.90)
Other head and neck								
2 mo- <1 year	26	4.06 (2.65, 5.95)	6	8.63 (3.17, 18.78)	3	2.87 (0.59, 8.39)	0	0 (0, 78.54)
1 - <5 years	87	3.27 (2.62, 4.03)	22	7.55 (4.73, 11.44)	16	3.00 (1.72, 4.87)	2	8.52 (1.03, 30.77)
5- <10 years	75	2.32 (1.83, 2.91)	4	1.14 (0.31, 2.92)	23	2.64 (1.67, 3.95)	2	4.65 (0.56, 16.81)
10-<20 years	132	1.98 (1.66, 2.35)	22	3.54 (2.22, 5.36)	39	1.59 (1.13, 2.18)	9	4.63 (2.12, 8.78)
20+ years	169	1.67 (1.42, 1.94)	10	1.43 (0.68, 2.63)	70	1.58 (1.23, 2.00)	23	2.82 (1.78, 4.22)
Breast								
2 mo- <1 year	54	2.29 (1.72, 2.98)	11	4.51 (2.25, 8.07)	11	2.34 (1.17, 4.18)	0	0 (0, 10.63)
1 - <5 years	206	1.93 (1.68, 2.22)	31	2.89 (1.97, 4.10)	56	2.27 (1.72, 2.95)	1	0.53 (0.01, 2.93)
5- <10 years	160	1.26 (1.07, 1.47)	17	1.42 (0.83, 2.28)	48	1.33 (0.98, 1.76)	2	0.59 (0.07, 2.14)
10-<20 years	303	1.13 (1.00, 1.26)	20	0.89 (0.54, 1.38)	112	1.18 (0.97, 1.42)	11	0.77 (0.38, 1.38)
20+ years	481	1.11 (1.01, 1.21)	38	1.21 (0.86, 1.66)	232	1.34 (1.18, 1.53)	36	0.74 (0.52, 1.02)

Cervix/uterus								
2 mo- <1 year	47	4.82 (3.54, 6.41)	10	11.05 (5.30, 20.32)	10	5.65 (2.71, 10.38)	0	0 (0, 28.47)
1 - <5 years	109	2.45 (2.01, 2.95)	20	4.81 (2.94, 7.42)	20	2.12 (1.30, 3.28)	1	1.40 (0.04, 7.82)
5- <10 years	126	2.10 (1.75, 2.50)	14	2.52 (1.38, 4.23)	33	2.07 (1.43, 2.91)	2	1.43 (0.17, 5.16)
10-<20 years	304	2.06 (1.83, 2.30)	24	1.89 (1.21, 2.82)	102	2.03 (1.66, 2.47)	12	1.74 (0.90, 3.05)
20+ years	559	1.84 (1.69, 2.00)	44	1.97 (1.43, 2.64)	196	1.64 (1.42, 1.88)	60	1.88 (1.44, 2.42)
Colon and rectum								
2 mo- <1 year	60	5.55 (4.23, 7.14)	23	18.64 (11.82, 27.97)	7	3.82 (1.53, 7.86)	0	0 (0, 40.62)
1 - <5 years	116	2.92 (2.42, 3.51)	44	9.64 (7.01, 12.94)	21	2.53 (1.57, 3.87)	1	2.46 (0.06, 13.73)
5- <10 years	89	2.10 (1.68, 2.58)	21	4.56 (2.82, 6.96)	18	1.52 (0.90, 2.40)	1	1.52 (0.04, 8.47)
10-<20 years	109	1.32 (1.08, 1.59)	14	1.87 (1.02, 3.13)	37	1.19 (0.84, 1.65)	2	0.73 (0.09, 2.64)
20+ years	139	1.19 (1.00, 1.41)	7	0.87 (0.35, 1.79)	57	1.13 (0.85, 1.46)	8	0.77 (0.33, 1.52)
Testicular								
2 mo- <1 year	51	2.22 (1.65, 2.92)	12	5.96 (3.08, 10.40)	4	1.64 (0.45, 4.20)	0	0 (0, 37.31)
1 - <5 years	135	1.28 (1.07, 1.51)	26	2.46 (1.60, 3.60)	12	0.82 (0.42, 1.43)	0	0 (0, 6.76)
5- <10 years	126	0.95 (0.79, 1.13)	19	1.30 (0.78, 2.03)	24	0.87 (0.56, 1.29)	0	0 (0, 3.49)
10-<20 years	276	0.99 (0.87, 1.11)	41	1.55 (1.11, 2.11)	82	0.92 (0.73, 1.14)	3	0.56 (0.12, 1.65)
20+ years	410	1.12 (1.01, 1.23)	35	1.42 (0.99, 1.97)	173	1.13 (0.96, 1.31)	16	0.74 (0.42, 1.20)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Excludes Kaposi sarcoma

Table 5.8 SMRs for mortality from gastrointestinal (GI) and liver diseases, renal diseases, external causes, and other causes among AYAs with cancer according to time since diagnosis, stratified by cancer type

	GI and liver		Renal		External		Other	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Leukemias								
2 mo- <1 year	0	0 (0, 17.05)	2	41.18 (4.99, 148.74)	18	3.72 (2.20, 5.88)	75	53.15 (41.81, 66.62)
1 - <5 years	7	8.24 (3.31, 16.99)	5	28.50 (9.25, 66.50)	24	1.72 (1.10, 2.56)	127	26.87 (22.40, 31.98)
5- <10 years	5	4.67 (1.52, 10.91)	1	4.80 (0.12, 26.76)	13	1.23 (0.65, 2.10)	29	6.03 (4.04, 8.66)
10-<20 years	6	2.66 (0.98, 5.79)	3	6.28 (1.29, 18.34)	14	1.19 (0.65, 2.00)	27	3.15 (2.08, 4.59)
20+ years	7	3.96 (1.59, 8.15)	5	7.69 (2.50, 17.94)	2	0.37 (0.05, 1.34)	17	2.05 (1.19, 3.28)
Non-Hodgkin lymphoma								
2 mo- <1 year	4	10.18 (2.77, 26.07)	6	68.24 (25.04, 148.53)	14	1.92 (1.05, 3.21)	63	26.38 (20.27, 33.75)
1 - <5 years	3	1.58 (0.33, 4.62)	5	12.89 (4.19, 30.08)	30	1.18 (0.80, 1.69)	89	9.12 (7.33, 11.23)
5- <10 years	0	0 (0, 1.31)	3	5.54 (1.14, 16.20)	29	1.26 (0.84, 1.81)	37	3.14 (2.21, 4.33)
10-<20 years	3	0.48 (0.10, 1.39)	6	4.44 (1.63, 9.65)	39	1.39 (0.98, 1.89)	44	1.91 (1.39, 2.56)
20+ years	8	1.45 (0.63, 2.86)	3	1.25 (0.26, 3.64)	13	0.90 (0.48, 1.54)	48	1.69 (1.25, 2.24)
Hodgkin lymphoma								
2 mo- <1 year	0	0 (0, 13.47)	0	0 (0, 50.87)	9	1.03 (0.47, 1.95)	20	8.69 (5.31, 13.42)
1 - <5 years	4	2.47 (0.67, 6.33)	3	8.09 (1.67, 23.63)	41	1.13 (0.81, 1.53)	55	4.99 (3.76, 6.50)
5- <10 years	2	0.71 (0.09, 2.56)	1	1.79 (0.05, 9.97)	45	1.28 (0.94, 1.72)	56	3.88 (2.93, 5.03)
10-<20 years	8	1.00 (0.43, 1.96)	4	2.48 (0.68, 6.36)	53	1.10 (0.83, 1.44)	86	2.67 (2.14, 3.30)
20+ years	11	1.04 (0.52, 1.86)	16	4.67 (2.67, 7.59)	41	1.27 (0.91, 1.72)	130	2.83 (2.36, 3.36)
CNS tumors								
2 mo- <1 year	0	0 (0, 15.22)	1	20.03 (0.51, 111.58)	8	1.46 (0.63, 2.88)	19	12.01 (7.23, 18.75)
1 - <5 years	3	2.82 (0.58, 8.25)	4	19.65 (5.35, 50.31)	35	1.89 (1.31, 2.62)	48	7.88 (5.81, 10.44)
5- <10 years	1	0.74 (0.02, 4.11)	0	0 (0, 15.15)	24	1.64 (1.05, 2.44)	31	4.90 (3.33, 6.96)
10-<20 years	4	1.43 (0.39, 3.65)	3	5.32 (1.10, 15.54)	29	1.78 (1.19, 2.56)	53	4.80 (3.59, 6.28)
20+ years	1	0.38 (0.01, 2.13)	2	2.37 (0.29, 8.55)	18	2.14 (1.27, 3.38)	60	5.22 (3.98, 6.72)

Soft tissue sarcomas [a]								
2 mo- <1 year	0	0 (0, 17.27)	0	0 (0, 71.47)	8	1.88 (0.81, 3.70)	15	10.80 (6.04, 17.81)
1 - <5 years	0	0 (0, 3.36)	0	0 (0, 15.38)	16	1.02 (0.58, 1.66)	22	3.65 (2.28, 5.52)
5- <10 years	2	1.19 (0.14, 4.31)	0	0 (0, 10.51)	16	1.09 (0.62, 1.77)	18	2.35 (1.39, 3.71)
10-<20 years	5	1.16 (0.38, 2.71)	0	0 (0, 3.43)	19	0.94 (0.57, 1.47)	23	1.31 (0.83, 1.96)
20+ years	5	0.90 (0.29, 2.10)	4	1.37 (0.37, 3.51)	25	1.70 (1.10, 2.51)	40	1.26 (0.90, 1.72)
Melanoma								
2 mo- <1 year	0	0 (0, 5.21)	0	0 (0, 28.47)	6	0.50 (0.18, 1.08)	9	2.10 (0.96, 3.99)
1 - <5 years	3	0.71 (0.15, 2.07)	0	0 (0, 5.43)	30	0.59 (0.40, 0.84)	23	1.09 (0.69, 1.64)
5- <10 years	4	0.56 (0.15, 1.42)	0	0 (0, 3.47)	32	0.65 (0.42, 0.87)	27	0.94 (0.62, 1.36)
10-<20 years	4	0.21 (0.06, 0.55)	3	0.89 (0.18, 2.61)	54	0.73 (0.55, 0.95)	41	0.60 (0.43, 0.82)
20+ years	9	0.42 (0.19, 0.80)	2	0.21 (0.03, 0.76)	34	0.67 (0.47, 0.94)	96	0.80 (0.65, 0.98)
Thyroid								
2 mo- <1 year	0	0 (0, 7.02)	0	0 (0, 28.48)	9	1.06 (0.48, 2.01)	5	1.36 (0.44, 3.16)
1 - <5 years	3	0.97 (0.20, 2.84)	1	1.49 (0.04, 8.31)	20	0.55 (0.34, 0.86)	24	1.34 (0.86, 2.00)
5- <10 years	4	0.80 (0.22, 2.05)	1	1.02 (0.03, 5.71)	25	0.69 (0.45, 1.03)	22	0.95 (0.60, 1.45)
10-<20 years	8	0.67 (0.29, 1.31)	5	1.87 (0.61, 4.36)	31	0.62 (0.42, 0.88)	48	0.97 (0.71, 1.28)
20+ years	6	0.39 (0.14, 0.86)	12	1.48 (0.76, 2.59)	27	0.73 (0.48, 1.06)	85	0.89 (0.71, 1.10)
Other head and neck								
2 mo- <1 year	1	4.01 (0.10, 22.36)	3	66.77 (13.77, 195.13)	3	0.95 (0.20, 2.78)	10	8.60 (4.12, 15.81)
1 - <5 years	1	0.83 (0.02, 4.63)	2	9.98 (1.21, 36.04)	22	1.87 (1.17, 2.83)	22	4.40 (2.76, 6.66)
5- <10 years	2	2.26 (0.62, 5.80)	0	0 (0, 12.78)	26	2.32 (1.52, 3.40)	16	2.51 (1.44, 4.08)
10-<20 years	9	2.23 (1.02, 4.23)	4	4.84 (1.32, 12.38)	18	1.19 (0.71, 1.88)	31	2.20 (1.50, 3.13)
20+ years	4	0.94 (0.26, 2.40)	2	0.86 (0.10, 3.10)	24	2.36 (1.51, 3.51)	36	1.43 (1.00, 1.98)
Breast								
2 mo- <1 year	2	1.86 (0.23, 6.73)	2	7.38 (0.89, 26.65)	10	1.18 (0.57, 2.17)	18	2.85 (1.69, 4.51)
1 - <5 years	5	0.92 (0.30, 2.15)	4	3.13 (0.85, 8.01)	31	0.91 (0.62, 1.29)	78	2.74 (2.17, 3.42)
5- <10 years	10	1.39 (0.67, 2.55)	1	0.58 (0.01, 3.24)	29	0.89 (0.60, 1.28)	53	1.55 (1.16, 2.03)
10-<20 years	15	1.04 (0.58, 1.71)	3	0.61 (0.13, 1.79)	44	1.01 (0.73, 1.35)	98	1.32 (1.07, 1.61)
20+ years	8	0.59 (0.25, 1.16)	12	0.96 (0.50, 1.67)	22	0.82 (0.51, 1.24)	133	1.04 (0.87, 1.23)

Cervix/uterus								
2 mo- <1 year	4	9.47 (2.58, 24.26)	2	19.10 (2.31, 69.01)	7	1.82 (0.73, 3.76)	14	5.44 (2.98, 9.13)
1 - <5 years	4	1.83 (0.50, 4.68)	3	6.01 (1.24, 17.58)	22	1.40 (0.88, 2.12)	39	3.31 (2.35, 4.53)
5- <10 years	4	1.20 (0.33, 3.08)	2	2.68 (0.32, 9.68)	27	1.59 (1.05, 2.31)	44	2.75 (2.00, 3.70)
10-<20 years	10	1.24 (0.60, 2.29)	6	2.47 (0.91, 5.37)	47	1.73 (1.27, 2.30)	103	2.56 (2.09, 3.10)
20+ years	16	1.57 (0.90, 2.55)	29	3.39 (2.27, 4.87)	32	1.48 (1.01, 2.09)	182	2.05 (1.76, 2.37)
Colon and rectum								
2 mo- <1 year	1	2.50 (0.06, 13.95)	4	47.01 (12.81, 120.36)	3	0.59 (0.12, 1.72)	22	10.59 (6.64, 16.04)
1 - <5 years	2	1.14 (0.14, 4.13)	4	11.53 (3.14, 29.51)	27	1.65 (1.09, 2.39)	17	2.15 (1.25, 3.44)
5- <10 years	5	2.17 (0.70, 5.06)	2	4.47 (0.54, 16.13)	17	1.25 (0.73, 1.99)	25	2.82 (1.82, 4.16)
10-<20 years	5	1.03 (0.33, 2.40)	3	2.46 (0.51, 7.19)	20	1.19 (0.72, 1.83)	28	1.53 (1.01, 2.20)
20+ years	8	1.79 (0.77, 3.53)	5	1.71 (0.55, 3.98)	7	0.70 (0.28, 1.45)	47	1.55 (1.14, 2.07)
Testicular								
2 mo- <1 year	0	0 (0, 7.17)	2	22.24 (2.69, 80.34)	17	1.17 (0.68, 1.88)	16	4.83 (2.76, 7.84)
1 - <5 years	2	0.63 (0.08, 2.26)	1	2.08 (0.05, 11.61)	57	0.95 (0.72, 1.23)	37	2.28 (1.60, 3.14)
5- <10 years	6	1.01 (0.37, 2.19)	1	1.26 (0.03, 7.02)	50	0.83 (0.61, 1.09)	26	1.15 (0.75, 1.68)
10-<20 years	20	1.15 (0.70, 1.77)	4	1.57 (0.43, 4.01)	71	0.83 (0.65, 1.05)	55	1.03 (0.77, 1.34)
20+ years	21	0.99 (0.61, 1.51)	10	1.62 (0.78, 2.98)	54	0.96 (0.72, 1.25)	101	1.23 (1.00, 1.49)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Excludes Kaposi sarcoma

Table 5.9. SMRs for mortality from all noncancer causes, infectious diseases, cardiovascular diseases, and respiratory diseases among AYAs with cancer according to age at diagnosis, stratified by cancer type

