Survival of Adolescents and Young Adults with Prevalent Poor-Prognosis Metastatic Cancers: A Population-based Study of Contemporary Patterns and Their Implications

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Abstract

Background: Although survival has improved dramatically for most adolescents and young adults (AYAs, 15–39 years old) with cancer, it remains poor for those presenting with metastatic disease. To better characterize this subset, we conducted a landscape survival comparison with older adults (OAs, 40–79 years).

Methods: Using Surveillance, Epidemiology, and End Results Program data from 2000–2016, we examined incident cases of poor-prognosis metastatic cancers (5-year survival < 50%) among AYAs (n=11,518) and OAs (n=345,681) and compared cause-specific survival by sociodemographic characteristics (race/ethnicity, sex, and socioeconomic status). Adjusted hazard ratios (aHRs) for death from metastatic disease (95% confidence intervals [95%CI]) were compared between AYAs and OAs (p_{int}).

Results: AYAs had significantly better survival than OAs for every cancer site except kidney, where it was equivalent (range of aHRs: 0.91 [95%CI 0.82–1.02] for kidney cancer to 0.33 [0.26–0.42] for rhabdomyosarcoma). Compared to their OA counterparts, greater survival disparities existed for AYAs who were non-Hispanic Black with uterine cancer (aHR=2.20 [1.25–3.86] versus 1.40 [1.28–1.54]; p_{int}=0.049) and kidney cancer (aHR=1.51 [1.15–1.98] versus 1.10 [1.03–1.17]; p_{int}=0.04); non-Hispanic Asian/Pacific Islanders with ovarian cancer (aHR=1.47 [1.12–1.93]

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versus 0.89 [0.84–0.95], p_{int}<0.001); and males with colorectal cancer (aHR=1.21 [1.10–1.32] versus 1.08 [1.06–1.10]; p_{int}=0.045)).

Conclusions: AYAs diagnosed with these metastatic cancers have better survival than OAs, but outcomes remain dismal.

Impact: Overcoming the impact of metastasis in these cancers is necessary for continuing progress in AYA oncology. Sociodemographic disparities affecting AYAs within kidney, uterine, ovarian, and colorectal cancer could indicate plausible effects of biology, environment, and/or access and should be explored.

Keywords

Adolescents; young adults; survival; metastatic cancer; AYAs

INTRODUCTION

Among the many challenges in adolescent and young adult (AYA, 15–39 years) oncology, overcoming survival disparities is a key priority. In landmark studies from the early 2000s, AYAs with cancer were shown to have lower overall survival improvement than both younger and older populations and poorer cancer-specific outcomes [1, 2]. Potential explanations for these disparities included unfavorable tumor biology, more advanced disease, impaired access to appropriate care, delayed diagnosis, use of suboptimal treatment regimens, and excess treatment-related toxicity [3–8]. It has been postulated that AYAs are more prone to developing higher-risk forms of cancer than other age groups [9, 10]. Regardless, therapeutic advances have led to improved diagnosis and treatment, with 5-year survival for all AYA cancers combined now being 85%, the highest of all age groups [11–21].

Unfortunately, some AYAs have been left behind. Lower survival persists for specific subsets defined by diagnosis, histology, stage, sex, race/ethnicity, and socioeconomic status (SES) [15, 16, 18, 22–25]. Of these, being diagnosed with metastatic disease carries the worst prognosis. In AYAs with metastatic cancer, five-year survival is below 40% for most types and much lower for many. For metastatic breast and colorectal carcinoma, 5-year survival is only 15–20% and is less than 10% for metastatic melanoma and metastatic carcinomas of the kidney, stomach, and lung [18, 22]. In aggregate, adjusted mortality for AYAs diagnosed with metastatic cancer is 6-fold greater than those with localized disease [15]. For breast, lung, stomach, and colorectal carcinoma, as well as soft tissue sarcomas, AYAs with metastatic versus localized disease have an 8 to 14-fold higher risk of death, and a 30-fold higher risk with metastatic melanomas and carcinomas of the uterus and kidney [15].

Independent of cancer stage, AYAs who are racial/ethnic minorities, male, or low SES demonstrate significantly poorer survival compared to their non-Hispanic White, female and high SES counterparts [15, 19, 25]. Associations between sociodemographic and biological variables are documented for certain hematologic malignancies such as acute myeloid leukemia [26], as well as some high-risk metastatic and loco-regional cancers, including HER2/ER/PR-negative breast cancer in younger non-Hispanic Black [NHB] women and

colorectal cancer in younger patients and racial/ethnic minorities [27–35]. Yet, patterns of metastatic disease among AYAs, specifically in the context of sociodemographic factors, remain largely unexplored despite their potential for informing improved diagnosis and treatment.

As an initial step in exploring sociodemographic risk factors for presenting with metastatic disease, our group recently used Surveillance, Epidemiology, and End Results (SEER) registry data to compare incidence patterns and trends by age and sociodemographic factors among AYAs versus older patients for twelve poor-prognosis metastatic cancers (5-year survival less than 50%) relevant to AYAs between 2000–2016 [36]. Although that study showed AYAs are less likely than older adults to present with metastatic disease in all sites except breast and stomach, the incidence of metastatic breast, stomach, colorectal, and kidney cancer is rising significantly faster among AYAs compared to older adults. Additionally, AYAs who are racial/ethnic minorities or of low SES have a higher risk of presenting with metastatic disease in breast, stomach, and kidney cancer compared to their older counterparts.

Using the same SEER cohort of AYAs and older adults with the same poor-prognosis metastatic solid tumors prevalent among AYAs and older adults, we now report results of this current study that compares survival and its association with sociodemographic factors. Our overall objective was to determine whether AYAs with these select metastatic cancers, in aggregate and/or within sociodemographic subsets, are at greater risk of dying than older adults. By using this "landscape approach," our study was positioned to (1) examine whether the prevailing narrative of AYAs being uniformly predisposed to poorer outcomes is true within metastatic disease; and (2) look for evidence pointing towards potential age-related differences in cancer biology, treatment response, and/or cancer care delivery that could be exploited to improve outcomes in these high-risk patients.