	All noncancer		Infectious		Cardiovascular		Respiratory	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Leukemias								
15-19	103	6.39 (5.22-7.75)	24	24.51 (15.71-36.47)	11	5.23 (2.61-9.36)	2	11.94 (1.45-43.13)
20-24	109	8.02 (6.59-9.68)	23	22.28 (14.13-33.44)	8	3.62 (1.56-7.14)	4	22.29 (6.07-57.06)
25-29	122	6.28 (5.22-7.50)	37	19.51 (13.74-26.90)	26	5.87 (3.84-8.60)	3	7.87 (1.62-23.00)
30-34	150	4.88 (4.13-5.72)	39	13.51 (9.61-18.47)	25	2.84 (1.84-4.20)	2	2.25 (0.27-8.15)
35-39	219	4.06 (3.54-4.64)	64	13.19 (10.16-16.85)	41	2.19 (1.58-2.98)	7	3.15 (1.27-6.50)
Non-Hodgkin lymphoma								
15-19	67	3.88 (3.01-4.93	15	13.20 (7.39-21.77)	16	6.64 (3.80-10.79)	0	0 (0-19.96)
20-24	157	5.70 (4.84-6.67)	73	29.62 (23.21-37.24)	25	4.58 (2.97-6.77)	0	0 (0-7.81)
25-29	349	7.05 (6.33-7.83)	238	48.45 (42.49-55.01)	36	2.86 (2.01-3.96)	3	2.38 (0.49-6.96)
30-34	708	7.66 (7.10-8.24)	543	60.82 (55.81-66.16)	60	2.05 (1.56-2.63)	8	2.40 (1.03-4.72)
35-39	931	5.72 (5.36-6.10)	652	45.17 (41.77-48.77)	87	1.46 (1.17-1.80)	9	1.18 (0.54-2.24)
Hodgkin lymphoma								
15-19	206	3.67 (3.19-4.21)	32	7.29 (4.99-10.29)	79	8.71 (6.90-10.86)	5	6.28 (2.04-14.65)
20-24	337	3.57 (3.20-3.98)	58	6.76 (5.13-8.73)	138	7.01 (5.89-8.28)	6	3.25 (1.19-7.07)
25-29	354	2.99 (2.69-3.32)	75	6.50 (5.11-8.14)	141	4.45 (3.75-5.25)	6	1.79 (0.66-3.89)
30-34	343	2.95 (2.65-3.28)	79	7.23 (5.73-9.02)	132	3.50 (2.93-4.15)	7	1.56 (0.63-3.22)
35-39	311	2.76 (2.47-3.09)	64	6.51 (5.02-8.32)	135	3.17 (2.66-3.76)	9	1.68 (0.77-3.19)
CNS tumors								
15-19	52	2.23 (1.67-2.92)	5	2.93 (0.95-6.83)	12	3.35 (1.73-5.85)	0	0 (0-12.21)
20-24	108	4.32 (3.54-5.22)	16	7.72 (4.41-12.53)	15	3.24 (1.81-5.34)	1	2.54 (0.06-14.18)
25-29	119	3.83 (3.17-4.58)	28	9.17 (6.10-13.26)	28	3.96 (2.63-5.73)	3	4.25 (0.88-12.41)
30-34	157	3.77 (3.20-4.41)	26	6.22 (4.07-9.12)	41	3.55 (2.55-4.81)	2	1.75 (0.21-6.32)
35-39	157	2.87 (2.44-3.36)	16	3.24 (1.85-5.26)	54	2.95 (2.21-3.85)	2	0.93 (0.11-3.35)
Soft tissue sarcomas [a]								
15-19	30	1.68 (1.13-2.40)	4	2.75 (0.75-7.04)	4	1.31 (0.36-3.37)	0	0 (0-13.60)

20-24	44	1.53 (1.11-2.05)	3	1.06 (0.22-3.09)	8	1.21 (0.52-2.37)	0	0 (0-5.88)
25-29	60	1.23 (0.94-1.58)	9	1.79 (0.82-3.40)	14	1.01 (0.55-1.69)	3	1.96 (0.40-5.72)
30-34	109	1.57 (1.29-1.89)	15	2.18 (1.22-3.60)	28	1.18 (0.79-1.71)	4	1.34 (0.36-3.43)
35-39	147	1.26 (1.06-1.48)	20	1.98 (1.21-3.06)	53	1.16 (0.87-1.52)	7	1.01 (0.41-2.08)
Melanoma								
15-19	14	0.74 (0.41-1.25)	1	0.83 (0.02-4.60)	1	0.33 (0.01-1.84)	0	0 (0-11.62)
20-24	42	0.68 (0.49-0.92)	4	0.83 (0.23-2.12)	11	0.82 (0.41-1.48)	1	0.64 (0.02-3.55)
25-29	110	0.70 (0.58-0.84)	14	1.07 (0.59-1.80)	28	0.64 (0.43-0.93)	4	0.66 (0.18-1.69)
30-34	183	0.62 (0.53-0.71)	19	0.79 (0.47-1.23)	45	0.46 (0.34-0.62)	5	0.33 (0.11-0.76)
35-39	313	0.64 (0.57-0.71)	44	1.20 (0.87-1.61)	100	0.54 (0.44-0.66)	8	0.25 (0.11-0.49)
Thyroid								
15-19	24	1.10 (0.71-1.64)	1	0.61 (0.02-3.38)	7	1.78 (0.72-3.67)	0	0 (0-7.89)
20-24	56	0.85 (0.64-1.11)	4	0.73 (0.20-1.86)	16	1.05 (0.60-1.70)	0	0 (0-1.81)
25-29	120	0.90 (0.75-1.08)	10	0.91 (0.44-1.68)	36	0.97 (0.68-1.34)	6	1.02 (0.38-2.23)
30-34	164	0.73 (0.62-0.85)	13	0.71 (0.38-1.22)	56	0.75 (0.57-0.97)	7	0.54 (0.22-1.12)
35-39	242	0.79 (0.70-0.90)	14	0.60 (0.33-1.01)	89	0.80 (0.64-0.98)	11	0.54 (0.27-0.96)
Other head and neck								
15-19	14	2.49 (1.36-4.18)	2	4.43 (0.54-16.01)	6	6.59 (2.42-14.34)	0	0 (0-41.74)
20-24	23	1.72 (1.09-2.57)	3	2.24 (0.46-6.55)	6	1.91 (0.70-4.15)	1	3.36 (0.08-18.70)
25-29	60	2.18 (1.66-2.81)	12	4.56 (2.36-7.97)	18	2.25 (1.33-3.55)	3	3.25 (0.67-9.49)
30-34	92	1.64 (1.32-2.01)	15	2.87 (1.61-4.73)	24	1.24 (0.79-1.85)	8	3.27 (1.41-6.45)
35-39	300	2.29 (2.04-2.57)	32	2.99 (2.05-4.23)	97	1.85 (1.50-2.26)	24	3.39 (2.17-5.05)
Breast [b]								
15-24	12	2.08 (1.07-3.63)	0	0 (0-6.43)	7	5.01 (2.01-10.32)	0	0 (0-20.01)
25-29	84	1.71 (1.36-2.12)	5	1.07 (0.35-2.50)	26	1.87 (1.22-2.74)	6	2.61 (0.96-5.68)
30-34	316	1.44 (1.29-1.61)	36	1.87 (1.31-2.58)	114	1.61 (1.33-1.93)	12	0.90 (0.46-1.56)
35-39	792	1.16 (1.08-1.24)	76	1.40 (1.10-1.75)	312	1.26 (1.13-1.41)	32	0.61 (0.42-0.86)
Cervix/uterus [b]								
15-24	44	2.19 (1.59-2.94)	4	2.01 (0.55-5.14)	8	1.50 (0.65-2.96)	4	5.10 (1.39-13.06)
25-29	164	2.02 (1.72-2.36)	17	2.35 (1.37-3.76)	44	1.81 (1.31-2.43)	9	2.08 (0.95-3.95)
30-34	333	1.88 (1.68-2.09)	34	2.33 (1.61-3.25)	102	1.68 (1.37-2.05)	20	1.61 (0.99-2.49)

35-39	604	2.11 (1.95-2.29)	57	2.61 (1.98-3.38)	207	1.94 (1.68-2.22)	42	1.79 (1.29-2.42)
Colon and rectum [b]								
15-24	26	2.64 (1.73-3.87)	3	3.84 (0.79-11.21)	8	4.06 (1.75-7.99)	0	0 (0-17.12)
25-29	60	2.33 (1.78-3.00)	10	3.82 (1.83-7.03)	13	1.85 (0.98-3.16)	1	1.32 (0.03-7.38)
30-34	137	1.92 (1.61-2.27)	40	5.94 (4.24-8.08)	28	1.20 (0.80-1.74)	3	0.96 (0.20-2.82)
35-39	290	1.56 (1.39-1.76)	56	3.54 (2.67-4.59)	91	1.27 (1.03-1.56)	8	0.78 (0.34-1.54)
Testicular								
15-19	45	1.44 (1.05-1.93)	9	4.19 (1.91-7.95)	10	2.06 (0.99-3.79)	0	0 (0-12.05)
20-24	137	1.16 (0.97-1.37)	11	1.06 (0.53-1.90)	33	1.27 (0.88-1.79)	3	1.59 (0.33-4.64)
25-29	247	1.13 (0.99-1.28)	39	1.92 (1.37-2.63)	68	1.12 (0.87-1.41)	3	0.58 (0.12-1.70)
30-34	308	1.14 (1.02-1.28)	42	1.75 (1.26-2.37)	101	1.11 (0.91-1.35)	6	0.66 (0.24-1.44)
35-39	261	0.97 (0.85-1.09)	32	1.48 (1.01-2.09)	83	0.79 (0.63-0.98)	7	0.57 (0.23-1.18)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Excludes Kaposi sarcoma

[b] Ages 15-19 and 20-24 years were combined due to small numbers of patients diagnosed at ages 15-19 years

Table 5.10. SMRs for mortality from gastrointestinal (GI) and liver diseases, renal diseases, external causes, and other causes among AYAs with cancer according to age at diagnosis, stratified by cancer type

	GI and liver		Renal		External		Other	
	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)	N deaths	SMR (95% CI)
Leukemias								
15-19	2	5.26 (0.64-18.99)	3	30.82 (6.36-90.07)	14	1.45 (0.79-2.43)	47	17.19 (12.63-22.85)
20-24	5	12.20 (3.96-28.48)	1	9.36 (0.24-52.14)	18	2.54 (1.50-4.01)	50	19.58 (14.53-25.81)
25-29	2	2.44 (0.30-8.82)	3	14.78 (3.05-43.20)	10	1.29 (0.62-2.38)	41	10.46 (7.50-14.18)
30-34	4	2.55 (0.70-6.54)	4	10.59 (2.89-27.12)	15	1.56 (0.87-2.57)	61	9.24 (7.07-11.87)
35-39	12	4.02 (2.08-7.02)	5	6.44 (2.09-15.04)	14	1.13 (0.62-1.90)	76	6.34 (4.99-7.93)
Non-Hodgkin lymphoma								
15-19	1	2.27 (0.06-12.66)	2	18.27 (2.21-66.01)	12	1.20 (0.62-2.09)	21	7.15 (4.43-10.93)
20-24	3	3.05 (0.63-8.92)	3	11.90 (2.45-34.77)	22	1.74 (1.09-2.64)	31	5.85 (3.98-8.30)
25-29	3	1.36 (0.28-3.97)	5	8.68 (2.82-20.26)	22	1.25 (0.79-1.90)	42	4.04 (2.91-5.46)
30-34	4	0.85 (0.23-2.17)	3	2.39 (0.49-7.00)	25	1.01 (0.65-1.49)	65	3.24 (2.50-4.13)
35-39	7	0.82 (0.33-1.69)	10	3.86 (1.85-7.11)	44	1.32 (0.96-1.77)	122	3.33 (2.76-3.97)
Hodgkin lymphoma								
15-19	3	1.72 (0.36-5.04)	5	11.89 (3.86-27.74)	33	1.13 (0.78-1.59)	49	4.65 (3.44-6.15)
20-24	6	1.57 (0.57-3.41)	5	5.78 (1.88-13.48)	56	1.38 (1.04-1.80)	68	3.58 (2.78-4.54)
25-29	6	1.05 (0.38-2.28)	5	3.67 (1.19-8.57)	41	1.04 (0.75-1.41)	80	3.15 (2.50-3.92)
30-34	9	1.48 (0.68-2.82)	4	2.48 (0.68-6.35)	30	1.01 (0.68-1.45)	82	3.17 (2.52-3.94)
35-39	1	1.68 (0.77-3.19)	5	2.81 (0.91-6.56)	29	1.33 (0.89-1.90)	68	2.70 (2.10-3.43)
CNS tumors								
15-19	1	1.53 (0.04-8.50)	1	6.03 (0.15-33.58)	15	1.18 (0.66-1.94)	18	4.32 (2.56-6.83)
20-24	1	1.10 (0.03-6.13)	2	10.15 (1.23-36.66)	25	2.08 (1.34-3.07)	48	10.09 (7.44-13.38)
25-29	2	1.54 (0.19-5.56)	4	12.60 (3.43-32.26)	18	1.48 (0.87-2.33)	36	5.57 (3.90-7.72)
30-34	2	0.93 (0.11-3.36)	0	0 (0-7.70)	26	1.97 (1.29-2.88)	60	6.72 (5.13-8.65)
35-39	3	0.98 (0.20-2.86)	3	4.02 (0.83-11.74)	30	2.27 (1.53-3.25)	49	4.01 (2.97-5.30)
Soft tissue sarcomas [a]								
15-19	1	1.77 (0.04-9.84)	1	6.74 (0.17-37.55)	7	0.78 (0.31-1.61)	13	3.83 (2.04-6.55)
20-24	0	0 (0-3.23)	0	0 (0-11.28)	18	1.59 (0.94-2.52)	15	2.53 (1.42-4.18)
25-29	1	0.44 (0.01-2.46)	0	0 (0-5.43)	17	1.16 (0.68-1.86)	16	1.48 (0.85-2.41)

30-34	5	1.48 (0.48-3.46)	1	0.84 (0.02-4.70)	19	1.24 (0.75-1.94)	37	2.30 (1.62-3.17)
35-39	5	0.92 (0.30-2.14)	2	0.88 (0.11-3.17)	23	1.24 (0.79-1.87)	37	1.33 (0.93-1.83)
Melanoma								
15-19	0	0 (0-5.84)	0	0 (0-27.02)	10	1.02 (0.49-1.88	2	0.53 (0.06-1.92)
20-24	0	0 (0-1.36)	1	1.70 (0.04-9.46)	14	0.55 (0.30-0.93)	11	0.81 (0.41-1.45)
25-29	4	0.51 (0.14-1.30)	0	0 (1.95)	27	0.56 (0.37-0.82)	33	0.91 (0.62-1.27)
30-34	9	0.57 (0.26-1.09)	4	0.95 (0.26-2.43)	44	0.63 (0.46-0.85)	57	0.81 (0.61-1.05)
35-39	7	0.28 (0.11-0.57)	0	0 (0-0.46)	61	0.70 (0.54-0.91)	93	0.79 (0.64-0.96)
Thyroid								
15-19	1	1.26 (0.03-7.02)	0	0 (0-17.86)	6	0.61 (0.22-1.33)	9	1.82 (0.83-3.46)
20-24	2	0.68 (0.08-2.45)	4	5.01 (1.36-12.82)	17	0.73 (0.43-1.17)	13	0.82 (0.43-1.39)
25-29	3	0.46 (0.10-1.36)	5	2.57 (0.84-6.01)	26	0.71 (0.46-1.03)	34	1.01 (0.70-1.42)
30-34	6	0.54 (0.20-1.19)	3	0.77 (0.16-2.25)	31	0.67 (0.45-0.95)	15	0.26 (0.15-0.43)
35-39	9	0.61 (0.28-1.16)	7	1.22 (0.49-2.52)	32	0.63 (0.43-0.89)	80	1.02 (0.81-1.27)
Other head and neck								
15-19	0	0 (0-24.62)	0	0 (0-73.04)	3	1.04 (0.22-3.05)	3	2.73 (0.56-7.99)
20-24	0	0 (0-6.64)	1	6.49 (0.16-36.16)	7	1.36 (0.55-2.79)	5	1.81 (0.59-4.23)
25-29	1	0.74 (0.02-4.10)	0	0 (0-10.10)	11	1.34 (0.67-2.40)	15	2.48 (1.39-4.10)
30-34	4	1.38 (0.37-3.52)	0	0 (0-4.39)	18	1.41 (0.83-2.22)	23	1.85 (1.17-2.78)
35-39	14	2.14 (1.17-3.59)	10	4.38 (2.10-8.05)	54	2.42 (1.81-3.15)	69	2.34 (1.82-2.96)
Breast [b]								
15-24	1	4.73 (0.12-26.36)	0	0 (0-39.07)	3	1.73 (0.36-5.06)	1	0.63 (0.02-3.52)
25-29	1	0.47 (0.01-2.62)	3	3.38 (0.70-9.87)	17	1.47 (0.86-2.36)	26	1.89 (1.24-2.77)
30-34	10	1.03 (0.49-1.88)	5	1.11 (0.36-2.59)	43	1.09 (0.79-1.47)	96	1.56 (1.26-1.90)
35-39	28	0.94 (0.63-1.37)	14	0.92 (0.50-1.54)	73	0.78 (0.62-0.99)	257	1.33 (1.17-1.50)
Cervix/uterus [b]								
15-24	2	2.38 (0.29-8.61)	1	2.89 (0.07-16.13)	7	1.33 (0.53-2.73)	18	3.26 (1.93-5.14)
25-29	7	1.90 (0.76-3.91)	4	2.61 (0.71-6.68)	27	1.57 (1.03-2.28)	56	2.46 (1.86-3.19)
30-34	13	1.67 (0.89-2.85)	12	3.12 (1.61-5.45)	43	1.53 (1.10-2.05)	109	2.17 (1.78-2.62)
35-39	16	1.35 (0.77-2.20)	25	3.78 (2.45-5.58)	58	1.67 (1.27-2.16)	199	2.46 (2.13-2.83)
Colon and rectum [b]								
15-24	2	5.41 (0.65-19.54)	0	0 (0-40.39)	3	0.68 (0.14-1.98)	10	5.03 (2.41-9.25)

25-29	2	1.73 (0.21-6.24)	4	11.60 (3.16-29.70)	12	1.46 (0.75-2.55)	18	3.19 (1.89-5.05)
30-34	3	0.86 (0.18-2.52)	5	4.47 (1.45-10.44)	17	0.99 (0.58-1.59)	41	2.49 (1.79-3.38)
35-39	14	1.59 (0.87-2.67)	9	2.59 (1.18-4.92)	42	1.31 (0.94-1.76)	70	1.61 (1.26-2.04)
Testicular								
15-19	1	1.02 (0.03-5.69)	0	0 (0-20.98)	16	0.90 (0.51-1.46)	9	1.82 (0.83-3.46)
20-24	5	0.96 (0.31-2.24)	5	5.47 (1.78-12.76)	44	0.83 (0.60-1.11)	36	1.72 (1.21-2.38)
25-29	10	0.87 (0.42-1.60)	2	0.95 (0.11-3.42)	64	0.84 (0.64-1.07)	61	1.46 (1.12-1.88)
30-34	18	1.17 (0.70-1.85)	5	1.59 (0.52-3.72)	71	0.96 (0.75-1.22)	65	1.20 (0.92-1.53)
35-39	15	0.98 (0.55-1.62)	6	1.60 (0.59-3.49)	54	0.97 (0.73-1.26)	64	1.14 (0.88-1.45)

Abbreviations: SMR, standardized mortality ratio; AYAs, adolescents and young adults; GI, gastrointestinal

[a] Excludes Kaposi sarcoma

[b] Ages 15-19 and 20-24 years were combined due to small numbers of patients diagnosed at ages 15-19 years

Table 5.11. Sensitivity analysis varying the latency exclusion period

	0 month latency exclusion		6 month latency exclusion	
	Observed	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
All noncancer	13792	1.94 (1.91, 1.98)	11854	1.70 (1.67, 1.73)
Infectious	3590	5.97 (5.77, 6.17)	2311	3.92 (3.76, 4.08)
Tuberculosis	10	1.94 (0.93, 3.56)	9	1.80 (0.82, 3.41)
Syphilis	0	0 (0, 16.42)	0	0 (0, 16.88)
Septicemia	330	2.72 (2.43, 3.03)	298	2.47 (2.20, 2.77)
Other Infectious and Parasitic Diseases including HIV	2785	8.16 (7.86, 8.47)	1584	4.76 (4.53, 5.01)
Pneumonia and Influenza	465	3.48 (3.17, 3.82)	420	3.19 (2.89, 3.51)
Cardiovascular	3667	1.58 (1.53, 1.63)	3500	1.52 (1.47, 1.57)
Diseases of Heart	2977	1.61 (1.56, 1.67)	2847	1.55 (1.50, 1.61)
Hypertension without Heart Disease	77	1.35 (1.07, 1.69)	75	1.32 (1.04, 1.66)
Cerebrovascular Diseases	509	1.49 (1.36, 1.63)	478	1.41 (1.29, 1.55)
Atherosclerosis	21	2.04 (1.26, 3.12)	20	1.95 (1.19, 3.02)
Aortic Aneurysm and Dissection	37	1.00 (0.71, 1.38)	36	0.99 (0.69, 1.37)
Other Diseases of Arteries, Arterioles, Capillaries	46	1.77 (1.29, 2.36)	44	1.71 (1.24, 2.29)
Respiratory				
Chronic Obstructive Pulmonary Disease and Allied Conditions	411	1.17 (1.06, 1.29)	405	1.15 (1.04, 1.27)
Gastrointestinal and liver	385	1.14 (1.03, 1.26)	355	1.06 (0.95, 1.18)
Stomach and Duodenal Ulcers	35	2.55 (1.78, 3.54)	30	2.21 (1.49, 3.15)
Chronic Liver Disease and Cirrhosis	350	1.08 (0.97, 1.20)	325	1.01 (0.91, 1.13)
Renal				
Nephritis, Nephrotic Syndrome and Nephrosis	286	2.54 (2.25, 2.85)	260	2.33 (2.05, 2.63)

External	1834	1.09 (1.04, 1.14)	1746	1.07 (1.02, 1.13)
Accidents and Adverse Effects	1143	1.08 (1.02, 1.15)	1087	1.07 (1.01, 1.13)
Suicide and Self-Inflicted Injury	546	1.23 (1.13, 1.34)	524	1.23 (1.12, 1.33)
Homicide and Legal Intervention	145	0.75 (0.64, 0.89)	135	0.74 (0.62, 0.88)
Other	3619	2.15 (2.08, 2.22)	3277	1.98 (1.91, 2.04)
Diabetes Mellitus	378	1.24 (1.12, 1.37)	372	1.23 (1.11, 1.36)
Alzheimers (ICD-9 and 10 only)	28	0.97 (0.64, 1.40)	28	0.97 (0.64, 1.40)
Complications of Pregnancy, Childbirth, Puerperium	76	8.51 (6.71, 10.66)	56	6.70 (5.06, 8.70)
Congenital Anomalies	105	2.44 (2.00, 2.95)	91	2.18 (1.75, 2.67)
Certain Conditions Originating in Perinatal Period	4	11.85 (3.23, 30.33)	4	12.44 (3.39, 31.84)
Symptoms, Signs and Ill-Defined Conditions	260	1.81 (1.59, 2.04)	249	1.78 (1.56, 2.01)
Other Cause of Death	2768	2.40 (2.31, 2.49)	2477	2.18 (2.09, 2.27)

*Per 10,000 person-years

Table 5.12. Sensitivity analysis of cause of death misclassification, varying the extent to which observed deaths from noncancer causes among AYAs with cancer are overestimated

		10% overestimated		20% overestimated		30% overestimated	
	Expected	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**	**Observed**	**SMR (95% CI)**
All noncancer	7053.34	11653	1.65 (1.62, 1.68)	10358	1.47 (1.44, 1.50)	9064	1.29 (1.26, 1.31)
Infectious	597.58	2761	4.62 (4.45, 4.80)	2454	4.11 (3.95, 4.27)	2148	3.59 (3.44, 3.75)
Tuberculosis	5.11	8	1.59 (0.81, 3.09)	7	1.41 (0.68, 2.82)	6	1.23 (0.55, 2.56)
Syphilis	0.22	0	0	0	0	0	0
Septicemia	121.14	287	2.37 (2.11, 2.66)	255	2.11 (1.86, 2.38)	223	1.84 (1.62, 2.10)
Other Infectious and Parasitic Diseases including HIV	338.27	2063	6.10 (5.84, 6.36)	1834	5.42 (5.18, 5.67)	1604	4.74 (4.52, 4.98)
Pneumonia and Influenza	132.83	403	3.04 (2.75, 3.35)	358	2.70 (2.43, 2.99)	314	2.36 (2.11, 2.63)
Cardiovascular	2311.77	3216	1.39 (1.34, 1.44)	2858	1.24 (1.19, 1.28)	2501	1.08 (1.04, 1.13)
Diseases of Heart	1841.72	2615	1.42 (1.37, 1.48)	2325	1.26 (1.21, 1.31)	2034	1.11 (1.06, 1.15)
Hypertension without Heart Disease	56.89	68	1.19 (0.93, 1.50)	60	1.06 (0.80, 1.36)	53	0.92 (0.70, 1.20)
Cerebrovascular Diseases	340.24	440	1.29 (1.18, 1.42)	391	1.15 (1.04, 1.27)	342	1.01 (0.90, 1.12)
Atherosclerosis	10.26	18	1.75 (1.04, 2.77)	16	1.56 (0.89, 2.53)	14	1.36 (0.75, 2.29)
Aortic Aneurysm and Dissection	36.72	33	0.91 (0.64, 1.26)	30	0.81 (0.55, 1.13)	26	0.71 (0.46, 1.01)
Other Diseases of Arteries, Arterioles, Capillaries	25.93	41	1.60 (1.17, 2.15)	37	1.42 (1.01, 1.92)	32	1.24 (0.88, 1.74)
Respiratory							
Chronic Obstructive Pulmonary Disease and Allied Conditions	351.95	367	1.04 (0.94, 1.16)	326	0.93 (0.83, 1.03)	286	0.81 (0.72, 0.91)
Gastrointestinal and liver	336.63	333	0.99 (0.89, 1.10)	296	0.88 (0.78, 0.99)	259	0.77 (0.68, 0.87)
Stomach and Duodenal Ulcers	13.68	30	2.17 (1.48, 3.04)	26	1.93 (1.30, 2.78)	23	1.69 (1.12, 2.52)

Chronic Liver Disease and Cirrhosis	322.95	303	0.94 (0.84, 1.05)	270	0.83 (0.74, 0.94)	236	0.73 (0.64, 0.83)
Renal							
Nephritis, Nephrotic Syndrome and Nephrosis	112.39	243	2.16 (1.90, 2.45)	216	1.92 (1.67, 2.20)	189	1.68 (1.45, 1.94)
External	1668.25	1622	0.97 (0.93, 1.02)	1442	0.86 (0.82, 0.91)	1261	0.76 (0.72, 0.80)
Accidents and Adverse Effects	1042.17	1008	0.97 (0.91, 1.03)	896	0.86 (0.80, 0.92)	784	0.75 (0.70, 0.81)
Suicide and Self-Inflicted Injury	437.42	486	1.11 (1.01, 1.21)	432	0.99 (0.90, 1.09)	378	0.86 (0.78, 0.96)
Homicide and Legal Intervention	188.67	128	0.68 (0.57, 0.90)	114	0.60 (0.50, 0.72)	99	0.53 (0.43, 0.64)
Other	1674.78	3111	1.86 (1.79, 1.92)	2766	1.65 (1.59, 1.71)	2420	1.45 (1.39, 1.50)
Diabetes Mellitus	304.65	336	1.10 (0.99, 1.22)	298	0.98 (0.87, 1.10)	261	0.86 (0.76, 0.97)
Alzheimers (ICD-9 and 10 only)	28.93	25	0.87 (0.59, 1.28)	22	0.77 (0.50, 1.15)	20	0.68 (0.42, 1.03)
Complications of Pregnancy, Childbirth, Puerperium	8.73	59	6.80 (5.24, 8.71)	53	6.05 (4.55, 7.81)	46	5.29 (3.95, 7.03)
Congenital Anomalies	42.61	86	2.01 (1.62, 2.47)	76	1.78 (1.41, 2.23)	67	1.56 (1.22, 1.97)
Certain Conditions Originating in Perinatal Period	0.33	4	10.84 (3.28, 26.39)	3	9.63 (3.28, 26.39)	3	8.43 (1.86, 21.75)
Symptoms, Signs and Ill-Defined Conditions	142.55	232	1.63 (1.43, 1.85)	206	1.45 (1.26, 1.66)	181	1.27 (1.09, 1.46)
Other Cause of Death	1146.98	2370	2.07 (1.98, 2.15)	2106	1.84 (1.76, 1.92)	1843	1.61 (1.54, 1.68)

*Per 10,000 person-years

CHAPTER 6. DISPARITIES IN MORTALITY FROM NONCANCER CAUSES AMONG ADOLESCENTS AND YOUNG ADULTS WITH CANCER

6.1 Background

As a consequence of exposure to intensive treatment regimens, many cancer patients have increased risks of noncancer health conditions which may persist long after initial cancer treatment is complete. For patients diagnosed at younger ages, who have many potential years of life remaining after cancer, the implications of excess morbidity and mortality from noncancer conditions are especially profound. Several reports from the Childhood Cancer Survivor Study and other cohorts have described patterns of mortality from noncancer causes among long-term survivors of childhood cancers.[86, 134-138] However, for patients diagnosed as adolescents and young adults (AYAs, age 15-39 years), who represent approximately seven times more incident cancer diagnoses each year than in children under age 15,[4] little research has examined long-term patterns of mortality from causes other than cancer. Identifying subgroups of AYA patients at highest risk of adverse outcomes may facilitate planning for long-term survivorship care in this population.

In addition to cancer type and other cancer-related factors, sociodemographic characteristics may also be important predictors of noncancer health outcomes among AYAs with cancer in the U.S. Reports from California have demonstrated disparities in all-cause and cancer-specific mortality among AYA cancer survivors according to race/ethnicity and area-level socioeconomic status (SES).[89-92, 94] However, whether the risk of mortality from noncancer causes, such as cardiovascular diseases (CVD) and infectious diseases (ID), varies by

race/ethnicity, SES, and other factors has not been well-studied in the AYA cancer survivor population.

Using population-based data from the Surveillance, Epidemiology, and End Results (SEER) program, we investigated factors associated with noncancer mortality among AYAs with cancer, with a focus on disparities related to race/ethnicity, county-level SES indicators, geographic region, and the rural-urban continuum. Outcomes of interest included mortality from all noncancer causes combined and from the cause-specific categories of cardiovascular diseases and infectious diseases.

6.2 Methods

6.2.1 Study population

We identified AYA patients using data from the SEER 18 registries.[139] The SEER program is a system of population-based cancer registries that collects and reports data on cancer incidence and survival. SEER registries are located strategically across the U.S., currently cover approximately 35% of the total U.S. population, and are demographically representative.[98] Demographic information, primary tumor site and morphology, disease stage, and first course of treatment are collected by SEER, as are the number of months survived since cancer diagnosis and the cause of death ascertained from state death certificates. For our analyses, we included all patients with a first malignant primary cancer diagnosed at ages 15-39 years between 1985 and 2015. Death certificate and autopsy only cases were excluded, as were those for whom the death certificate was unavailable, or was available but lacked information on the specific cause of death. We also excluded patients with Kaposi sarcoma, due to its strong association with HIV infection,[116] and those with unknown race. We classified cancer type using an AYA recode of the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) primary site and

histology codes.[117] Testicular cancer, which is not classified separately within the AYA recode, was defined using the SEER ICD-O-3/WHO 2008 recode.[140]

6.2.2 Patient characteristics

Race/ethnicity was categorized for our analyses as non-Hispanic White, non-Hispanic Black, Hispanic (all races), and other non-Hispanic. SEER registry was used to determine geographic region, with categories of West (San-Francisco-Oakland, San-Jose Monterey, Los Angeles, Greater California, New Mexico, Seattle/Puget Sound, Utah), South (Atlanta, Rural Georgia, Greater Georgia, Kentucky, Louisiana), Northeast (Connecticut, New Jersey), and Midwest (Detroit, Iowa). Patients in the Alaska native and Hawaii registries were excluded from analyses according to geographic region, as sample sizes from these registries were too small to define them as separate regions.

To assess disparities according to socioeconomic characteristics, we used county-level information on the percent of persons below poverty and percent of persons with less than a high school education. These variables are based on data from the U.S. Census Bureau that are linked to patient data in SEER.[105] We used information from the 1990 U.S. Census for patients diagnosed in 1985-1994, from the 2000 U.S. Census for patients diagnosed in 1995-2004, and from the 2008-2012 American Community Survey for patients diagnosed in 2005-2015. Quartiles were created using the distribution of these variables for all U.S. counties for the specified years.

We also categorized AYA patients based on their county's rural-urban continuum code, a classification scheme which was developed by the U.S. Department of Agriculture and is also linked to patient data within the SEER database.[108] Counties are assigned to one of nine categories, with metropolitan counties classified based on population size, and nonmetropolitan

counties classified based on degree of urbanization and adjacency to metropolitan area(s). We used the rural-urban designation from the year 2003 for patients diagnosed in 1998-2007, and from the year 2013 for patients diagnosed in 2008-2015, allowing a maximum of 5 years between cancer diagnosis and the year for which the rural-urban continuum was defined. Patients diagnosed before 1998 were therefore excluded from analyses according to rural-urban code. For our analyses, we used rural-urban continuum code values to define the categories of metro (1-3), urban (4-6), and rural (7-9), as used previously.[109]

6.2.3 Noncancer deaths

SEER recodes cause of death information from state death certificates and reports deaths from noncancer causes in 26 major categories.[103] These categories have been defined consistently over time and include many of the leading causes of death in the U.S. population, such as 'Pneumonia and Influenza,' and 'Diseases of the Heart.' Although SEER includes deaths from 'In situ, benign or unknown behavior neoplasm' among its 26 categories of noncancer causes of death, we did not consider deaths from this cause as noncancer deaths. Outcomes in our analyses included deaths from all noncancer causes combined and deaths from CVD (diseases of the heart; hypertension without heart disease; cerebrovascular disease; atherosclerosis; aortic aneurysm and dissection; other diseases of arteries, arterioles, capillaries) or ID (tuberculosis; syphilis; septicemia; pneumonia and influenza; other infectious and parasitic diseases including HIV), the two cause-specific categories with the largest number of total deaths.

6.2.4 Statistical analysis

We estimated the cumulative incidence of death from all noncancer causes, CVD, and ID at 5, 10, and 20 years post-diagnosis using nonparametric methods to account for deaths from

other causes, including cancer, as a competing risk.[112] Person-time of follow-up was accrued from cancer diagnosis until death or end of December, 2015, whichever occurred first. Patients recorded in SEER as having 0 completed months of survival were assigned a survival time of 0.5 months for analysis.[111] To evaluate disparities according to race/ethnicity, county-level economic characteristics, rural-urban continuum, and geographic region, we estimated cause-specific hazard ratios using Cox proportional hazards regression models. Multivariable regression models included age at diagnosis, cancer type, calendar year of diagnosis, and race/ethnicity. All analyses were performed separately for men and women. The proportional hazards assumption was assessed through visual inspection of plots of the survival function versus time and the log(-log(survival)) versus log(time). Because cancer type and age at diagnosis appeared to violate this assumption, these variables were included as stratification variables in multivariable models. In sensitivity analyses, we excluded AYAs with Non-Hodgkin lymphoma (NHL) to minimize the potential influence of the HIV/AIDs epidemic on estimated associations with race/ethnicity, geographic region, county-level economic characteristics, and rural-urban continuum. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

6.3 Results

A total of 242,940 AYA women and 158,347 AYA men with cancer were included in these analyses. The most common cancer types among women were breast cancer (24%), thyroid cancer (17%), and melanoma (11%); those among men were testicular cancer (21%), melanoma (10%), and NHL (10%) (Table 6.1). The median follow-up was 7.1 years (IQR=2.5-13.5) among women and 6.1 years (IQR=1.7-13.1) among men.