METHODS

Data Source and Cancer Selection

This was a population-based study utilizing SEER-18 registry data. Patients were 15–79 years old when first diagnosed with selected poor-prognosis, metastatic primary malignancies (pragmatically defined by 5-year overall survival less than 50%) between January 2000 and December 2011. Patients up to age 79 were included to account for varied incidence rates for the selected cancers; those aged 80 and older were excluded given their frailty and limited ability to tolerate chemotherapy [37]. Metastatic disease was denoted by "distant" stage disease, defined by the SEER coding rule as "tumor which has spread to body areas distant or remote from the primary tumor" [38]. Cancer sites included in this analysis were common solid tumors relevant to AYAs: bone tumors (osteosarcoma, chondrosarcoma, Ewing sarcoma, and others), melanoma, rhabdomyosarcoma, other soft tissue sarcomas, and carcinomas of the breast, cervix, uterus, ovary, colon-rectum, kidney, lung, and stomach. Rhabdomyosarcoma was evaluated separately as it is clinically and biologically distinct from other soft tissue sarcomas [39]. Cervical and uterine cancers were examined individually due to differences in biology, risk factors, and screening. Consistent with our focus on poor-prognosis cancer, germ cell tumors were excluded as 5-year survival

is > 50% even with metastases [22]. Kaposi sarcoma and non-Hodgkin lymphoma were excluded due to their distinctive HIV-associated epidemiology [15, 40]. Leukemias were excluded as they are inherently disseminated at diagnosis and not staged as metastatic or non-metastatic. Patients with subsequent primary cancers were excluded.

Variable Definitions

Patients were classified as AYA (15–39 years) or older adult (40–79 years). For each case, sex (male, female); race and ethnicity (non-Hispanic White [NHW], NHB, non-Hispanic Asian/Pacific Islander [NHAPI], and Hispanic [all races]); and SES were assessed. For both age groups, the primary cancer site was identified using the SEER AYA site recode [41]. The SEER census tract level SES index is a time-dependent composite score constructed from seven relevant census tract variables: median household income, median house value, median rent, percent below 150% of poverty line, education index, percent working class, and percent unemployed [42, 43]). SES scores are calculated for each year using census data and American Community Survey 5-year estimates and subsequently categorized into tertiles with equal populations across the entire SEER catchment area. Tertiles were chosen instead of quintiles to optimize case numbers for all cancer types and were accessed through the SEER specialized census-tract level and rurality database.

Statistical Analyses

Survival data were obtained using SEER*Stat software version 8.3.6 [44]. Vital status was determined through information sharing from reporting hospitals, record linkage with vital statistics, Social Security Administration, driver license information, and credit records. Follow-up data were available through December 31, 2016. Patients alive at the end of the follow-up period or lost to follow-up were censored at the end of study date or date of last known previous contact while alive, respectively. The primary outcome was cause-specific survival, which accounts for competing risks. Cause-specific 5-year survival for each age group by cancer site was calculated using the nonparametric Kaplan-Meier survival function. Kaplan-Meier survival plots were utilized to compare survival patterns in AYAs and older adults in aggregate and by sociodemographic variables. Survival differences between age groups were assessed using the log-rank test.

Cox proportional hazards regression analysis was performed to determine the relative risk of cause-specific mortality by cancer site for AYAs, males, NHBs, NHAPIs, Hispanics, and low and middle SES (reference groups: older adults, females, NHWs, and high SES, respectively). Multivariate models were adjusted for sex, race/ethnicity, and SES for AYAs and older adults combined and separately to estimate adjusted hazard ratios (aHRs) with 95% confidence intervals (95%CI). Modifying effects of age group were assessed by including an interaction term in the multivariate analysis to compare aHRs for AYAs and older adults within each sociodemographic subgroup and are reported as p_{int}. Assumption of proportional hazards was tested by comparing Kaplan-Meier curves of study covariates and verifying the constant proportionality of hazards over time. All p-values were two-sided with significance defined as p<0.05. All statistical analyses were performed using SEER*Stat Version 8.3.6 and SAS Version 9.4.

Data Availability

Data were accessed from the SEER Census-Tract Level SES and Rurality Database and are publicly available (https://seer.cancer.gov/seertrack/data/request/).

RESULTS

General survival patterns

In aggregate, AYAs with these twelve poor-prognosis metastatic cancers demonstrated statistically significantly higher cause-specific survival than older adults ($p_{log-rank}$<0.001; Figure 1). After adjusting for cancer site, race/ethnicity, sex, and SES, the risk of death for all AYAs combined was 25% lower than older adults (aHR 0.75; 95%CI 0.73–0.77) (Table 1). Cause-specific survival was statistically significantly better for AYAs than older adults in all metastatic cancer sites except kidney cancer, where there was no statistically significant difference (Figure 1). After adjusting for all sociodemographic factors, the hazard ratio for death by cancer type among AYAs compared with older adults ranged from 0.91 (95%CI 0.82–1.02) for kidney cancer to 0.33 (95%CI 0.26–0.42) for rhabdomyosarcoma (Table 1). In aggregate, the 5-year cause-specific survival estimate was 21.4% (95%CI 20.7%–22.2%) for AYAs and 9.3% (95%CI 9.2%–9.4%) for older adults (Table 2). Five-year cause-specific survival estimates varied substantially by cancer type.

Sociodemographic patterns

Race and ethnicity—For several cancer sites in both age groups, racial/ethnic minorities were at higher risk for death compared to NHWs (Figure 2, Supplementary Table 1). Within NHBs, the excess risk of death was significantly higher in AYAs than older adults for uterine cancer (aHR 2.20 [95%CI 1.25–3.86] versus 1.40 [95%CI 1.28–1.54], respectively; p_{int}=0.049) and kidney cancer (aHR 1.51 [95%CI 1.15–1.98] versus 1.10 [95%CI 1.03–1.17], respectively; p_{int}=0.04). Within NHAPIs, the excess risk of death was statistically significantly higher in AYAs than older adults for ovarian cancer (aHR 1.47 [95%CI 1.12–1.93] versus 0.89 [95%CI 0.84–0.95], respectively; p_{int}<0.001). In contrast, for lung cancer, the lower mortality risk for Hispanics in general was more pronounced among AYAs than older adults (aHR 0.67 [95%CI 0.57–0.78] versus 0.91 [95%CI 0.89–0.93], respectively; p_{int}<0.001].

Sex—For most cancer sites, males within both age groups were at higher risk of death than females (Figure 3, Supplementary Table S1). This risk was statistically significantly higher for AYA males than older adult males only in colorectal cancer (aHR 1.21 [95%CI 1.10–1.32] versus 1.08 [95%CI 1.06–1.10], respectively; p_{int}=0.045).

Socioeconomic status—Compared to high SES, both AYAs and older adults of low SES exhibited a higher risk of death across cancer sites; these risks were statistically significant for carcinomas of the uterus, breast, colorectal, stomach, lung and melanoma (Figure 4, Supplemental Table S1). In bone cancer, the excess risk for low SES was statistically significant only for AYAs.