Among AYA women with cancer, 5,418 deaths from noncancer causes occurred during the follow-up period, with 1,216 deaths from CVD and 1,017 from ID. Overall, the cumulative incidence of all noncancer deaths among women was 1.24%, 1.94%, and 3.77% at 5, 10, and 20 years post-diagnosis, respectively (Table 6.2). When women with NHL were excluded, these values were 1.07%, 1.76% and 3.55% (*data not shown*). At 10 years, the cumulative incidence of all noncancer deaths was highest among women diagnosed with NHL (6.59%), leukemia (5.20%), and central nervous system tumors (2.54%). NHL and leukemia also had the highest 10-year incidence of deaths from CVD and ID (Tables 6.3-6.4). Across the study period, the cumulative incidence of all noncancer deaths, CVD deaths and ID deaths was consistently lowest among women with melanoma and thyroid cancer.

Among AYA men with cancer, there were a total of 8,452 deaths from noncancer causes, of which 1,268 and 3,789 were from CVD and ID, respectively. Overall, the cumulative incidence of all noncancer deaths was 3.83%, 4.99%, and 7.78% at 5, 10, and 20 years post-diagnosis, respectively (Table 6.5). When men with NHL were excluded, these values were 2.11%, 3.21%, and 5.96% (*data not shown*). At 10 years, the incidence of all noncancer deaths was highest among AYA men with NHL (20.31%) and leukemia (5.33%), followed by Hodgkin lymphoma (4.71%), head and neck cancers (4.29%), and colorectal cancers (4.23%). For CVD deaths, the 10-year incidence was highest among those with leukemia (0.85%) and NHL (0.74%), while that for ID deaths was highest among those with NHL (16.99%) and Hodgkin lymphoma (2.70%) (Tables 6.6-6.7).

The cumulative incidence of all noncancer mortality, cardiovascular mortality, and infectious disease mortality according to race/ethnicity is shown in Figures 6.1-6.6. In models accounting for age at diagnosis, calendar year, and cancer type, non-Hispanic Black women had

more than double the risk of all noncancer mortality (HR=2.31; 95% CI: 2.16-2.47), CVD mortality (HR=2.77; 95% CI: 2.41-3.18), and ID mortality (HR=5.24; 95% CI: 4.55-6.03) than non-Hispanic White women (Tables 6.8-6.10). ID mortality was also elevated among Hispanic women (HR=1.48; 95% CI: 1.22-1.80) relative to non-Hispanic White women. Further adjustment for county-level poverty resulted in little change in HRs according to race/ethnicity (*data not shown*). Compared to women in the Northeast region, those in the South had higher mortality from all noncancer causes (HR=1.18; 95% CI: 1.07-1.29) and from CVD (HR=1.40; 95% CI: 1.15-1.71). In contrast, ID mortality was higher among women in the Northeast than in any other geographic region. Both all noncancer mortality and CVD mortality were higher among women in urban and rural areas than in metro areas, and appeared to increase with increasing county-level poverty. Compared to women in the lowest quartile of county-level poverty, the HR for CVD mortality for women in the highest quartile was 1.41 (95% CI: 1.17-1.70). County-level poverty, education, and rural-urban continuum were not clearly associated with ID mortality among women.

Relative to non-Hispanic White men, non-Hispanic Black men had higher mortality from all noncancer causes (HR=2.17; 95% CI: 2.05-2.30), CVD (HR=2.44; 95% CI: 2.09-2.84), and ID (HR=2.39; 95% CI: 2.20-2.58) (Table 6.11-6.13). Hispanic men also had higher mortality from all noncancer causes (HR=1.43; 95% CI: 1.34-1.52) and ID (HR=1.74; 95% CI: 1.59-1.90) than non-Hispanic White men. In contrast, all noncancer mortality (HR=0.75; 95% CI: 0.67-0.83) and ID mortality (HR=0.59; 95% CI: 0.49-0.71) were significantly lower among men of other non-Hispanic race/ethnicities than among non-Hispanic White men. Additional adjustment for quartile of county-level poverty did not appreciably alter HRs according to race/ethnicity (*data not shown*). Compared to AYA men with cancer in the Northeast region, those in the South

had higher mortality from all noncancer causes, CVD, and ID, while those in the West had higher mortality from all noncancer causes and from ID. No clear trends were observed for associations with county-level poverty or education. Men in rural areas had higher all noncancer mortality (HR=1.57; 95% CI: 1.33-1.86) and CVD mortality (HR=2.13; 95% CI: 1.47-3.09) than men in metro areas; CVD mortality was also elevated among men in urban areas (HR=1.55; 95% CI: 1.15-2.07).

Patterns were generally similar in sensitivity analyses excluding women with NHL (Tables 6.14-6.16), although the HR for ID mortality among non-Hispanic Black women was somewhat attenuated (HR=4.20; 95% CI: 3.52-5.01). When men with NHL were excluded (Tables 6.17-6.19), the HR for ID mortality for non-Hispanic Black compared to non-Hispanic White was of greater magnitude (HR=3.97), while that for Hispanic men was slightly attenuated (HR=1.57). An increase in ID mortality among men in rural counties (vs metro) was also apparent (HR=1.61), while the HR for ID mortality among those in the West region (vs Northeast) was attenuated in analyses were restricted to non-NHL patients.

6.4 Discussion

AYAs with cancer continue to represent an understudied patient population in the U.S. In this population-based study, we investigated long-term patterns of mortality from noncancer causes after an AYA cancer diagnosis, and examined disparities according to race/ethnicity and other patient characteristics. Among AYAs of all cancer types, we found a cumulative incidence of deaths from noncancer causes of approximately 2% and 5% among women and men, respectively, at 10 years post-diagnosis. Accounting for cancer type, patient characteristics associated with higher risk of mortality from all noncancer causes combined included non-Hispanic Black race/ethnicity and living in the South or in rural counties. Non-Hispanic Black

race/ethnicity was also a consistent predictor of mortality from both CVD and ID. Our analyses highlight disparities in noncancer mortality among AYAs with cancer, and identify subgroups of survivors that may be targeted for increased medical surveillance.

A number of reports have demonstrated that cancer survivors, including those diagnosed as AYAs, have elevated mortality from noncancer causes relative to the general population,[76-78, 86, 97, 134-136] likely resulting from both the direct effects of cancer therapies on the risk and severity of noncancer health conditions, and the indirect effects of cancer and its treatment on overall health and well-being. Our results, like those reported among childhood cancer survivor cohorts,[86, 134-138] suggest that cancer type is an important predictor of noncancer mortality among survivors, with some of the highest risks among patients with hematologic malignancies and central nervous system tumors. In our analyses among AYAs, we also identified head and neck cancers and colorectal cancers, especially those among AYA men, as cancer types with relatively high mortality from noncancer causes throughout the survivorship period.

While previous studies have documented disparities in both all-cause and cancer-specific mortality according to race/ethnicity among AYAs with cancer in the U.S.,[89-92, 94] considerably less research has examined race-related disparities in noncancer health outcomes in this population. Racial differences in CVD mortality may be particularly critical to examine, as a cancer diagnosis and treatment could exacerbate disparities in cardiovascular outcomes reported in the general population.[141] In a study of 79,176 AYA cancer patients diagnosed in California during 1996-2012, the 10-year risk of incident CVD among African-Americans was 1.55 (95% CI: 1.33-1.81) times that among non-Hispanic whites with adjustment for cancer type.[75] Likewise, a prior SEER-based analysis of AYAs diagnosed at ages 15-34 from 1973 to 2011

found a non-significant increase in death from CVD among Black survivors compared to White (HR=1.33; 95% CI: 0.60, 2.95), though estimates were imprecise and models did not appear to account for cancer type.[95] Results of the current study also indicate a higher burden of CVD mortality among non-Hispanic Black AYAs with cancer, but suggest that the magnitude of this disparity may be considerably greater than previously reported. Differences between non-Hispanic Black AYAs and other race/ethnicities persisted over time since cancer diagnosis, underscoring the importance of long-term follow-up care for cardiovascular health, particularly for non-Hispanic Black AYA cancer survivors.

Although our analyses indicate that deaths from ID are relatively rare among AYAs with cancer types other than NHL, characteristics that we identified as predictors of higher ID mortality may also be those associated with a higher incidence of life-threatening infections in this population. We found that non-Hispanic Black AYAs had a higher risk of ID mortality after cancer than non-Hispanic White AYAs, a relationship which remained apparent when NHL patients were excluded to minimize the influence of potential differences in HIV-related deaths according to race/ethnicity. Most ID deaths occurred within the first few years after cancer diagnosis, suggesting that many of these may be the result of acute complications of treatment for the primary cancer or relapse. Little large-scale research has examined infections among cancer patients and survivors, particularly those with solid tumors, and further investigation may be needed to identify cancer treatment-related and other contributors to disparities in ID incidence and mortality after AYA cancer.

To our knowledge, our study is the first to investigate variability in noncancer mortality among AYA cancer survivors according to U.S. geographic region and county-level characteristics such as poverty, education, and rural-urban continuum. One prior study, using

data from the California Cancer Registry, reported that living in a lower SES neighborhood, defined based on a composite index of census tract-level poverty, education, and other characteristics, was associated with a higher risk of developing CVD after AYA cancer.[75] In our analyses, we observed few clear trends in noncancer mortality outcomes according to county-level poverty and education, aside from relatively weak increases in all noncancer mortality and CVD mortality with increasing county-level poverty among women. On the other hand, living in the South or in a rural county was associated with higher mortality from all noncancer causes and CVD among both men and women. AYA patients with cancer in the South and/or in rural areas may therefore be priority groups for efforts to improve health outcomes throughout survivorship.

Strengths of the current study include the large population-based sample of AYA cancer patients and the long follow-up, which allowed us to estimate the cumulative incidence of noncancer death up to 20+ years post-diagnosis and to investigate disparities according to race/ethnicity and other characteristics. Our study also has limitations. Cause of death, as recoded from state death certificates, is subject to misclassification, potentially leading to some misattribution of cancer deaths to noncancer causes. However, we do not expect that this misclassification would be strongly differential with respect to factors such as race and other patient characteristics that we examined. Additionally, SEER registries do not collect individual-level SES characteristics, and our analyses thus relied on county-level characteristics to investigate disparities related to SES. Estimates therefore reflect the impact of living in a county with, for example, high poverty, rather than the impact of living in a household below the poverty level. We were also unable to consider the impact of health insurance status on noncancer mortality risk, as this information has only been available in SEER since 2007.[142]

Future investigations of noncancer outcomes in AYA cancer survivors may wish to consider joint associations between insurance status and race/ethnicity or other patient characteristics. Finally, the number of deaths among AYAs in our study was too small to conduct meaningful analyses of noncancer mortality from cause-specific categories other than CVD and ID, or to examine individual causes within the categories of CVD and ID.

In conclusion, results of the current study suggest that the risk of noncancer mortality after AYA cancer is highest among survivors who are non-Hispanic Black or live in the South or in rural counties. Identifying subgroups of AYA cancer survivors at increased risk of adverse noncancer health outcomes may inform the development of surveillance recommendations and interventions to ensure access to coordinated care in survivorship.

6.5 Tables and figures

Table 6.1. Characteristics of AYAs diagnosed with cancer, SEER 18, 1985-2015

	Women		Men	
	N	%	N	%
Total	242,940	100%	158,347	100%
Cancer type				
Leukemia	7,691	3%	10,977	7%
Non-Hodgkin lymphoma	9,387	4%	16,418	10%
Hodgkin lymphoma	11,658	5%	12,310	8%
Central nervous system tumors	7,674	3%	10,019	6%
Soft tissue sarcomas	6,853	3%	6,886	4%
Melanoma	25,645	11%	16,454	10%
Thyroid carcinoma	41,414	17%	8,598	5%
Other head and neck carcinomas	4,063	2%	5,499	3%
Colorectal carcinomas	9,583	4%	10,474	7%
Breast carcinoma [a]	59,472	24%	--	--
Testicular cancer	--	--	32,739	21%
Cervical/uterine carcinomas	27,623	11%	--	--
Other	31,877	13%	27,973	18%
Age at diagnosis				
15-19	12,168	5%	14,029	9%
20-24	21,491	9%	20,642	13%
25-29	38,522	16%	29,265	18%
30-34	65,525	27%	39,473	25%
35-39	105,234	43%	54,938	35%
Calendar year				
1985-1994	38,449	16%	26,987	17%
1995-2004	79,249	33%	52,322	33%
2005-2015	125,242	52%	79,038	50%
Race/ethnicity				
Non-Hispanic White	151,716	62%	104,370	66%
Non-Hispanic Black	26,628	11%	13,925	9%
Hispanic	41,443	17%	28,165	18%
Other Non-Hispanic	23,153	10%	11,887	8%
Geographic region [b]				
West	126,560	53%	86,611	56%
South	45,811	19%	27,423	18%
Northeast	35,105	15%	21,895	14%
Midwest	29,686	13%	18,785	12%
% of persons below poverty (quartiles, Q) [c]				
Q1	91,689	38%	59,806	38%
Q2	58,791	24%	39,617	25%
Q3	57,346	24%	36,496	23%
Q4	35,031	14%	22,383	14%
Missing	83		45	
% persons with <high school education (quartiles, Q)[d]				
Q1	87,705	36%	58,162	37%
Q2	58,624	24%	38,051	24%
Q3	45,208	19%	28,702	18%
Q4	51,320	21%	33,387	21%
Missing	83		45	
Rural-urban continuum code [e]				

Metro	171,295	91%	109,340	91%
Urban	11,794	6%	7,501	6%
Rural	5,464	3%	3,489	3%
Missing	715		430	

[a] Male breast carcinomas (N=146) are included in the 'Other' category
[b] Alaska native and Hawaii registries are omitted
[c] Quartile cutpoints were 11.15%, 15.15%, and 20.4% for AYAs diagnosed in 1985-1994; 9.54%, 12.95%, and 17.52% for AYAs diagnosed in 1995-2004; and 11.68%, 15.58%, and 19.81% for AYAs diagnosed in 2005-2015.
[d] Quartile cutpoints were 22.77%, 28.58%, and 38.07% for AYAs diagnosed in 1985-1994; 15.99%, 20.78%, and 28.71% for AYAs diagnosed in 1995-2004; and 10.56%, 14.41%, and 20.35% for AYAs diagnosed in 2005-2015.
[e] Includes AYAs diagnosed in 1998-2015 only

Table 6.2. Cumulative incidence of all noncancer deaths among AYA women with cancer, SEER 18, 1985-2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	1.24 (1.19, 1.28)	1.94 (1.88, 2.01)	3.77 (3.64, 3.89)
Cancer type			
Leukemia	4.26 (3.80, 4.76)	5.20 (4.66, 5.78)	7.48 (6.59, 8.43)
Non-Hodgkin lymphoma	5.37 (4.91, 5.86)	6.59 (6.05, 7.15)	9.28 (8.43, 10.17)
Hodgkin lymphoma	1.08 (0.90, 1.30)	1.93 (1.66, 2.23)	4.32 (3.76, 4.95)
Central nervous system tumors	1.57 (1.30, 1.89)	2.54 (2.16, 2.98)	4.84 (4.09, 5.69)
Soft tissue sarcomas	1.20 (0.95, 1.49)	1.94 (1.59, 2.34)	3.89 (3.21, 4.67)
Melanoma	0.36 (0.29, 0.45)	0.66 (0.55, 0.78)	1.64 (1.40, 1.91)
Thyroid carcinoma	0.32 (0.27, 0.39)	0.71 (0.61, 0.83)	1.81 (1.56, 2.09)
Other head and neck carcinomas	1.16 (0.85, 1.56)	2.25 (1.76, 2.84)	4.88 (3.87, 6.06)
Breast carcinoma	0.76 (0.69, 0.84)	1.38 (1.28, 1.50)	2.96 (2.75, 3.19)
Cervical/uterine carcinomas	1.14 (1.01, 1.28)	2.02 (1.83, 2.22)	4.69 (4.30, 5.12)
Colorectal carcinomas	1.31 (1.08, 1.57)	2.15 (1.83, 2.53)	4.10 (3.42, 4.87)
Age at diagnosis			
15-19	1.35 (1.14, 1.58)	1.81 (1.56, 2.09)	2.57 (2.18, 3.02)
20-24	1.19 (1.05, 1.36)	1.76 (1.57, 1.98)	3.27 (2.89, 3.68)
25-29	1.28 (1.17, 1.41)	1.79 (1.65, 1.95)	3.27 (2.99, 3.56)
30-34	1.16 (1.08, 1.26)	1.78 (1.67, 1.90)	3.53 (3.30, 3.77)
35-39	1.26 (1.19, 1.33)	2.14 (2.04, 2.24)	4.31 (4.11, 4.51)
Calendar year			
1985-1994	1.40 (1.29, 1.52)	2.06 (1.92, 2.21)	3.69 (3.50, 3.88)
1995-2004	1.24 (1.17, 1.32)	1.96 (1.86, 2.06)	3.83 (3.61, 4.06)
2005-2015	1.17 (1.11, 1.24)	1.91 (1.79, 2.04)	--
Race/ethnicity			
Non-Hispanic White	0.99 (0.94, 1.03)	1.64 (1.57, 1.71)	3.37 (3.23, 3.51)
Non-Hispanic Black	2.96 (2.75, 3.18)	4.14 (3.88, 4.42)	7.25 (6.75, 7.77)
Hispanic	1.23 (1.11, 1.35)	1.84 (1.68, 2.00)	3.34 (3.01, 3.71)
Other Non-Hispanic	0.89 (0.77, 1.03)	1.57 (1.38, 1.77)	3.09 (2.72, 3.49)

Table 6.3 Cumulative incidence of cardiovascular disease death among AYA women with cancer, SEER 18, 1985-2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	0.21 (0.19, 0.23)	0.37 (0.34, 0.40)	0.92 (0.86, 0.99)
Cancer type			
Leukemia	0.47 (0.33, 0.65)	0.62 (0.44, 0.85)	1.35 (0.93, 1.90)
Non-Hodgkin lymphoma	0.41 (0.29, 0.57)	0.78 (0.59, 1.01)	1.46 (1.09, 1.92)
Hodgkin lymphoma	0.19 (0.12, 0.29)	0.34 (0.23, 0.48)	1.39 (1.06, 1.80)
Central nervous system tumors	0.38 (0.25, 0.55)	0.61 (0.43, 0.85)	1.20 (0.84, 1.67)
Soft tissue sarcomas	0.15 (0.07, 0.27)	0.35 (0.22, 0.55)	1.28 (0.87, 1.83)
Melanoma	0.10 (0.06, 0.15)	0.13 (0.09, 0.19)	0.32 (0.23, 0.45)
Thyroid carcinoma	0.08 (0.06, 0.12)	0.17 (0.13, 0.23)	0.50 (0.37, 0.66)
Other head and neck carcinomas	0.25 (0.13, 0.47)	0.54 (0.32, 0.86)	1.24 (0.76, 1.92)
Breast carcinoma	0.17 (0.14, 0.21)	0.33 (0.28, 0.39)	0.91 (0.78, 1.05)
Cervical/uterine carcinomas	0.20 (0.15, 0.26)	0.38 (0.30, 0.47)	1.17 (0.96, 1.40)
Colorectal carcinomas	0.17 (0.10, 0.28)	0.35 (0.23, 0.53)	0.69 (0.44, 1.05)
Other			
Age at diagnosis			
15-19	0.15 (0.09, 0.24)	0.18 (0.11, 0.28)	0.25 (0.15, 0.39)
20-24	0.15 (0.11, 0.22)	0.26 (0.19, 0.35)	0.66 (0.49, 0.88)
25-29	0.15 (0.11, 0.20)	0.25 (0.19, 0.31)	0.62 (0.50, 0.77)
30-34	0.19 (0.15, 0.22)	0.31 (0.26, 0.36)	0.86 (0.74, 0.99)
35-39	0.25 (0.22, 0.29)	0.49 (0.44, 0.54)	1.20 (1.09, 1.32)
Calendar year			
1985-1994	0.25 (0.21, 0.31)	0.45 (0.38, 0.52)	0.96 (0.87, 1.06)
1995-2004	0.21 (0.18, 0.24)	0.37 (0.33, 0.42)	0.93 (0.81, 1.07)
2005-2015	0.18 (0.16, 0.21)	0.30 (0.26, 0.36)	--
Race/ethnicity			
Non-Hispanic White	0.17 (0.15, 0.19)	0.31 (0.28, 0.35)	0.80 (0.72, 0.87)
Non-Hispanic Black	0.52 (0.44, 0.62)	0.88 (0.75, 1.01)	2.22 (1.91, 2.55)
Hispanic	0.16 (0.12, 0.21)	0.25 (0.19, 0.32)	0.63 (0.48, 0.82)
Other Non-Hispanic	0.16 (0.11, 0.23)	0.31 (0.23, 0.41)	0.67 (0.51, 0.86)

Table 6.4 Cumulative incidence of infectious disease deaths among AYA women with cancer, SEER 18, 1985-2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	0.33 (0.30, 0.35)	0.42 (0.39, 0.45)	0.60 (0.55, 0.64)
Cancer type			
Leukemia	1.14 (0.91, 1.42)	1.28 (1.03, 1.58)	1.62 (1.27, 2.04)
Non-Hodgkin lymphoma	3.65 (3.27, 4.05)	4.00 (3.60, 4.44)	4.54 (4.05, 5.06)
Hodgkin lymphoma	0.31 (0.22, 0.43)	0.50 (0.37, 0.66)	0.79 (0.57, 1.06)
Central nervous system tumors	0.30 (0.19, 0.45)	0.37 (0.25, 0.55)	0.41 (0.27, 0.61)
Soft tissue sarcomas	0.21 (0.12, 0.36)	0.26 (0.15, 0.43)	0.36 (0.20, 0.60)
Melanoma	0.01 (0.00, 0.04)	0.03 (0.01, 0.06)	0.11 (0.06, 0.20)
Thyroid carcinoma	0.02 (0.01, 0.04)	0.04 (0.02, 0.07)	0.09 (0.04, 0.17)
Other head and neck carcinomas	0.17 (0.07, 0.36)	0.29 (0.14, 0.55)	0.64 (0.33, 1.14)
Breast carcinoma	0.12 (0.09, 0.15)	0.18 (0.15, 0.22)	0.33 (0.26, 0.41)
Cervical/uterine carcinomas	0.27 (0.21, 0.34)	0.37 (0.30, 0.46)	0.63 (0.50, 0.78)
Colorectal carcinomas	0.20 (0.12, 0.32)	0.25 (0.16, 0.39)	0.37 (0.23, 0.56)
Other			
Age at diagnosis			
15-19	0.32 (0.23, 0.44)	0.39 (0.28, 0.53)	0.59 (0.40, 0.85)
20-24	0.24 (0.18, 0.32)	0.30 (0.23, 0.39)	0.47 (0.34, 0.63)
25-29	0.37 (0.31, 0.44)	0.46 (0.39, 0.54)	0.59 (0.49, 0.70)
30-34	0.35 (0.30, 0.40)	0.43 (0.38, 0.49)	0.65 (0.57, 0.75)
35-39	0.32 (0.28, 0.36)	0.42 (0.38, 0.47)	0.59 (0.53, 0.66)
Calendar year			
1985-1994	0.49 (0.43, 0.57)	0.59 (0.52, 0.67)	0.76 (0.68, 0.85)
1995-2004	0.38 (0.34, 0.42)	0.47 (0.43, 0.52)	0.63 (0.56, 0.71)
2005-2015	0.24 (0.21, 0.27)	0.30 (0.26, 0.35)	--
Race/ethnicity			
Non-Hispanic White	0.19 (0.17, 0.21)	0.24 (0.22, 0.27)	0.39 (0.35, 0.44)
Non-Hispanic Black	1.28 (1.15, 1.43)	1.54 (1.39, 1.71)	1.98 (1.76, 2.21)
Hispanic	0.29 (0.24, 0.35)	0.36 (0.33, 0.47)	0.52 (0.42, 0.65)
Other Non-Hispanic	0.20 (0.15, 0.27)	0.31 (0.23, 0.41)	0.54 (0.39, 0.71)

Table 6.5. Cumulative incidence of all noncancer deaths among AYA men with cancer, SEER 18, 1985-2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	3.83 (3.73, 3.93)	4.99 (4.87, 5.11)	7.78 (7.58, 7.98)
Cancer type			
Leukemia	4.08 (3.70, 4.49)	5.33 (4.86, 5.82)	8.20 (7.35, 9.10)
Non-Hodgkin lymphoma	18.60 (17.99, 19.21)	20.31 (19.67, 20.97)	23.43 (22.62, 24.24)
Hodgkin lymphoma	2.87 (2.57, 3.19)	4.71 (4.30, 5.15)	9.50 (8.71, 10.32)
Central nervous system tumors	2.39 (2.08, 2.72)	3.35 (2.96, 3.76)	5.73 (5.06, 6.44)
Soft tissue sarcomas	1.97 (1.64, 2.34)	2.74 (2.33, 3.19)	4.28 (3.64, 4.99)
Melanoma	0.76 (0.63, 0.92)	1.53 (1.33, 1.76)	3.47 (3.05, 3.94)
Thyroid carcinoma	0.98 (0.77, 1.23)	1.82 (1.49, 2.19)	4.57 (3.78, 5.45)
Other head and neck carcinomas	2.71 (2.28, 3.19)	4.29 (3.70, 4.93)	8.41 (7.32, 9.59)
Colorectal carcinomas	2.85 (2.52, 3.21)	4.23 (3.80, 4.70)	6.81 (6.05, 7.61)
Testicular cancer	1.13 (1.01, 1.26)	2.05 (1.88, 2.24)	4.63 (4.26, 5.03)
Age at diagnosis			
15-19	1.57 (1.36, 1.80)	2.24 (1.97, 2.54)	4.03 (3.51, 4.60)
20-24	2.09 (1.89, 2.31)	3.00 (2.74, 3.28)	4.91 (4.45, 5.39)
25-29	3.06 (2.85, 3.27)	3.99 (3.75, 4.25)	6.40 (5.99, 6.83)
30-34	4.67 (4.46, 4.89)	5.79 (5.55, 6.05)	8.47 (8.08, 8.87)
35-39	4.85 (4.67, 5.04)	6.36 (6.14, 6.59)	9.92 (9.55, 10.29)
Calendar year			
1985-1994	7.62 (7.31, 7.94)	8.91 (8.57, 9.26)	11.48 (11.10, 11.87)
1995-2004	3.88 (3.71, 4.04)	4.99 (4.80, 5.18)	7.48 (7.17, 7.80)
2005-2015	2.35 (2.23, 2.47)	3.29 (3.11, 3.48)	--
Race/ethnicity			
Non-Hispanic White	3.22 (3.11, 3.33)	4.30 (4.17, 4.44)	7.03 (6.80, 7.25)
Non-Hispanic Black	9.00 (8.51, 9.50)	11.04 (10.48, 11.62)	15.34 (14.47, 16.23)
Hispanic	4.22 (3.97, 4.48)	5.52 (5.21, 5.85)	8.27 (7.66, 8.90)
Other Non-Hispanic	2.29 (2.01, 2.59)	2.99 (2.65, 3.36)	5.31 (4.66, 6.02)

Table 6.6 Cumulative incidence of cardiovascular disease deaths among AYA men with cancer, SEER 18, 1985-2015

	Cumulative incidence		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	0.34 (0.31, 0.37)	0.58 (0.53, 0.62)	1.42 (1.32, 1.52)
Cancer type			
Leukemia	0.52 (0.39, 0.68)	0.85 (0.66, 1.07)	1.59 (1.21, 2.07)
Non-Hodgkin lymphoma	0.48 (0.38, 0.60)	0.74 (0.60, 0.90)	1.31 (1.06, 1.60)
Hodgkin lymphoma	0.28 (0.20, 0.40)	0.71 (0.55, 0.91)	2.75 (2.28, 3.28)
Central nervous system tumors	0.53 (0.40, 0.70)	0.66 (0.50, 0.85)	1.36 (1.04, 1.75)
Soft tissue sarcomas	0.33 (0.21, 0.50)	0.56 (0.38, 0.79)	0.82 (0.57, 1.15)
Melanoma	0.12 (0.08, 0.19)	0.28 (0.20, 0.39)	0.95 (0.73, 1.23)
Thyroid carcinoma	0.25 (0.15, 0.39)	0.45 (0.30, 0.66)	1.14 (0.77, 1.65)
Other head and neck carcinomas	0.39 (0.24, 0.60)	0.80 (0.57, 1.12)	1.84 (1.36, 2.43)
Colorectal carcinomas	0.38 (0.27, 0.53)	0.66 (0.50, 0.87)	1.30 (0.96, 1.72)
Testicular cancer	0.09 (0.06, 0.14)	0.20 (0.15, 0.27)	0.89 (0.72, 1.10)
Other			
Age at diagnosis			
15-19	0.18 (0.12, 0.27)	0.27 (0.18, 0.38)	0.73 (0.51, 1.02)
20-24	0.22 (0.16, 0.30)	0.33 (0.25, 0.43)	0.81 (0.62, 1.06)
25-29	0.23 (0.18, 0.30)	0.42 (0.34, 0.52)	1.08 (0.89, 1.30)
30-34	0.33 (0.27, 0.39)	0.56 (0.48, 0.65)	1.35 (1.17, 1.56)
35-39	0.49 (0.43, 0.55)	0.83 (0.75, 0.93)	2.00 (1.81, 2.20)
Calendar year			
1985-1994	0.48 (0.40, 0.57)	0.69 (0.60, 0.80)	1.50 (1.35, 1.65)
1995-2004	0.34 (0.29, 0.39)	0.57 (0.51, 0.64)	1.31 (1.15, 1.48)
2005-2015	0.29 (0.25, 0.33)	0.50 (0.43, 0.58)	--
Race/ethnicity			
Non-Hispanic White	0.28 (0.25, 0.31)	0.49 (0.44, 0.54)	1.34 (1.23, 1.46)
Non-Hispanic Black	0.92 (0.76, 1.10)	1.42 (1.20, 1.66)	2.57 (2.15, 3.04)
Hispanic	0.29 (0.23, 0.37)	0.58 (0.47, 0.71)	1.22 (0.96, 1.53)
Other Non-Hispanic	0.31 (0.22, 0.44)	0.44 (0.32, 0.60)	1.25 (0.91, 1.67)

Table 6.7 Cumulative incidence of infectious disease deaths among AYA men with cancer, SEER 18, 1985-2015

	Cumulative incidence		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	2.22 (2.15, 2.30)	2.48 (2.40, 2.56)	2.84 (2.74, 2.94)
Cancer type			
Leukemia	1.25 (1.04, 1.48)	1.45 (1.21, 1.71)	2.02 (1.64, 2.47)
Non-Hodgkin lymphoma	16.12 (15.55, 16.70)	16.99 (16.40, 17.59)	18.18 (17.51, 18.85)
Hodgkin lymphoma	1.54 (1.33, 1.78)	2.10 (1.84, 2.40)	2.70 (2.35, 3.08)
Central nervous system tumors	0.30 (0.21, 0.44)	0.38 (0.27, 0.54)	0.59 (0.41, 0.83)
Soft tissue sarcomas	0.44 (0.30, 0.63)	0.57 (0.40, 0.79)	0.73 (0.50, 1.06)
Melanoma	0.17 (0.11, 0.25)	0.26 (0.19, 0.37)	0.38 (0.27, 0.52)
Thyroid carcinoma	0.07 (0.03, 0.16)	0.13 (0.06, 0.25)	0.37 (0.18, 0.71)
Other head and neck carcinomas	0.71 (0.50, 0.98)	0.76 (0.55, 1.04)	1.28 (0.92, 1.75)
Colorectal carcinomas	1.17 (0.97, 1.41)	1.59 (1.33, 1.88)	2.02 (1.66, 2.42)
Testicular cancer	0.20 (0.16, 0.26)	0.32 (0.26, 0.40)	0.51 (0.41, 0.64)
Other			
Age at diagnosis			
15-19	0.24 (0.16, 0.34)	0.31 (0.22, 0.43)	0.38 (0.27, 0.54)
20-24	0.66 (0.55, 0.78)	0.75 (0.63, 0.88)	1.00 (0.84, 1.20)
25-29	1.74 (1.59, 1.90)	1.96 (1.80, 2.14)	2.31 (2.11, 2.53)
30-34	3.06 (2.89, 3.24)	3.37 (3.19, 3.56)	3.77 (3.55, 4.00)
35-39	2.97 (2.83, 3.12)	3.30 (3.14, 3.46)	3.74 (3.55, 3.93)
Calendar year			
1985-1994	5.70 (5.43, 5.98)	6.12 (5.84, 6.42)	6.47 (6.18, 6.77)
1995-2004	2.38 (2.25, 2.52)	2.60 (2.46, 2.74)	2.92 (2.76, 3.08)
2005-2015	0.79 (0.72, 0.86)	0.89 (0.82, 0.97)	
Race/ethnicity			
Non-Hispanic White	1.82 (1.73, 1.90)	2.03 (1.94, 2.12)	2.33 (2.22, 2.44)
Non-Hispanic Black	5.77 (5.38, 6.18)	6.44 (6.01, 6.88)	7.42 (6.89, 7.98)
Hispanic	2.56 (2.37, 2.76)	2.81 (2.60, 3.03)	3.23 (2.96, 3.52)
Other Non-Hispanic	0.92 (0.75, 1.11)	1.08 (0.89, 1.31)	1.39 (1.11, 1.72)

Figure 6.1. Cumulative incidence of mortality from all noncancer causes according to race/ethnicity among AYA women with cancer, SEER 18, 1985-2015

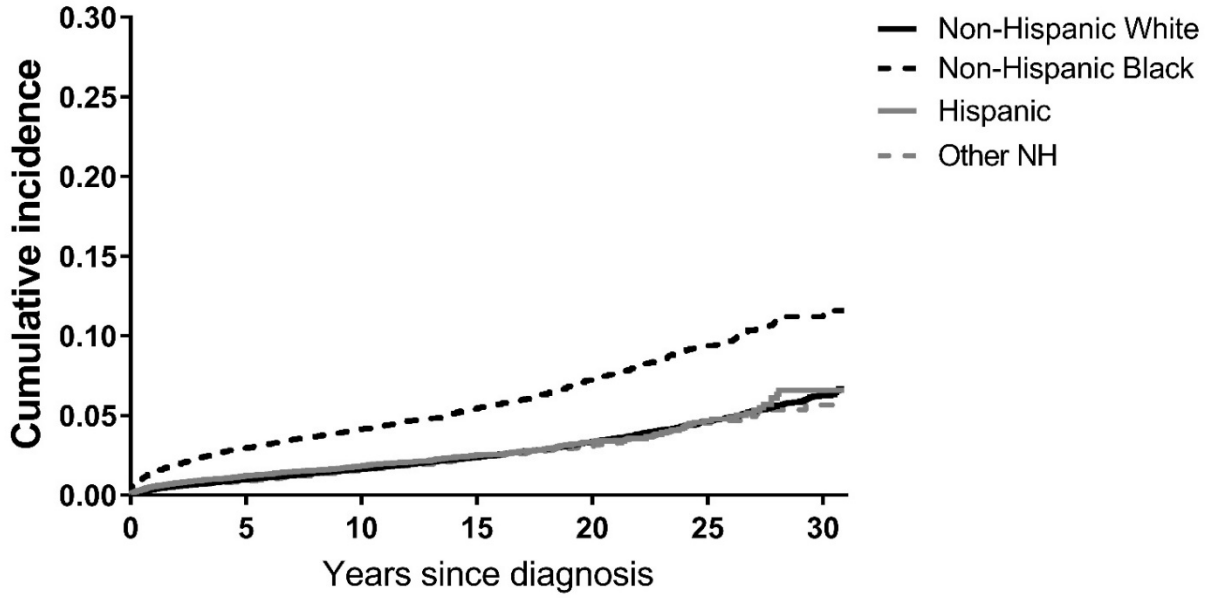

Figure 6.2. Cumulative incidence of mortality from cardiovascular diseases according to race/ethnicity among AYA women with cancer, SEER 18, 1985-2015