DISCUSSION

Although recent analyses have documented impressive survival improvements among most AYAs, those with poor-prognosis metastatic cancers remain at the highest risk of death [15, 17, 18, 22]. These patients pose a formidable challenge to further advancing survival for AYAs. It is postulated that AYAs, compared to younger and older patients, are generally more prone to developing poor-prognosis cancers due to a propensity for adverse tumor biology and clinically aggressive disease, as well as delayed diagnosis, limited access to care, and inadequate treatment [3, 45, 46]. Contrary to that hypothesis, we found in this study, using a novel "landscape" approach, that AYAs with these twelve poor-prognosis metastatic cancers have superior survival than older adults in all but one, where it was equivalent. These findings, along with several observed survival disparities in sociodemographic subgroups, offer insights into the AYA as a cancer host and carry implications for AYA cancer care, prevention, and research by highlighting multiple ongoing disparities that preclude equitable survival improvements.

Our finding that AYAs experience better cause-specific survival than older adults across multiple cancer sites has at least two potential explanations. First, AYAs might receive and tolerate more intensive treatment regimens than older adults, who may be given reduced intensity regimens to improve tolerance [37]. Second, for cancer types where the survival advantage for AYAs was most striking, particularly rhabdomyosarcoma [47] and ovarian [48], AYAs could have more favorable tumor biology. Future systematic tumor-specific studies could explore this hypothesis utilizing histological data available through SEER. Regardless, it seems clear that AYAs, compared with older adults, are not uniformly disadvantaged in ways that translate into poorer survival across multiple cancers.

Our analysis demonstrated notable sociodemographic disparities in several domains. First, patients of low SES were at increased risk of death in virtually every cancer site regardless of age. This raises questions as to how access to care, insurance, and poverty may determine survival outcomes, regardless of biological predictors. Poverty, in particular, is increasingly recognized as a key predictor of survival outcomes, especially in childhood cancers [49, 50]. Second, while racial/ethnic minorities are at higher risk of death in all age groups for most cancer sites, notable age-related disparities were seen in NHB AYAs with metastatic kidney and uterine cancer and NHAPI AYAs with ovarian cancer. Third, in metastatic lung cancer, minorities of both age groups, especially Hispanics, were unexpectedly less likely to die compared to NHWs. Finally, while males in most cancer sites were at higher risk of death, male AYAs with metastatic colorectal cancer were disproportionately more likely to die of their disease than older males. These observations require further investigation into mechanisms through which sociodemographic factors impact survival.

In this study, metastatic kidney cancer was the only site where AYAs did not have better survival than older adults. This may be partially explained by NHB AYAs, where significantly higher mortality was noted, possibly reflecting distinct biological factors associated with aggressive disease. Additionally, the higher incidence in AYAs of translocation-positive renal cell carcinoma, an aggressive subtype associated with metastatic disease, may partially account for age-related survival disparities [51, 52]. Future studies

investigating biological subtypes of kidney cancer as well as potential treatment disparities are warranted, particularly in light of the rising incidence of kidney cancer in AYAs [53].

An increased risk of death for NHB AYAs with uterine cancer was also noted. Although patient numbers were relatively small, their risk of mortality was the highest of all cancer sites we examined. Among women of all ages, studies of uterine cancer comparing NHBs with NHWs show increased mortality, later stage disease and poor-prognostic histologic types [54]. Additionally, in light of studies linking low SES and insurance status to higher mortality, our finding of increased mortality risk in low SES women with metastatic uterine cancer prompts concerns about their access to optimal cancer care [55, 56]. Histology and SES could play critical roles in the survival disparity of these NHB women, particularly among AYAs.

As a whole, AYAs with metastatic ovarian carcinoma have significantly better outcomes than older women. However, we found NHAPI AYAs have statistically significantly poorer survival, raising questions about potentially unique risk factors in that subset. NHAPI women of all ages are at increased risk of ovarian clear cell carcinoma, a rare histological subtype of ovarian cancer known to have particularly poor outcomes in advanced stages [57, 58]. To our knowledge, survival in AYAs with metastatic ovarian carcinoma has not been evaluated for biological, environmental, or treatment-related associations that may predispose NHAPI AYAs to worse survival.

Although the prognosis with metastatic lung cancer is dismal at any age, we unexpectedly found AYAs have better survival than their older counterparts. Surprisingly and contrary to most of the other cancers, racial/ethnic minorities were significantly less likely to die, particularly Hispanic AYAs. Recent literature examining the distinctive epidemiological and clinical characteristics of AYAs with lung cancer documents a predominance of non-smokers with adenocarcinoma histology and more advanced stages at diagnosis [59]. Further investigation exploring the histological and molecular profiles of racial/ethnic subgroups of AYAs and older adults may elucidate biological mechanisms underlying superior AYA outcomes that could be translated to older patients.

In light of recent studies showing a disproportionate rise in the incidence of metastatic colon cancer among AYAs and middle-aged adults coupled with high rates of metastatic disease in NHBs overall [36], the increased risk of death in male AYAs raises important questions about potential biological or treatment-related disparities in this subgroup. Studies examining the impact of sex on survival in young-onset metastatic colorectal cancer have suggested premenopausal women may have potential hormone-mediated protection [60]. Although NHB men of all ages are at higher risk of death, this risk is similar between AYAs and older adults, potentially indicating underlying aggressive tumor biology and/or reduced access to effective treatment [61].

This study has both strengths and limitations. A key strength is the use of SEER registry data, a robust and reliable resource [62] offering large sample sizes, that permits identification of broad trends across a variety of cancers, including rare tumors such as rhabdomyosarcoma, a biologically distinct form of sarcoma prone to present with metastases

in AYAs [36]. Although evaluation of sociodemographic trends for rhabdomyosarcoma was limited due to relatively few patients even in this national sample, this study highlights the need for large-scale collaborations for investigating age-related risk factors in such rare tumors. Additionally, the use of a "landscape" approach allows survival patterns to emerge across cancer types that speak to AYAs as a group, which may be masked when focusing on single cancers. Potential limitations are those inherent to registry-based research, including possible misclassification of race/ethnicity provided by the reporting site and use of area-based SES rather than individual level. Additionally, the SEER registry currently does not report molecular subtypes of cancer or detailed patient-level treatment and clinical data, which limits study of biologically focused characteristics [63] and potential therapy-related disparities, including treatment intensity, that could differ by age. Furthermore, an in-depth histological evaluation was not performed as this was outside the scope of the "landscape" analysis of this manuscript. Future studies evaluating histology in a tumor-specific manner are needed.