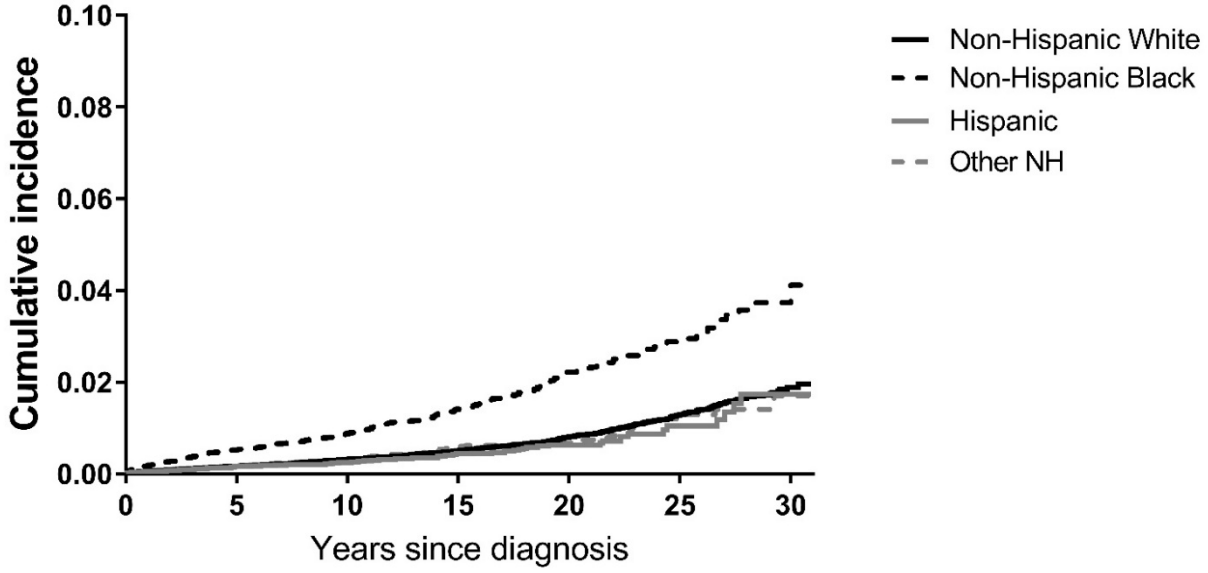

Figure 6.3. Cumulative incidence of mortality from infectious diseases according to race/ethnicity among AYA women with cancer, SEER 18, 1985-2015

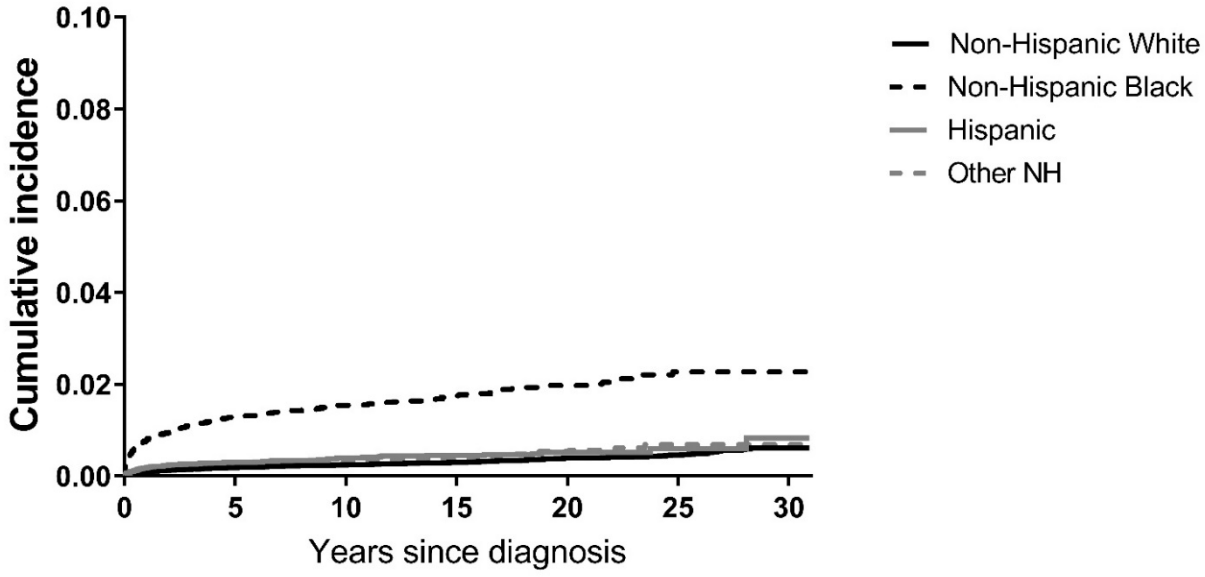

Figure 6.4. Cumulative incidence of mortality from all noncancer causes according to race/ethnicity among AYA men with cancer, SEER 18, 1985-2015

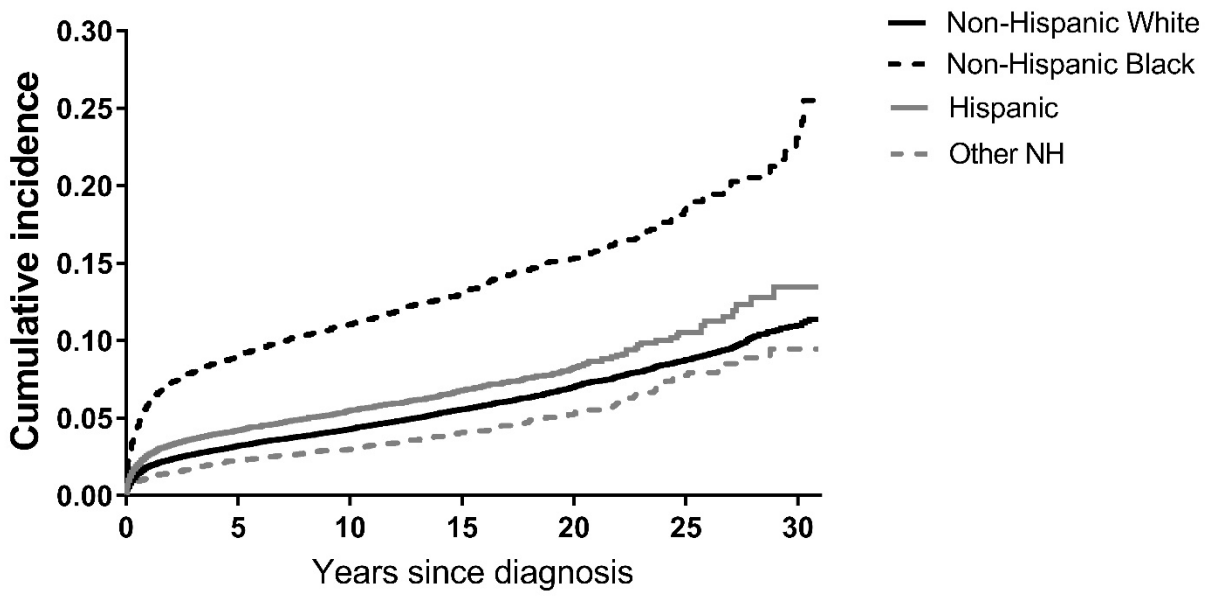

Figure 6.5. Cumulative incidence of mortality from cardiovascular diseases according to race/ethnicity among AYA men with cancer, SEER 18, 1985-2015

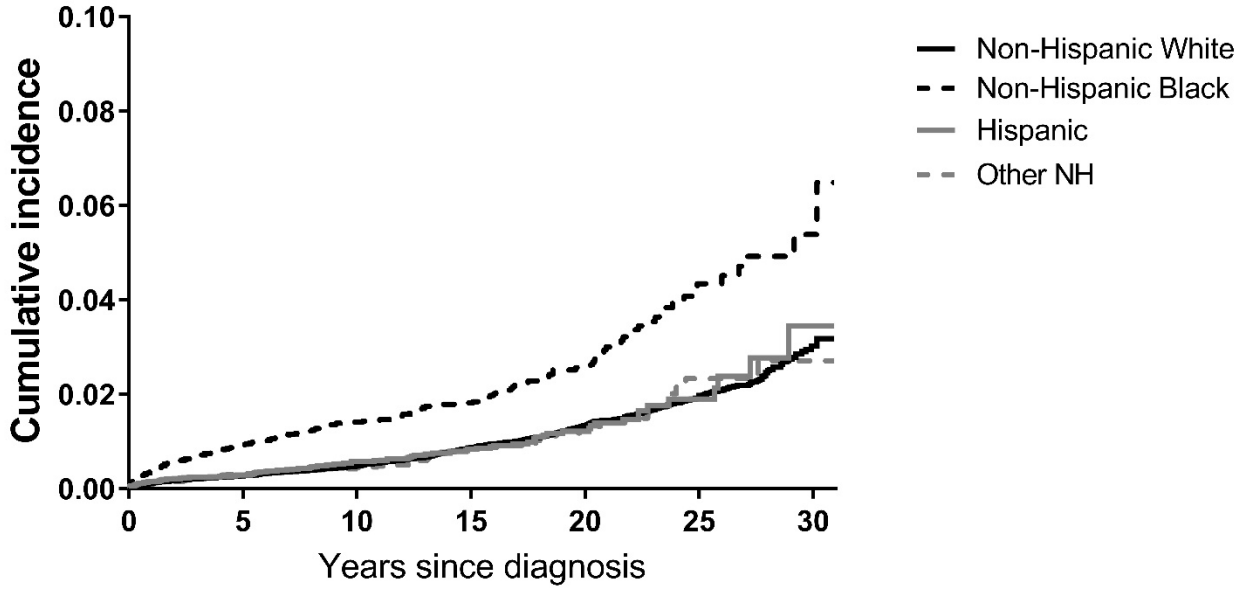

Figure 6.6. Cumulative incidence of mortality from infectious diseases according to race/ethnicity among AYA men with cancer, SEER 18, 1985-2015

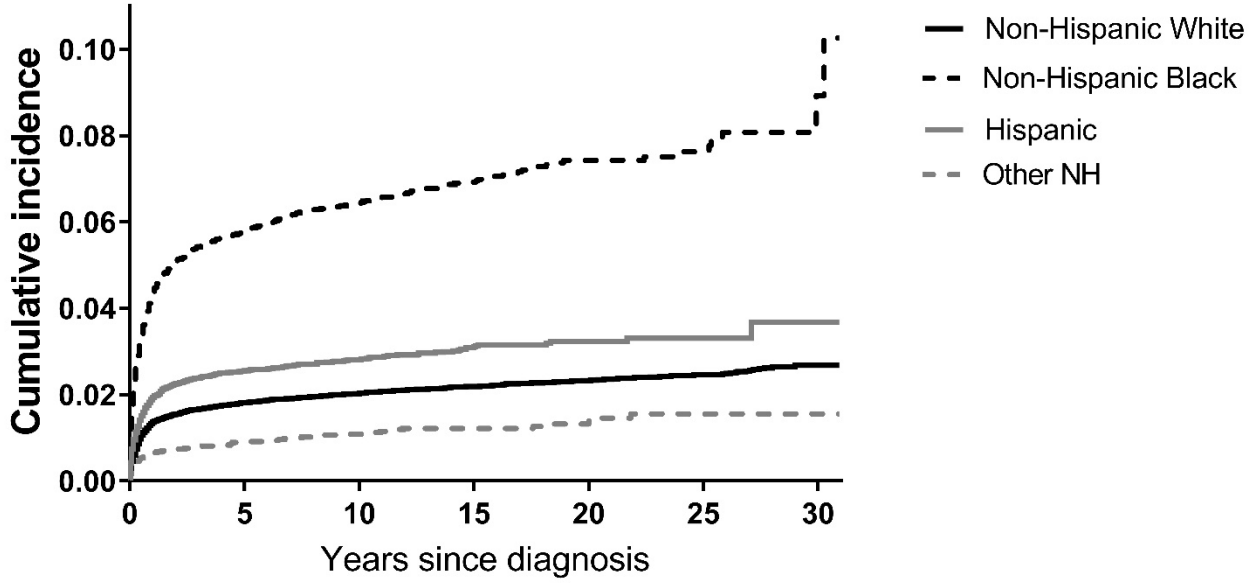

Table 6.8. Hazard ratios for all noncancer deaths according to patient characteristics among AYA women with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,492,030	3135	1	1
Non-Hispanic Black	206,468	1203	2.75 (2.57, 2.94)	2.31 (2.16, 2.47)
Hispanic	285,446	690	1.14 (1.05, 1.24)	1.04 (0.95, 1.13)
Other non-Hispanic	188,076	390	0.98 (0.89, 1.09)	0.91 (0.82, 1.01)
Geographic region				
West	1,121,237	2372	0.83 (0.76, 0.89)	0.88 (0.81, 0.95)
South	341,555	1171	1.34 (1.22, 1.47)	1.18 (1.07, 1.29)
Northeast	303,211	777	1	1
Midwest	342,289	950	1.06 (0.97, 1.17)	1.03 (0.94, 1.13)
% of persons below poverty (quartiles, Q)				
Q1	991,051	2164	1	1
Q2	482,194	1155	1.12 (1.04, 1.20)	1.10 (1.03, 1.19)
Q3	414,122	1263	1.40 (1.31, 1.50)	1.21 (1.12, 1.30)
Q4	283,828	836	1.44 (1.32, 1.56)	1.27 (1.17, 1.38)
% persons with <HS education (quartiles, Q)				
Q1	1,030,204	2351	1	1
Q2	454,285	1083	1.10 (1.02, 1.18)	1.07 (0.99, 1.15)
Q3	345,265	1129	1.45 (1.35, 1.56)	1.23 (1.14, 1.32)
Q4	341,442	855	1.15 (1.06, 1.24)	1.09 (1.00, 1.19)
Rural-urban continuum code [b]				
Metro	1,136,296	2655	1	1
Urban	80,490	231	1.24 (1.08, 1.41)	1.27 (1.11, 1.45)
Rural	35,891	137	1.63 (1.38, 1.94)	1.74 (1.47, 2.07)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.9. Hazard ratios for cardiovascular disease deaths according to patient characteristics among AYA women with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,492,030	720	1	1
Non-Hispanic Black	206,468	299	3.16 (2.76, 3.62)	2.77 (2.41, 3.18)
Hispanic	285,446	109	0.88 (0.71, 1.07)	0.85 (0.69, 1.04)
Other non-Hispanic	188,076	88	1.02 (0.82, 1.27)	0.96 (0.77, 1.20)
Geographic region				
West	1,121,237	496	0.85 (0.71, 1.02)	0.93 (0.77, 1.11)
South	341,555	273	1.64 (1.34, 1.99)	1.40 (1.15, 1.71)
Northeast	303,211	156	1	1
Midwest	342,289	256	1.28 (1.05, 1.56)	1.20 (0.98, 1.47)
% of persons below poverty (quartiles, Q)				
Q1	991,051	502	1	1
Q2	482,194	251	1.16 (1.00, 1.35)	1.18 (1.01, 1.38)
Q3	414,122	289	1.57 (1.36, 1.82)	1.37 (1.18, 1.60)
Q4	283,828	174	1.51 (1.27, 1.80)	1.41 (1.17, 1.70)
% persons with <HS education (quartiles, Q)				
Q1	1,030,204	552	1	1
Q2	454,285	217	1.13 (0.96, 1.32)	1.15 (0.97, 1.36)
Q3	345,265	280	1.77 (1.53, 2.04)	1.53 (1.32, 1.79)
Q4	341,442	167	1.22 (1.02, 1.46)	1.29 (1.06, 1.57)
Rural-urban continuum code [b]				
Metro	1,136,296	473	1	1
Urban	80,490	50	1.50 (1.12, 2.00)	1.52 (1.14, 2.04)
Rural	35,891	33	2.22 (1.56, 3.15)	2.37 (1.66, 3.39)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.10. Hazard ratios for infectious disease deaths according to patient characteristics among AYA women with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,492,030	408	1	1
Non-Hispanic Black	206,468	400	6.48 (5.64, 7.44)	5.24 (4.55, 6.03)
Hispanic	285,446	140	1.56 (1.29, 1.89)	1.48 (1.22, 1.80)
Other non-Hispanic	188,076	69	1.25 (0.97, 1.61)	1.20 (0.93, 1.55)
Geographic region				
West	1,121,237	387	0.53 (0.45, 0.63)	0.59 (0.49, 0.70)
South	341,555	240	1.00 (0.83, 1.20)	0.79 (0.65, 0.96)
Northeast	303,211	201	1	1
Midwest	342,289	162	0.80 (0.65, 0.99)	0.72 (0.58, 0.88)
% of persons below poverty (quartiles, Q)				
Q1	991,051	407	1	1
Q2	482,194	186	0.84 (0.71, 1.00)	0.82 (0.68, 0.97)
Q3	414,122	256	1.27 (1.08, 1.48)	0.98 (0.83, 1.15)
Q4	283,828	168	1.30 (1.08, 1.55)	1.00 (0.82, 1.21)
% persons with <HS education (quartiles, Q)				
Q1	1,030,204	409	1	1
Q2	454,285	226	1.06 (0.90, 1.25)	1.06 (0.89, 1.26)
Q3	345,265	247	1.51 (1.29, 1.77)	1.15 (0.97, 1.36)
Q4	341,442	135	0.78 (0.64, 0.95)	0.78 (0.63, 0.96)
Rural-urban continuum code [b]				
Metro	1,136,296	527	1	1
Urban	80,490	33	0.90 (0.63, 1.27)	1.05 (0.74, 1.49)
Rural	35,891	17	1.02 (0.63, 1.65)	1.41 (0.87, 2.29)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.11. Hazard ratios for all noncancer deaths according to patient characteristics among AYA men with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	978,730	5163	1	1
Non-Hispanic Black	86,152	1552	3.02 (2.85, 3.20)	2.17 (2.05, 2.30)
Hispanic	165,373	1358	1.35 (1.27, 1.43)	1.43 (1.34, 1.52)
Other non-Hispanic	81,894	379	0.80 (0.72, 0.89)	0.75 (0.67, 0.83)
Geographic region				
West	704,855	4605	1.30 (1.21, 1.40)	1.31 (1.22, 1.40)
South	186,783	1518	1.52 (1.40, 1.65)	1.42 (1.31, 1.55)
Northeast	182,410	912	1	1
Midwest	202,449	1208	1.28 (1.17, 1.40)	1.09 (1.00, 1.19)
% of persons below poverty (quartiles, Q)				
Q1	605,693	3132	1	1
Q2	300,442	2289	1.36 (1.29, 1.44)	1.42 (1.34, 1.50)
Q3	240,034	1781	1.26 (1.18, 1.33)	1.29 (1.21, 1.37)
Q4	165,527	1248	1.37 (1.28, 1.46)	1.37 (1.28, 1.47)
% persons with <HS education (quartiles, Q)				
Q1	632,247	3855	1	1
Q2	278,332	1590	0.84 (0.79, 0.89)	1.02 (0.96, 1.09)
Q3	198,167	1625	1.17 (1.10, 1.24)	1.17 (1.10, 1.25)
Q4	202,951	13380	0.93 (0.87, 0.99)	1.13 (1.06, 1.22)
Rural-urban continuum code [b]				
Metro	680,340	3445	1	1
Urban	47,994	243	1.01 (0.89, 1.15)	1.10 (0.97, 1.26)
Rural	21,468	145	1.33 (1.13, 1.57)	1.57 (1.33, 1.86)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.12. Hazard ratios for cardiovascular disease deaths according to patient characteristics among AYA men with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	978,730	828	1	1
Non-Hispanic Black	86,152	221	3.19 (2.74, 3.70)	2.44 (2.09, 2.84)
Hispanic	165,373	146	1.15 (0.96, 1.37)	1.18 (0.99, 1.42)
Other non-Hispanic	81,894	73	1.10 (0.87, 1.40)	0.98 (0.77, 1.25)
Geographic region				
West	704,855	549	0.86 (0.73, 1.03)	0.91 (0.76, 1.09)
South	186,783	247	1.56 (1.28, 1.90)	1.42 (1.16, 1.73)
Northeast	182,410	164	1	1
Midwest	202,449	265	1.32 (1.09, 1.61)	1.24 (1.01, 1.51)
% of persons below poverty (quartiles, Q)				
Q1	605,693	550	1	1
Q2	300,442	265	1.07 (0.93, 1.25)	1.11 (0.96, 1.29)
Q3	240,034	285	1.46 (1.27, 1.69)	1.35 (1.16, 1.57)
Q4	165,527	168	1.35 (1.13, 1.61)	1.31 (1.09, 1.58)
% persons with <HS education (quartiles, Q)				
Q1	632,247	609	1	1
Q2	278,332	225	1.03 (0.88, 1.20)	1.08 (0.92, 1.27)
Q3	198,167	248	1.48 (1.27, 1.72)	1.32 (1.13, 1.54)
Q4	202,951	186	1.21 (1.02, 1.43)	1.28 (1.06, 1.54)
Rural-urban continuum code [b]				
Metro	680,340	483	1	1
Urban	47,994	50	1.47 (1.10, 1.97)	1.55 (1.15, 2.07)
Rural	21,468	30	1.97 (1.36, 2.84)	2.13 (1.47, 3.09)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.13. Hazard ratios for infectious disease deaths according to patient characteristics among AYA men with cancer, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	978,730	2093	1	1
Non-Hispanic Black	86,152	865	3.63 (3.35, 3.90)	2.39 (2.20, 2.58)
Hispanic	165,373	709	1.47 (1.35, 1.60)	1.74 (1.59, 1.90)
Other non-Hispanic	81,894	122	0.57 (0.48, 0.69)	0.59 (0.49, 0.71)
Geographic region				
West	704,855	2322	1.80 (1.61, 2.02)	1.72 (1.53, 1.93)
South	186,783	671	1.71 (1.50, 1.95)	1.59 (1.39, 1.82)
Northeast	182,410	332	1	1
Midwest	202,449	383	1.26 (1.09, 1.46)	0.92 (0.80, 1.07)
% of persons below poverty (quartiles, Q)				
Q1	605,693	1225	1	1
Q2	300,442	1250	1.67 (1.54, 1.81)	1.76 (1.63, 1.91)
Q3	240,034	769	1.16 (1.06, 1.27)	1.33 (1.21, 1.47)
Q4	165,527	545	1.30 (1.18, 1.44)	1.37 (1.23, 1.52)
% persons with <HS education (quartiles, Q)				
Q1	632,247	1798	1	1
Q2	278,332	647	0.60 (0.55, 0.66)	0.90 (0.81, 0.99)
Q3	198,167	747	0.95 (0.87, 1.03)	1.08 (0.99, 1.18)
Q4	202,951	597	0.67 (0.61, 0.73)	1.00 (0.90, 1.11)
Rural-urban continuum code [b]				
Metro	680,340	1306	1	1
Urban	47,994	58	0.64 (0.49, 0.83)	0.79 (0.60, 1.02)
Rural	21,468	30	0.72 (0.50, 1.04)	1.07 (0.74, 1.54)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.14 Hazard ratios for all noncancer deaths according to patient characteristics among AYA women with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,441,573	2869	1	1
Non-Hispanic Black	196,682	975	2.50 (2.33, 2.69)	2.11 (1.96, 2.27)
Hispanic	274,657	588	1.09 (1.00, 1.19)	0.97 (0.89, 1.07)
Other non-Hispanic	180,900	359	1.00 (0.90, 1.12)	0.92 (0.82, 1.03)
Geographic region				
West	1,080,253	2131	0.89 (0.81, 0.97)	0.94 (0.86, 1.03)
South	329,879	1019	1.41 (1.28, 1.56)	1.24 (1.12, 1.37)
Northeast	290,801	643	1	1
Midwest	330,698	859	1.13 (1.02, 1.25)	1.09 (0.99, 1.21)
% of persons below poverty				
Q1	956,002	1922	1	1
Q2	465,338	1030	1.14 (1.06, 1.23)	1.13 (1.04, 1.22)
Q3	398,929	1120	1.44 (1.33, 1.55)	1.25 (1.16, 1.35)
Q4	272,731	719	1.43 (1.31, 1.56)	1.28 (1.17, 1.41)
% persons with <HS education				
Q1	995,397	2120	1	1
Q2	436,400	931	1.08 (1.00, 1.17)	1.05 (0.97, 1.14)
Q3	332,767	987	1.45 (1.34, 1.56)	1.23 (1.14, 1.34)
Q4	328,435	753	1.17 (1.08, 1.28)	1.11 (1.01, 1.21)
Rural-urban continuum code [b]				
Metro	1,091,102	2309	1	1
Urban	77,613	207	1.27 (1.10, 1.46)	1.27 (1.10, 1.46)
Rural	35,037	124	1.67 (1.40, 2.01)	1.68 (1.40, 2.02)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.15 Hazard ratios for cardiovascular disease death according to patient characteristics among AYA women with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,441,573	672	1	1
Non-Hispanic Black	196,682	282	3.24 (2.82, 3.73)	2.84 (2.46, 3.27)
Hispanic	274,657	98	0.85 (0.69, 1.05)	0.82 (0.66, 1.02)
Other non-Hispanic	180,900	86	1.07 (0.86, 1.34)	1.01 (0.80, 1.26)
Geographic region				
West	1,080,253	461	0.84 (0.70, 1.02)	0.92 (0.76, 1.11)
South	329,879	250	1.60 (1.31, 1.97)	1.35 (1.10, 1.67)
Northeast	290,801	145	1	1
Midwest	330,698	247	1.31 (1.07, 1.61)	1.23 (1.00, 1.52)
% of persons below poverty				
Q1	956,002	475	1	1
Q2	465,338	236	1.16 (0.99, 1.35)	1.17 (1.00, 1.38)
Q3	398,929	269	1.56 (1.34, 1.81)	1.35 (1.15, 1.58)
Q4	272,731	158	1.47 (1.22, 1.76)	1.37 (1.13, 1.66)
% persons with <HS education				
Q1	995,397	523	1	1
Q2	436,400	199	1.11 (0.93, 1.31)	1.13 (0.95, 1.34)
Q3	332,767	265	1.78 (1.53, 2.07)	1.53 (1.31, 1.79)
Q4	328,435	151	1.18 (0.98, 1.43)	1.24 (1.02, 1.52)
Rural-urban continuum code [b]				
Metro	1,091,102	438	1	1
Urban	77,613	45	1.45 (1.07, 1.97)	1.46 (1.07, 1.99)
Rural	35,037	29	2.07 (1.42, 3.01)	2.17 (1.48, 3.17)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.16 Hazard ratios for infectious disease death according to patient characteristics among AYA women with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	1,441,573	306	1	1
Non-Hispanic Black	196,682	221	5.03 (4.23, 5.99)	4.20 (3.52, 5.01)
Hispanic	274,657	72	1.14 (0.88, 1.48)	1.02 (0.79, 1.33)
Other non-Hispanic	180,900	54	1.35 (1.01, 1.80)	1.27 (0.95, 1.70)
Geographic region				
West	1,080,253	254	0.62 (0.49, 0.77)	0.67 (0.53, 0.84)
South	329,879	144	1.09 (0.85, 1.40)	0.83 (0.64, 1.07)
Northeast	290,801	112	1	1
Midwest	330,698	121	1.01 (0.78, 1.31)	0.84 (0.65, 1.10)
% of persons below poverty				
Q1	956,002	275	1	1
Q2	465,338	115	0.81 (0.65, 1.01)	0.81 (0.65, 1.01)
Q3	398,929	168	1.33 (1.09, 1.61)	1.06 (0.86, 1.30)
Q4	272,731	95	1.15 (0.91, 1.46)	0.98 (0.76, 1.25)
% persons with <HS education				
Q1	995,397	287	1	1
Q2	436,400	133	0.96 (0.78, 1.19)	1.02 (0.82, 1.27)
Q3	332,767	152	1.43 (1.17, 1.74)	1.14 (0.92, 1.40)
Q4	328,435	81	0.74 (0.58, 0.96)	0.77 (0.59, 1.01)
Rural-urban continuum code [b]				
Metro	1,091,102	316	1	1
Urban	77,613	20	0.90 (0.57, 1.41)	0.92 (0.59, 1.45)
Rural	35,037	15	1.48 (0.88, 2.48)	1.62 (0.96, 2.74)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.17 Hazard ratios for all noncancer deaths according to patient characteristics among AYA men with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	903,333	3311	1	1
Non-Hispanic Black	73,023	853	3.09 (2.86, 3.33)	2.38 (2.20, 2.57)
Hispanic	150,011	728	1.28 (1.18, 1.39)	1.26 (1.16, 1.37)
Other non-Hispanic	73,717	287	1.04 (0.92, 1.17)	0.90 (0.79, 1.01)
Geographic region				
West	645,009	2533	1.03 (0.94, 1.12)	1.07 (0.98, 1.17)
South	169,763	983	1.50 (1.35, 1.65)	1.36 (1.22, 1.50)
Northeast	165,616	634	1	1
Midwest	186,245	878	1.23 (1.11, 1.36)	1.14 (1.03, 1.26)
% of persons below poverty				
Q1	557,071	2070	1	1
Q2	273,435	1150	1.13 (1.05, 1.22)	1.17 (1.09, 1.26)
Q3	218,900	1154	1.39 (1.29, 1.49)	1.29 (1.20, 1.39)
Q4	150,258	803	1.49 (1.37, 1.62)	1.41 (1.30, 1.54)
% persons with <HS education				
Q1	581,538	2276	1	1
Q2	252,910	1039	1.07 (0.99, 1.15)	1.12 (1.04, 1.21)
Q3	180,340	979	1.37 (1.27, 1.48)	1.23 (1.14, 1.33)
Q4	184,876	883	1.22 (1.13, 1.32)	1.25 (1.15, 1.37)
Rural-urban continuum code [b]				
Metro	618,108	2356	1	1
Urban	43,895	201	1.21 (1.04, 1.39)	1.25 (1.08, 1.45)
Rural	19,943	125	1.64 (1.37, 1.96)	1.76 (1.47, 2.11)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.18 Hazard ratios for cardiovascular disease death according to patient characteristics among AYA men with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	903,333	744	1	1
Non-Hispanic Black	73,023	183	3.22 (2.73, 3.79)	2.37 (2.00, 2.80)
Hispanic	150,011	131	1.18 (0.98, 1.42)	1.20 (0.99, 1.46)
Other non-Hispanic	73,717	65	1.13 (0.87, 1.45)	0.98 (0.76, 1.26)
Geographic region				
West	645,009	482	0.84 (0.70, 1.01)	0.89 (0.73, 1.07)
South	169,763	218	1.54 (1.25, 1.90)	1.41 (1.14, 1.75)
Northeast	165,616	147	1	1
Midwest	186,245	239	1.31 (1.06, 1.60)	1.24 (1.01, 1.52)
% of persons below poverty				
Q1	557,071	495	1	1
Q2	273,435	227	1.04 (0.89, 1.22)	1.08 (0.92, 1.27)
Q3	218,900	250	1.45 (1.25, 1.70)	1.34 (1.14, 1.57)
Q4	150,258	151	1.38 (1.15, 1.67)	1.34 (1.10, 1.63)
% persons with <HS education				
Q1	581,538	536	1	1
Q2	252,910	204	1.08 (0.92, 1.28)	1.12 (0.95, 1.34)
Q3	180,340	220	1.53 (1.30, 1.79)	1.35 (1.15, 1.60)
Q4	184,876	163	1.24 (1.03, 1.49)	1.28 (1.05, 1.57)
Rural-urban continuum code [b]				
Metro	618,108	421	1	1
Urban	43,895	45	1.51 (1.11, 2.05)	1.58 (1.16, 2.15)
Rural	19,943	27	1.99 (1.35, 2.93)	2.12 (1.43, 3.14)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

Table 6.19 Hazard ratios for infectious disease death according to patient characteristics among AYA men with cancers other than Non-Hodgkin lymphoma, 1985-2015

	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity				
Non-Hispanic White	903,333	584	1	1
Non-Hispanic Black	73,023	296	5.44 (4.73, 6.26)	3.97 (3.43, 4.59)
Hispanic	150,011	164	1.41 (1.19, 1.68)	1.57 (1.31, 1.88)
Other non-Hispanic	73,717	54	1.01 (0.76, 1.34)	0.92 (0.69, 1.22)
Geographic region				
West	645,009	542	1.12 (0.92, 1.36)	1.20 (0.99, 1.47)
South	169,763	242	1.73 (1.39, 2.15)	1.46 (1.17, 1.82)
Northeast	165,616	125	1	1
Midwest	186,245	153	1.23 (0.97, 1.55)	0.94 (0.74, 1.20)
% of persons below poverty				
Q1	557,071	383	1	1
Q2	273,435	267	1.26 (1.08, 1.47)	1.43 (1.22, 1.68)
Q3	218,900	272	1.50 (1.28, 1.75)	1.43 (1.22, 1.69)
Q4	150,258	176	1.50 (1.25, 1.79)	1.50 (1.24, 1.82)
% persons with <HS education				
Q1	581,538	477	1	1
Q2	252,910	218	0.87 (0.74, 1.02)	1.04 (0.88, 1.24)
Q3	180,340	218	1.20 (1.02, 1.42)	1.09 (0.92, 1.29)
Q4	184,876	185	0.93 (0.78, 1.10)	1.12 (0.92, 1.36)
Rural-urban continuum code [b]				
Metro	618,108	496	1	1
Urban	43,895	33	0.94 (0.66, 1.34)	1.04 (0.73, 1.49)
Rural	19,943	21	1.31 (0.84, 2.02)	1.61 (1.04, 2.51)

[a] Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables

[b] Includes AYAs diagnosed in 1998-2015 only

CHAPTER 7. DISCUSSION

7.1 Main findings

For our first aim, we examined noncancer mortality after AYA cancer among patients identified in the SEER database. Overall, mortality from noncancer causes among AYAs with cancer was 1.84 (95% CI: 1.80-1.87) times that in the general population, with adjustment for age, sex, race, and calendar year. Across cause-specific categories of noncancer death, standardized mortality ratios comparing AYAs with cancer to the general population were particularly elevated for infectious diseases, cardiovascular diseases, and renal diseases, and remained significantly increased for more than 20 years after cancer diagnosis. Cancer types associated with the highest SMRs for all noncancer mortality included leukemias, Hodgkin lymphoma, non-Hodgkin lymphoma, central nervous system tumors, head and neck cancers, and cervical/uterine cancers.