What implications follow from these results? First, although these results do not support the narrative that AYAs generally have poorer outcomes than older adults, the fact that their 5-year survival remains 25% or worse for most of these cancers is sobering. With up to two thirds of these AYAs presenting with metastatic disease [36], our results suggest that for AYAs in aggregate, further meaningful survival gains are unlikely unless and until survival can be improved in this difficult subset of patients. Given the complex challenges, this might be achievable only through strategic initiatives targeting metastatic disease and its biological, sociological, and environmental determinants, as part of the continuing "war on cancer" [64]. As a practical first step, improved accrual of AYAs to existing adult-focused clinical trials for these poor-prognosis metastatic cancers would help ensure that potential benefits of novel therapies reach AYAs [6, 65]. Second, low SES clearly confers a higher mortality risk across all age groups for most poor-prognosis metastatic cancers, raising concerns about treatment availability and access to care. Efforts to define underlying mechanisms for this effect, including epigenetic modifications and biological pathways related to toxic stress, have potential for improving outcomes in both AYAs and older adults [66, 67]. Third, the marked racial/ethnic disparities found in most cancers, with notably higher risks in certain AYA subgroups, present opportunities for comprehensive genomic ancestry analysis relevant to the development of metastatic disease and/or potential therapeutic targets. Fourth, certain poor-prognosis cancers, such as stomach cancer, disproportionately burden minority AYAs [36] and show dismal survival across all age groups and sociodemographic characteristics. This suggests there may be value in targeted research efforts regarding early detection strategies, cancer prevention, and novel therapeutic options for these cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

REFERENCES

1. Adolescent and Young Adult Progress Review Group. Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer. Bethesdam MD: US Department of Health and Human Services, National Institutes of Health, Nattional Cancer Institute, LIVESTRONG Young Adult Alliance; 2006.

2. Barr RD, Ferrari A, Ries L et al. Cancer in Adolescents and Young Adults. JAMA Pediatrics 2016; 170: 495. [PubMed: 26999630]

3. Tricoli J, Bleyer, Archie. Adolescent and Young Adult Cancer Biology. Cancer J. 2018; 24: 267–274. [PubMed: 30480571]

4. Bukowinski AJ, Burns KC, Parsons K et al. Toxicity of Cancer Therapy in Adolescents and Young Adults (AYAs). Seminars in Oncology Nursing 2015; 31: 216–226. [PubMed: 26210200]

5. Albritton KH, Wiggins CH, Nelson HE, Weeks JC. Site of Oncologic Specialty Care for Older Adolescents in Utah. 2007; 25: 4616–4621.

6. Freyer DR, Seibel NL. The Clinical Trials Gap for Adolescents and Young Adults with Cancer: Recent Progress and Conceptual Framework for Continued Research. Current Pediatrics Reports 2015; 3: 137–145. [PubMed: 30613438]

7. Salsman JM, Bingen K, Barr RD, Freyer DR. Understanding, measuring, and addressing the financial impact of cancer on adolescents and young adults. Pediatric Blood & Cancer 2019; 66: e27660. [PubMed: 30756484]

8. Zebrack B, Isaacson S. Psychosocial Care of Adolescent and Young Adult Patients With Cancer and Survivors. Journal of Clinical Oncology 2012; 30: 1221–1226. [PubMed: 22412147]

9. Tricoli JV, Seibel NL, Blair DG et al. Unique Characteristics of Adolescent and Young Adult Acute Lymphoblastic Leukemia, Breast Cancer, and Colon Cancer. JNCI: Journal of the National Cancer Institute 2011; 103: 628–635. [PubMed: 21436065]

10. Bleyer A, Barr R, Hayes-Lattin B et al. The distinctive biology of cancer in adolescents and young adults. Nature Reviews Cancer 2008; 8: 288–298. [PubMed: 18354417]

11. Freyer DR, Felgenhauer J, Perentesis J. Children's Oncology Group's 2013 blueprint for research: Adolescent and young adult oncology. 2013; 60: 1055–1058.

12. Orellana-Noia VM, Douvas MG. Recent Developments in Adolescent and Young Adult (AYA) Acute Lymphoblastic Leukemia. Current Hematologic Malignancy Reports 2018; 13: 100–108. [PubMed: 29442287]

13. Shaw PH, Reed DR, Yeager N et al. Adolescent and Young Adult (AYA) Oncology in the United States. J Pediatr Hematol Oncol 2015; 37: 161–169. [PubMed: 25757020]

14. Smith AW, Seibel NL, Lewis DR et al. Next steps for adolescent and young adult oncology workshop: An update on progress and recommendations for the future. 2016; n/a-n/a.

15. Moke DJ, Tsai K, Hamilton AS et al. Emerging Cancer Survival Trends, Disparities, and Priorities in Adolescents and Young Adults: A California Cancer Registry-Based Study. JNCI Cancer Spectr 2019; 3: pkz031. [PubMed: 31276099]

16. Liu L, Moke DJ, Tsai K-Y et al. A Reappraisal of Sex-Specific Cancer Survival Trends Among Adolescents and Young Adults in the United States. JNCI: Journal of the National Cancer Institute 2019; 111: 509–518. [PubMed: 30321398]

17. Lewis DR, Seibel NL, Smith AW, Stedman MR. Adolescent and Young Adult Cancer Survival. JNCI Monographs 2014; 2014: 228–235.

18. Keegan THM, Ries LAG, Barr RD et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. Cancer 2016; 122: 1009–1016. [PubMed: 26848927]

19. Miller KD, Fidler-Benaoudia M, Keegan TH et al. Cancer statistics for adolescents and young adults, 2020. CA: A Cancer Journal for Clinicians 2020.

20. Howlader NNA, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

21. Surveillance, Epidemiology, and End Results (SEER) Program: Cancer Stat Facts: Cancer Among Adolescents and Young Adults (AYAs) (Ages 15–39).

22. Liu LHA, Moke D, Tsai KY, Wojcik KY, Cockburn M, Deapen D (eds.). Cancer in Los Angeles County: Survival among Adolescents and Young Adults 1988–2014. Los Angeles Cancer Surveillance Program 2017; University of Southern California.

23. Albano JD, Ward E, Jemal A et al. Cancer Mortality in the United States by Education Level and Race. JNCI: Journal of the National Cancer Institute 2007; 99: 1384–1394. [PubMed: 17848670]

24. Kish JK, Yu M, Percy-Laurry A, Altekruse SF. Racial and Ethnic Disparities in Cancer Survival by Neighborhood Socioeconomic Status in Surveillance, Epidemiology, and End Results (SEER) Registries. 2014; 2014: 236–243.

25. Murphy CC, Lupo PJ, Roth ME et al. Disparities in cancer survival among adolescents and young adults: a population-based study of 88,000 patients. JNCI: Journal of the National Cancer Institute 2021.

26. Bhatnagar B, Kohlschmidt J, Mrózek K et al. Poor Survival and Differential Impact of Genetic Features of Black Patients with Acute Myeloid Leukemia. Cancer Discovery 2021; 11: 626–637. [PubMed: 33277314]

27. Tao L, Gomez SL, Keegan THM et al. Breast Cancer Mortality in African-American and Non-Hispanic White Women by Molecular Subtype and Stage at Diagnosis: A Population-Based Study. Cancer Epidemiology Biomarkers & Prevention 2015; 24: 1039–1045.

28. Sineshaw HM, Gaudet M, Ward EM et al. Association of race/ethnicity, socioeconomic status, and breast cancer subtypes in the National Cancer Data Base (2010–2011). 2014; 145: 753–763.

29. Keegan THM, Press DJ, Tao L et al. Impact of breast cancer subtypes on 3-year survival among adolescent and young adult women. Breast Cancer Research 2013; 15: R95. [PubMed: 24131591]

30. Press DJ, Miller ME, Liederbach E et al. De novo metastasis in breast cancer: occurrence and overall survival stratified by molecular subtype. Clinical & Experimental Metastasis 2017; 34: 457–465. [PubMed: 29288366]

31. Murphy CC, Wallace K, Sandler RS, Baron JA. Racial Disparities in Incidence of Young-Onset Colorectal Cancer and Patient Survival. Gastroenterology 2019; 156: 958–965. [PubMed: 30521807]

32. Stewart SL, Wike JM, Kato I et al. A population-based study of colorectal cancer histology in the United States, 1998–2001. Cancer 2006; 107: 1128–1141. [PubMed: 16802325]

33. Holowatyj AN, Lewis MA, Pannier ST et al. Clinicopathologic and Racial/Ethnic Differences of Colorectal Cancer Among Adolescents and Young Adults. Clinical and Translational Gastroenterology 2019; 1.

34. Wang R, Wang MJ, Ping J. Clinicopathological Features and Survival Outcomes of Colorectal Cancer in Young Versus Elderly: A Population-Based Cohort Study of SEER 9 Registries Data (1988–2011). Medicine (Baltimore) 2015; 94: e1402. [PubMed: 26334895]

35. O'Connell JB, Maggard MA, Livingston EH, Yo CK. Colorectal cancer in the young. The American Journal of Surgery 2004; 187: 343–348. [PubMed: 15006562]

36. Sheth Bhutada J, Hwang A, Liu L et al. Poor-Prognosis Metastatic Cancers in Adolescents and Young Adults: Incidence Patterns, Trends, and Disparities. JNCI Cancer Spectrum 2021.

37. Kim J, Hurria A. Determining Chemotherapy Tolerance in Older Patients With Cancer. Journal of the National Comprehensive Cancer Network 2013; 11: 1494–1502. [PubMed: 24335684]

38. SEER Summary Staging Definition.

39. Skapek SX, Ferrari A, Gupta AA et al. Rhabdomyosarcoma. Nature Reviews Disease Primers 2019; 5.

40. Shiels MS, Cole SR, Wegner S et al. Effect of HAART on Incident Cancer and Noncancer AIDS Events Among Male HIV Seroconverters. 2008; 48: 485–490.

41. Barr RD, Holowaty EJ, Birch JM. Classification schemes for tumors diagnosed in adolescents and young adults. 2006; 106: 1425–1430.

42. Liu L, Deapen D, Bernstein L. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). Cancer Causes and Control 1998; 9: 369–380. [PubMed: 9794168]

43. Yost K, Perkins C, Cohen R et al. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. Cancer Causes and Control 2001; 12: 703–711. [PubMed: 11562110]

44. SEER*Stat. Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version <8.3>.

45. Bleyer A Latest Estimates of Survival Rates of the 24 Most Common Cancers in Adolescent and Young Adult Americans. Journal of Adolescent and Young Adult Oncology 2011; 1: 37–42. [PubMed: 26812567]

46. Fardell JE, Patterson P, Wakefield CE et al. A Narrative Review of Models of Care for Adolescents and Young Adults with Cancer: Barriers and Recommendations. Journal of Adolescent and Young Adult Oncology 2018; 7: 148–152. [PubMed: 29298105]

47. Leiner J, Le Loarer F. The current landscape of rhabdomyosarcomas: an update. Virchows Archiv 2020; 476: 97–108. [PubMed: 31696361]

48. Lockley M, Stoneham SJ, Olson TA. Ovarian cancer in adolescents and young adults. Pediatric Blood & Cancer 2019; 66: e27512. [PubMed: 30350916]

49. Wolfson JA. Poverty and Survival in Childhood Cancer: A Framework to Move Toward Systemic Change. JNCI: Journal of the National Cancer Institute 2020.

50. Bona K, Li Y, Winestone LE et al. Poverty and Targeted Immunotherapy: Survival in Children's Oncology Group Clinical Trials for High-Risk Neuroblastoma. JNCI: Journal of the National Cancer Institute 2020.

51. Ellis CL, Eble JN, Subhawong AP et al. Clinical heterogeneity of Xp11 translocation renal cell carcinoma: impact of fusion subtype, age, and stage. Modern Pathology 2014; 27: 875–886. [PubMed: 24309327]

52. Choo MS, Jeong CW, Song C et al. Clinicopathologic Characteristics and Prognosis of Xp11.2 Translocation Renal Cell Carcinoma: Multicenter, Propensity Score Matching Analysis. Clin Genitourin Cancer 2017; 15: e819–e825. [PubMed: 28549862]

53. Scott AR, Stoltzfus KC, Tchelebi LT et al. Trends in Cancer Incidence in US Adolescents and Young Adults, 1973–2015. JAMA Netw Open 2020; 3: e2027738. [PubMed: 33258907]

54. Long B, Liu FW, Bristow RE. Disparities in uterine cancer epidemiology, treatment, and survival among African Americans in the United States. Gynecologic Oncology 2013; 130: 652–659. [PubMed: 23707671]

55. Fedewa SA, Lerro C, Chase D, Ward EM. Insurance status and racial differences in uterine cancer survival: A study of patients in the National Cancer Database. Gynecologic Oncology 2011; 122: 63–68. [PubMed: 21463888]

56. Madison T, Schottenfeld D, James SA et al. Endometrial Cancer: Socioeconomic Status and Racial/Ethnic Differences in Stage at Diagnosis, Treatment, and Survival. American Journal of Public Health 2004; 94: 2104–2111. [PubMed: 15569961]

57. Takano M, Kikuchi Y, Yaegashi N et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. British Journal of Cancer 2006; 94: 1369–1374. [PubMed: 16641903]