For our second aim, we investigated long-term patterns of noncancer mortality after AYA cancer and evaluated disparities according to race/ethnicity and other patient characteristics. For all cancer types combined, the 10-year cumulative incidence of noncancer death after AYA cancer was 2% and 5% among women and men, respectively. With adjustment for cancer type, all noncancer mortality was increased among non-Hispanic Black AYAs and those in the South or in rural counties. In analyses focused on mortality from cardiovascular and infectious diseases, Non-Hispanic Black race/ethnicity was associated with elevated mortality from both cardiovascular diseases and infectious diseases, while living in the South or in a rural county was associated with increased mortality from cardiovascular diseases only.

Taken together, these analyses suggest that AYAs with cancer have an elevated burden of mortality from noncancer causes, and identify subgroups at particularly increased risk. AYAs with hematologic malignancies, central nervous system tumors, head and neck cancers, and cervical/uterine cancers, and those who are non-Hispanic Black or diagnosed with cancer in the South or in rural areas may be priority groups for increased surveillance and/or behavioral interventions throughout survivorship.

7.2 Strengths and limitations

This research utilized freely and publicly available data from SEER, the largest source of cancer incidence and mortality data in the U.S., to investigate noncancer deaths among AYAs with cancer. The long history of the SEER program, with data available from as early as the 1970s, allowed us to evaluate whether the risk of death from noncancer causes remains elevated among AYA cancer survivors relative to the general population long after the cessation of cancer treatment. With information on race and county-level socioeconomic status, we were able to highlight potential disparities in noncancer mortality within a national sample of AYAs with cancer.

These analyses have several limitations, including those inherent to the use of data from cancer registries such as those in SEER. Cause of death information in SEER is ascertained from death certificates, and may be subject to misclassification. However, for several causes of death, including suicide[131] and coronary heart disease,[132] prior studies have suggested moderate to high concordance between cause of death codes abstracted from the death certificate and the gold standard measure of cause of death determination by a physician review panel.[131-133] In Aim 1, we investigated the robustness of our SMR estimates to potential cause of death misclassification in sensitivity analyses, and found that even with 30% misattribution of cancer

deaths to noncancer causes, AYAs with cancer would still experience a significantly elevated burden of noncancer deaths relative to the general population. An additional limitation is the lack of information on lifestyle factors, comorbidities, and individual-level socioeconomic status. These characteristics are not available in registry data, so we were unable to consider their impact on noncancer mortality risk in our analyses. Treatment information available in SEER is limited to crude categories indicating whether chemotherapy and/or radiation was received as part of the first course of therapy, thus precluding any analysis of associations between specific chemotherapeutic agents or targeted therapies, or radiation doses, and noncancer causes of death. Furthermore, prior research has suggested that the chemotherapy and radiation data that is available in SEER is of moderate validity,[143] and therefore we elected not to use this information in our analyses. However, though an imperfect proxy, our site-specific analyses according to cancer stage and time period of diagnosis may be informative for considering potential treatment-related effects on mortality, given fairly standardized treatment protocols for cancers of a particular stage within a given time period.

7.3. Public health implications

With >80% five-year relative survival for all cancer types combined, the vast majority of AYAs with cancer will go on to become long-term survivors, prompting the need for research on survivorship issues for patients diagnosed in this age range. This research estimated the extent to which mortality from cardiovascular diseases, infectious diseases, and other causes is greater among AYA cancer survivors than the general population, an important consideration for patients and physicians planning long-term follow-up care. We considered variability in noncancer mortality according to cancer type, time since diagnosis, and other factors to identify patient subgroups with the greatest excess risk, for whom additional medical surveillance may be

indicated. Our findings of long-term excess mortality for certain cancer types diagnosed at the older end of the AYA age range—particularly colorectal cancer, head and neck cancers, and cervical/uterine cancers—provide critical information for patient groups that have seldom been the focus of survivorship research. Additionally, our analyses according to race, county-level socioeconomic status, and other factors highlighted mortality disparities among AYA cancer survivors, with the potential to help motivate the direction of resources toward vulnerable patient subgroups.

7.4 Future Directions

Few large cohort studies to date have examined long-term health outcomes among AYA cancer survivors, and current guidelines for follow-up care for this age group continue to be based largely on findings from studies of patients diagnosed as children.[4] While our findings describe the burden of excess mortality from noncancer causes experienced by AYAs with cancer, we were unable to evaluate the potential contribution of cancer treatment-related exposures to this excess risk. Future AYA studies, with access to detailed cancer treatment information and long-term follow-up, should investigate patterns of noncancer morbidity and mortality from particular causes according to receipt of specific chemotherapeutic agents and chemo- and radiotherapy doses. For cancer types that span both the childhood and AYA age range, such as hematologic malignancies and central nervous system tumors, this would enable comparisons with findings from the Childhood Cancer Survivor Study and other large childhood cancer cohorts, and further our understanding of potential age-related differences in late effects of cancer treatments. For cancer types nearly exclusive to the older end of the AYA age range, such as breast cancer, colorectal cancer, and head and neck cancers, long-term health outcomes remain largely undescribed, and investigation of treatment-specific late effects would facilitate

the development of age-appropriate guidelines for AYAs with these cancers. Such studies should also consider potential modification of noncancer morbidity and mortality risk according to patient factors such as race/ethnicity, comorbidities, family history, and health behaviors to further refine guidelines for follow-up care.

APPENDIX 1. SEER AYA SITE RECODE/WHO 2008 DEFINITION

Site Group	ICD-O-3 Behavior Recode	Primary Site	ICD-O-3 Histology
1 Leukemias			
1.1 Acute lymphoid leukemia	3	C000-C809	9826,9835-9836
	3	C420-C421,C424	9811-9818,9837
1.2 Acute myeloid leukemia	3	C000-C809	9840,9861,9865-9867,9869,9871-9874,9891,9895-9898,9910-9911,9920
1.3 Chronic myeloid leukemia	3	C000-C809	9863,9875-9876,9945-9946
1.4 Other and unspecified leukemia	3	C000-C809	9742,9800-9801,9805-9809,9820,9831-9834,9860,9870,9930-9931,9940,9948,9963-9964
	3	C420-C421,C424	98,239,827
2 Lymphomas			
2.1 Non-Hodgkin lymphoma	3	C000-C809	9590-9591,9596-9597,9670-9671,9673,9675,9678-9680,9684,9687-9691,9695,9698-9702,9705,9708-9709,9712,9714,9716-9719,9725-9729,9735,9737-9738
	3	C000-C419,C422-C423,C425-C809	9811-9818,9823,9827,9837
2.2 Hodgkin lymphoma	3	C000-C809	9650-9655,9659,9661-9665,9667
3 CNS and Other Intracranial and Intraspinal Neoplasms (all behaviors)			
3.1. Astrocytoma			
3.1.1 Specified low-grade astrocytic tumors	0,1,3	C723	9380
	0,1,3	C000-C809	9410-9411,9420-9421,9424
3.1.2 Glioblastoma and anaplastic astrocytoma	0,1,3	C000-C809	9401,9440-9442
3.1.3 Astrocytoma, NOS	0,1,3	C000-C809	9400
3.2 Other glioma	0,1,3	C000-C722,C724-C809	9380
	0,1,3	C000-C809	9381-9384,9423,9430,9450-9451,9460
3.3 Ependymoma	0,1,3	C000-C809	9391-9394
3.4. Medulloblastoma and other PNET			
3.4.1 Medulloblastoma	0,1,3	C716	9470-9474
3.4.2 Supratentorial PNET	0,1,3	C000-C715,C717-C809	9470-9474
3.5 Other specified intracranial and intraspinal neoplasms	0,1,3	C000-C699,C730-C750,C754-C809	9350-9351,9360-9362,9390,9480,9530-9535,9537-9539,9541,9550,9562,9570
	0,1,3	C700-C729,C751-C753	9161,9361-9362,9390,9530-9531,9535,9538,9540,9560,9571
	0,1,3	C700	9,532,953,495,379,530
	0,1,3	C753	9360
	0,1,3	C711	94,809,539

	0,1,3	C713	94,809,533
	0,1,3	C719	9350
	0,1,3	C714,C717	9480
	0,1,3	C709	9539
3.6 Unspecified intracranial and intraspinal neoplasms			
3.6.1 Unspecified malignant intracranial and intraspinal neoplasms	3	C700-C729,C751-C753	8000-8005
3.6.2 Unspec. ben/border intracran. and intraspin. Neo.	0,1	C700-C729,C751-C753	8000-8005
4 Osseous & Chondromatous Neoplasms			
4.1 Osteosarcoma	3	C000-C809	9180-9187,9192-9194
4.2 Chondrosarcoma	3	C000-C809	9220-9221,9230-9231,9240,9242-9243
4.3 Ewing tumor	3	C000-C809	9260,9364-9365
4.4 Other specified and unspecified bone tumors	3	C000-C809	8812,9250,9261,9370-9372
	3	C400-C419	8000-8005,8800-8803,8805-8806,9200
5 Soft Tissue Sarcomas			
5.1 Fibromatous neoplasms	3	C000-C809	8810-8811,8813-8815,8820-8824,8830,8832-8833,8835-8836,9252
5.2 Rhabdomyosarcoma	3	C000-C809	8900-8904,8910,8912,8920-8921,8991
5.3 Other soft tissue sarcoma			
5.3.1 Specified soft tissue sarcoma			
5.3.1.1 Specified (excluding Kaposi sarcoma)	3	C000-C809	8804,8825,8840-8897,8982-8983,8990,9040-9044,9120-9139,9141-9150,9170,9251,9561,9580-9581
	3	C000-C699,C730-C750,C754-C809	954,095,609,571
5.3.1.2 Kaposi sarcoma	3	C000-C809	9140
5.3.2 Unspecified soft tissue sarcoma	3	C000-C399,C420-C809	8800-8803,8805-8806
6 Germ Cell and Trophoblastic Neoplasms			
6.1 Germ cell and trophoblastic neoplasms of gonads	3	C569,C620-C629	9060-9065,9070-9073,9080-9085,9090-9091,9100-9102,9105
6.2 Germ cell and trophoblastic neoplasms of nongonadal sites			
6.2.1 Intracranial (all behaviors)	0,1,3	C700-C729,C751-C753	9060-9065,9070-9073,9080-9085,9090-9091,9100-9102,9105
6.2.2 Other nongonadal	3	C000-C568,C570-C619,C630-C699,C730-C750,C754-C809	9060-9065,9070-9073,9080-9085,9090-9091,9100-9102,9104-9105
7 Melanoma and Skin Carcinomas			
7.1 Melanoma	3	C000-C809	8720-8723,8726,8728,8730,8740-8746,8761,8770-8774,8780
7.2 Skin carcinomas	3	C440-C449	8010-8589

8 Carcinomas			
8.1 Thyroid carcinoma	3	C739	8010-8589
8.2 Other carcinoma of head and neck			
8.2.1 Nasopharyngeal carcinoma	3	C110-C119	8010-8589
8.2.2 Other sites in lip, oral cavity and pharynx	3	C000-C109,C120-C148	8010-8589
8.2.3 Nasal cav,mid ear, sinuses, larynx, other ill-defined head/neck	3	C300-C329,C760	8010-8589
8.3 Carcinoma of trachea, bronchus, and lung	3	C330-C349	8010-8589
8.4 Carcinoma of breast	3	C500-C509	8010-8589
8.5 Carcinoma of genitourinary tract			
8.5.1 Carcinoma of kidney	3	C649	8010-8589
8.5.2 Carcinoma of bladder	3	C670-C679	8010-8589
8.5.3 Carcinoma of gonads	3	C569,C620-C629	8010-8589
	3	C000-C809	8590-8593
8.5.4 Carcinoma of cervix and uterus	3	C530-C559	8010-8589
8.5.5 Carcinoma of other and ill-defined sites, genitourinary tract	3	C510-C529,C570-C579,C600-C619,C630-C639,C659,C669,C680-C689	8010-8589
8.6 Carcinoma of gastrointestinal tract			
8.6.1 Carcinoma of colon and rectum	3	C180-C218	8010-8589
8.6.2 Carcinoma of stomach	3	C160-C169	8010-8589
8.6.3 Carcinoma of liver and intrahepatic bile ducts	3	C220-C221	8010-8589
8.6.4 Carcinoma of pancreas	3	C250-C259	8010-8589
8.6.5 Carc other and ill-def sites, gastrointestinal tract	3	C150-C159,C170-C179,C230-C249,C260-C269	8010-8589
8.7 Carcinoma of other and ill-defined sites			
8.7.1 Adrenocortical carcinoma	3	C740-C749	8010-8589
8.7.2 Carcinoma of other and ill-defined sites, NOS	3	C149,C219,C222-C229,C270-C299,C350-C439,C450-C499,C561-C568,C580-C599,C640-C648,C650-C658,C660-C668,C690-C738,C750-C759,C761-C809	8010-8589
	3	C809	9010
9 Miscellaneous specified neoplasms, NOS			
9.1 Other pediatric and embryonal tumors, NOS			

9.1.1 Wilms tumor	3	C000-C809	8959-8960
9.1.2 Neuroblastoma	3	C000-C809	94,909,500
9.1.3 Other pediatric and embryonal tumors, NOS	3	C000-C809	8963-8964,8970-8973,8981,9363,9501-9523
9.2 Other specified and embryonal tumors, NOS			
9.2.1 Paraganglioma and glomus tumors	3	C000-C809	8680-8711
9.2.2 Other specified gonadal tumors	3	C000-C809	8600-8650,9000
	3	C569	8670,9013-9015,9054
9.2.3 Myeloma, mast cell, misc. lymphoreticular neo., NOS	3	C000-C809	9724,9731-9734,9740-9741,9743-9764,9766,9769,9960,9965-9967,9970-9971
9.2.4 Other specified neoplasms, NOS	3	C000-C809	8930-8951,8980,9020,9050-9053,9110,9160,9270-9330,9950,9961-9962,9975,9980,9982,9989,9991-9992
	3	C000-C699,C730-C750,C754-C809	9161
10 Unspecified Malignant Neoplasms			
	3	C000-C399,C420-C699,C730-C750,C754-C809	8000-8005
Adapted from ref [117]			

APPENDIX 2. NONCANCER CAUSE OF DEATH CLASSIFICATION IN SEER

Noncancer Causes of Death	ICD-8 (1968-1978)	ICD-9 (1979-1998)	ICD-10 (1999+)
Infectious diseases			
Tuberculosis	010-018	010-018	A15-A19
Syphilis	090-097	090-097	A50-A53
Septicemia	38	38	A40-A41
Other Infectious and Parasitic Diseases (including Human Immunodeficiency Virus [HIV] [1987+])	001-009, 020-037, 039-043, 045-065, 067-076, 078-089, 098-130.1, 130.3-136	001-009, 020-037, 039-041, 045-088, 098-139; 042-044 (HIV)	A00-A08, A20-A33, A35-A39, A42-A49, A54-B19, B25-B99; B20-B24 (HIV)
Pneumonia and Influenza	470-474, 480-486	480-487	J09-J18
Cardiovascular diseases			
Diseases of Heart	390-398, 402, 404, 410-429	390-398, 402, 404, 410-429	I00-I09, I11, I13, I20-I51
Hypertension without Heart Disease	400-401, 403	401, 403	I10, I12
Cerebrovascular Diseases	430-438	430-438	I60-I69
Atherosclerosis	440	440	I70
Aortic Aneurysm and Dissection	441	441	I71
Other Diseases of Arteries, Arterioles, Capillaries	442-448	442-448	I72-I78
Respiratory			
Chronic Obstructive Pulmonary Disease and Allied Cond	490-493, 519.3	490-496	J40-J47
Gastrointestinal and liver			
Stomach and Duodenal Ulcers	531-533	531-533	K25-K28
Chronic Liver Disease and Cirrhosis	571	571	K70, K73-K74
Renal			
Nephritis, Nephrotic Syndrome and Nephrosis	580-584, 593.0-593.3, 593.5	580-589	N00-N07, N17-N19, N25-N27
External causes			
Accidents and Adverse Effects	800-949	800-949	V01-X59, Y85-Y86

Suicide and Self-Inflicted Injury	950-959	950-959	U03, X60-X84, Y87.0
Homicide and Legal Intervention	960-978	960-978	U01-U02, X85-Y09, Y35, Y87.1, Y89.0
Other			
Diabetes Mellitus	250	250	E10-E14
Alzheimers (ICD-9 and 10 only)	N/A	331	G30
Complications of Pregnancy, Childbirth, Puerperium	630-678	630-676	A34, O00-O95, O98-O99
Congenital Anomalies	740-759	740-759	Q00-Q99
Certain Conditions Originating in Perinatal Period	760-779	760-779	P00-P96
Symptoms, Signs and Ill-Defined Conditions	780-796	780-799	R00-R99
Other Cause of Death	--	--	--
In situ, benign or unknown behavior neoplasm	208-239	210-237, 238.0-238.5, 238.7-238.9, 239	D00-D48

Adapted from ref [103]

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