58. Korenaga T-R, Ward KK, Saenz C et al. The elevated risk of ovarian clear cell carcinoma among Asian Pacific Islander women in the United States is not affected by birthplace. Gynecologic Oncology 2020; 157: 62–66. [PubMed: 32008796]

59. Viñal D, Martínez D, Higuera O, De Castro J. Genomic profiling in non-small-cell lung cancer in young patients. A systematic review. ESMO Open 2021; 6: 100045. [PubMed: 33516149]

60. Hendifar A, Yang D, Lenz F et al. Gender Disparities in Metastatic Colorectal Cancer Survival. Clinical Cancer Research 2009; 15: 6391–6397. [PubMed: 19789331]

61. Augustus GJ, Ellis NA. Colorectal Cancer Disparity in African Americans. The American Journal of Pathology 2018; 188: 291–303. [PubMed: 29128568]

62. SEER QI Process.

63. Pollock BH. What's Missing in the Assessment of Adolescent and Young Adult (AYA) Cancer Outcomes? JNCI: Journal of the National Cancer Institute 2020.

64. National Cancer Institute

65. Weiss AR, Hayes-Lattin B, Kutny MA et al. Inclusion of Adolescents and Young Adults in Cancer Clinical Trials. Seminars in Oncology Nursing 2015; 31: 197–205. [PubMed: 26210198]

66. Jiang S, Postovit L, Cattaneo A et al. Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma. Frontiers in Psychiatry 2019; 10.

67. Deguzman PB, Schminkey DL. Influencing Genomic Change and Cancer Disparities through Neighborhood Chronic Toxic Stress Exposure: A Research Framework. Public Health Nursing 2016; 33: 547–557. [PubMed: 27592689]
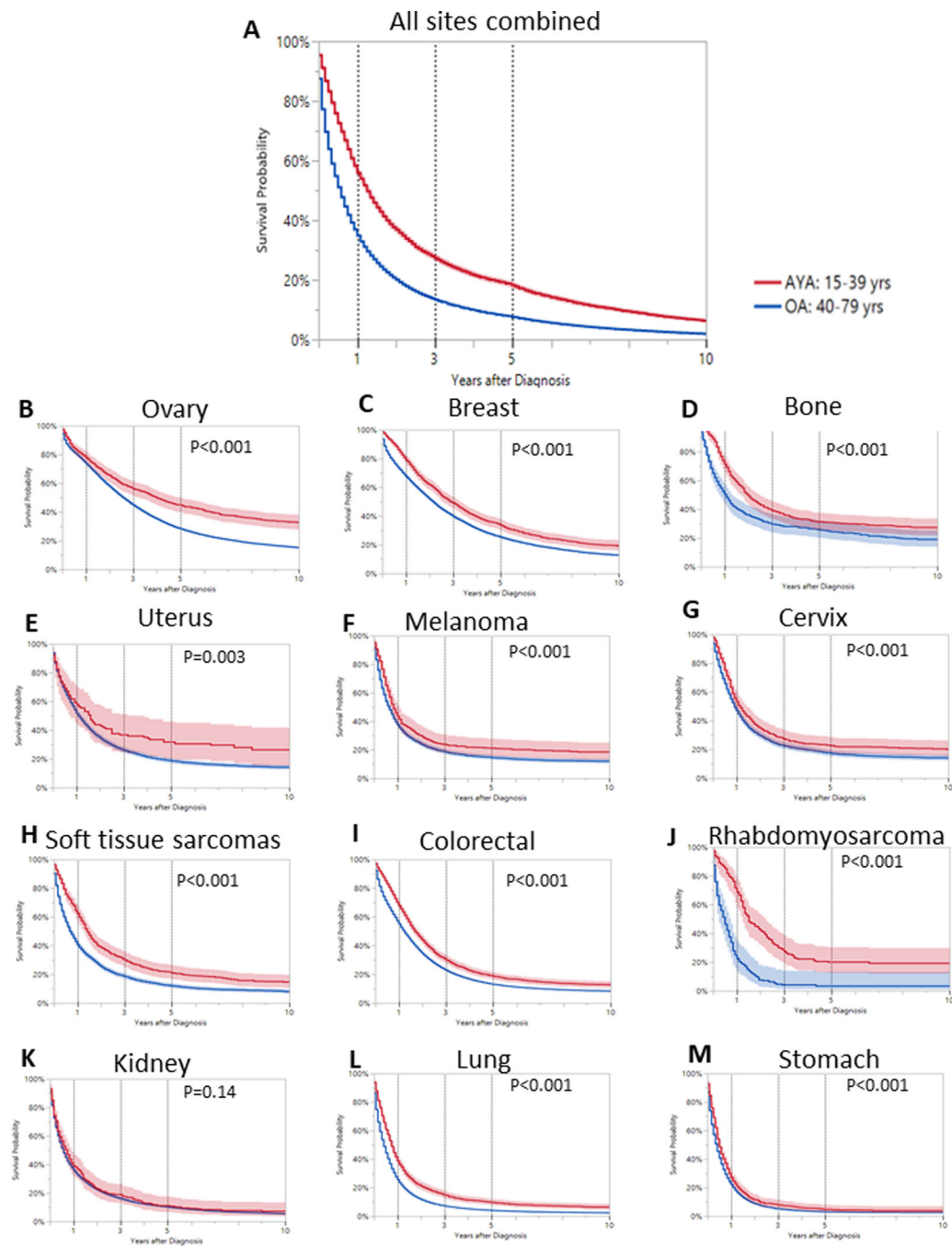
Figure 1:
Kaplan-Meier survival curves for adolescents and young adults (AYAs) and older adults, Surveillance, Epidemiology, and End Results Program (2000–2016). Log-rank two-sided p-values are reported. (A) all sites combined; (B) ovary; (C) breast; (D) bone; (E) uterus; (F) melanoma; (G) cervix; (H) soft tissue sarcomas; (I) colorectal; (J) rhabdomyosarcoma; (K) kidney; (L) lung; (M) stomach
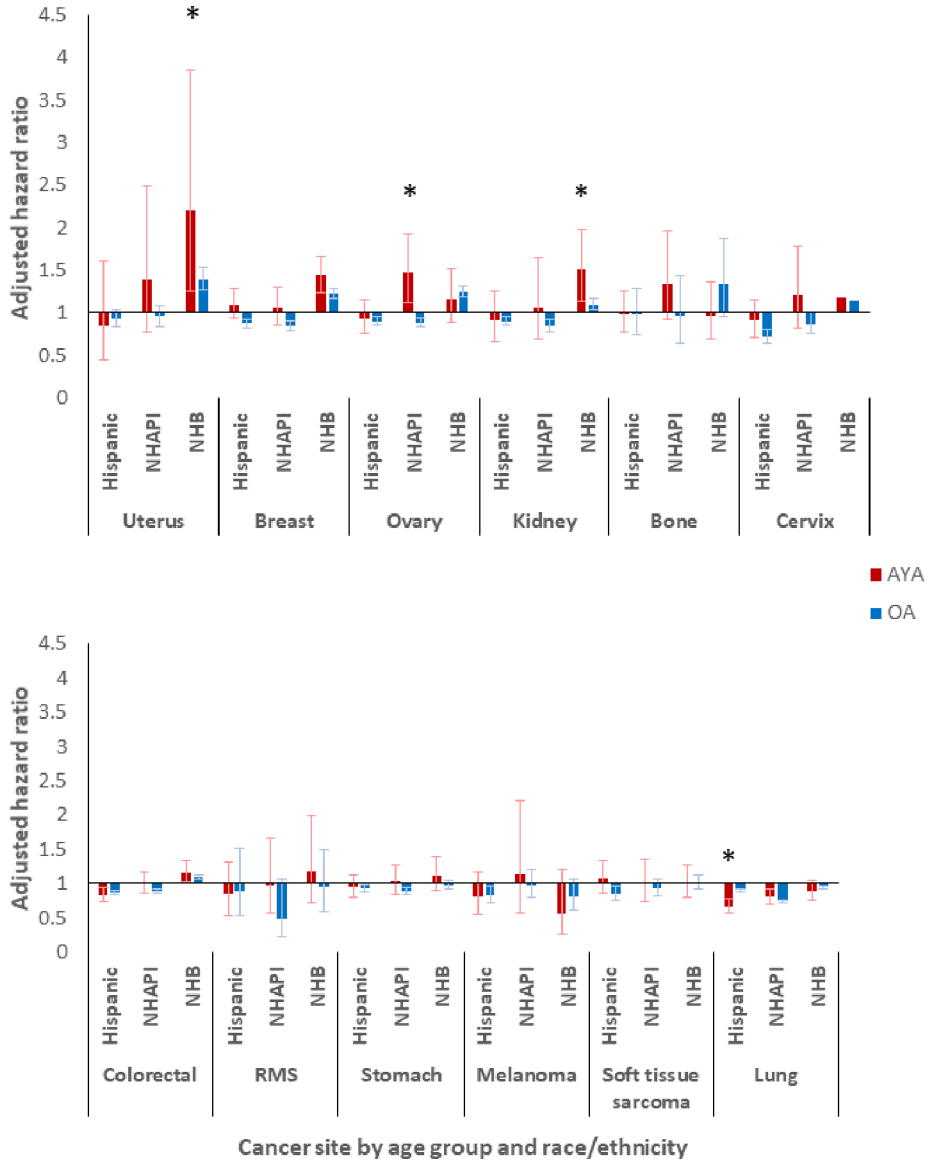
Figure 2:
Adjusted hazard ratios (adjusted for age, sex and socioeconomic status) by age group and race/ethnicity: Surveillance, Epidemiology, and End Results Program (2000–2016). Reference group is non-Hispanic Whites. Error bars indicate 95% confidence intervals. NHB = non-Hispanic Black; NHAPI = non-Hispanic Asian/Pacific Islander; RMS = rhabdomyosarcoma; AYA = adolescent and young adult, OA = older adults.

Figure 3:
Adjusted hazard ratios (adjusted for age, race/ethnicity and SES) by age group and sex: Surveillance, Epidemiology, and End Results Program (2000–2016). Reference group is females. Error bars indicate 95% confidence intervals. NHB = non-Hispanic Black; NHAPI = non-Hispanic Asian/Pacific Islander; RMS = rhabdomyosarcoma; AYA = adolescent and young adult, OA = older adults.
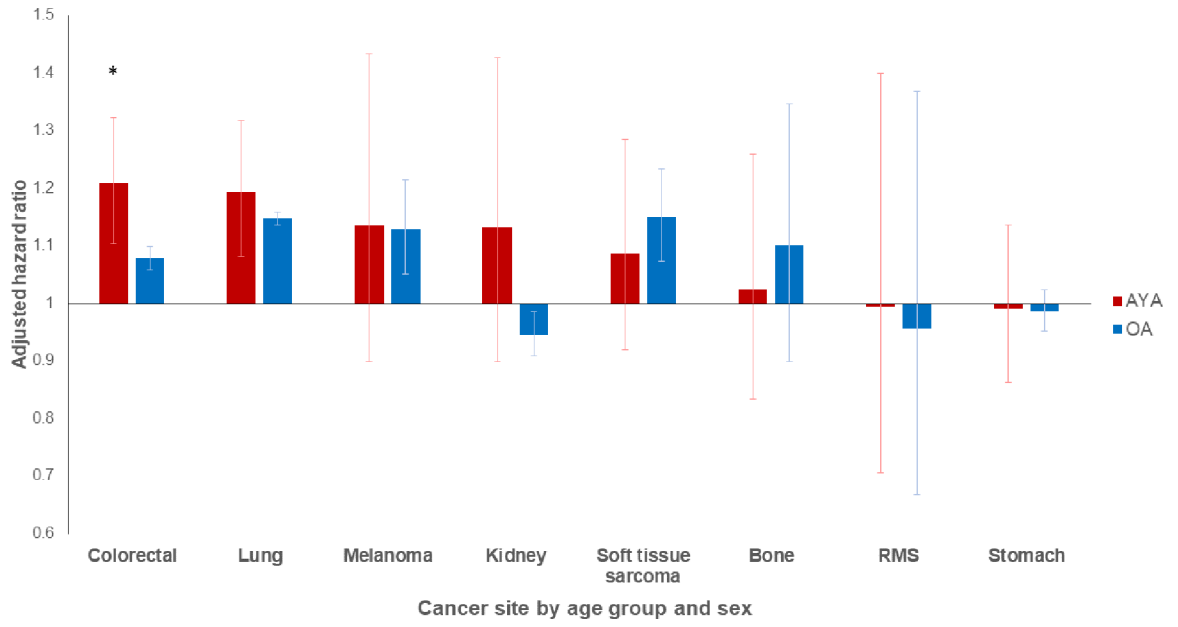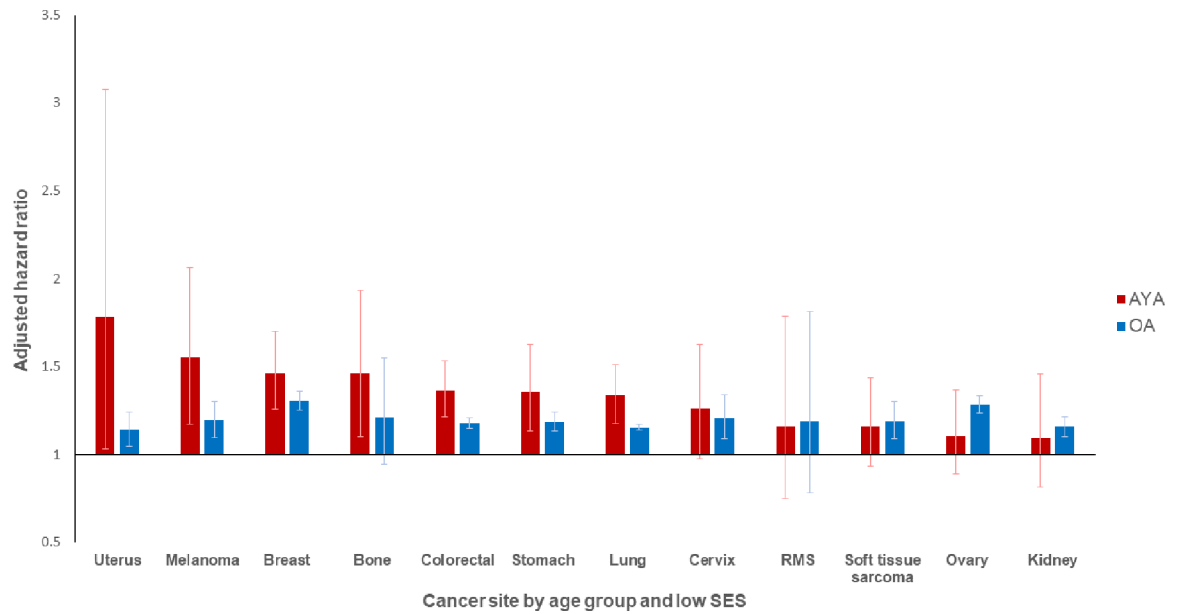
Figure 4:
Adjusted hazard ratios (adjusted for age, race/ethnicity and sex) by age group for lowest socioeconomic status (SES) tertile: Surveillance, Epidemiology, and End Results Program (2000–2016). Reference group is highest SES tertiles. Error bars indicate 95% confidence intervals. RMS = rhabdomyosarcoma; AYA = adolescent and young adult, OA = older adults.

Table 1:

Adjusted hazard ratios for death by site among AYAs compared to older adults: Surveillance, Epidemiology, and End Results Program (2000–2016)

Cancer Site	Age Group	N	Crude HR (95% CI)	aHR (95% CI)
All Sites*	OA	345,681	---	---
	AYA	11,518	0.61 (0.60 to 0.62)	0.75 (0.73 to 0.77)
Kidney	OA	13,332	---	---
	AYA	392	0.92 (0.83 to 1.03)	0.91 (0.82 to 1.02)
Stomach*	OA	15,203	---	---
	AYA	1,094	0.83 (0.77 to 0.88)	0.83 (0.78 to 0.90)
Cervix*	OA	3,462	---	---
	AYA	620	0.81 (0.73 to 0.89)	0.80 (0.72 to 0.89)
Melanoma*	OA	4,496	---	---
	AYA	469	0.79 (0.71 to 0.88)	0.79 (0.71 to 0.89)
Colorectal*	OA	53,218	---	---
	AYA	2,520	0.78 (0.74 to 0.81)	0.79 (0.76 to 0.83)
Breast*	OA	20,220	---	---
	AYA	1641	0.77 (0.73 to 0.82)	0.77 (0.73 to 0.82)
Uterus*	OA	24,949	---	---
	AYA	141	0.74 (0.60 to 0.90)	0.75 (0.60 to 0.92)
Lung*	OA	201,069	---	---
	AYA	1,977	0.70 (0.67 to 0.73)	0.72 (0.68 to 0.76)
Soft tissue sarcoma*	OA	4,050	---	---
	AYA	795	0.67 (0.61 to 0.73)	0.65 (0.60 to 0.72)
Bone*	OA	569	---	---
	AYA	646	0.68 (0.59 to 0.77)	0.64 (0.56 to 0.74)
Ovary*	OA	24,949	---	---
	AYA	1004	0.64 (0.59 to 0.70)	0.63 (0.58 to 0.68)
Rhabdomyosarcoma*	OA	163	---	---
	AYA	219	0.35 (0.28 to 0.44)	0.33 (0.26 to 0.42)

*
Indicates statistically significant difference in aHR for AYAs compared to OAs (p<0.05)

Adjusted hazard ratio involves adjustment for cancer site (for "all sites" analysis) and all other sociodemographic factors (socioeconomic status [SES], race/ethnicity, sex). Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; OA = older adult.

Table 2.

5-year cause-specific survival by cancer site for AYAs and older adults: Surveillance, Epidemiology, and End Results Program (2000–2016)

Cancer Site	AYA		OA	
	N	Survival Estimate % (95% CI)	N	Survival Estimate % (95% CI)
All sites combined	11,389	21.4 (20.7 to 22.2)	343,601	9.3 (9.2 to 9.4)
Ovarian	996	44.6 (41.4 to 47.8)	24,852	28.4 (27.9 to 29.0)
Breast	1,631	34.0 (31.6 to 36.3)	20,130	25.4 (24.8 to 26.0)
Uterine	139	31.6 (23.7 to 39.8)	4,909	18.6 (17.5 to 19.8)
Bone	645	31.0 (27.4 to 34.7)	565	25.4 (21.8 to 29.2)
Cervical	621	22.3 (19.0 to 25.7)	3,423	17.1 (15.8 to 18.4)
Soft tissue sarcomas	777	20.8 (17.9 to 23.8)	4,027	12.0 (10.9 to 13.0)
Melanoma	464	20.7 (17.1 to 24.6)	4,468	14.7 (13.6 to 15.8)
Colorectal	2,500	18.6 (17.1 to 20.2)	52,891	13.0 (12.7 to 13.3)
RMS	215	19.4 (14.3 to 25.2)	163	3.5 (1.3 to 7.5)
Kidney	391	10.7 (7.8 to 14.2)	13,301	10.0 (9.5 to 10.5)
Lung	1,948	9.5 (8.2 to 10.9)	199,841	3.9 (3.8 to 4.0)
Stomach	1,062	4.3 (3.1 to 5.9)	15,031	2.9 (2.6 to 3.2)

Abbreviations: CI = confidence interval; AYA = adolescent and young adult; OA = older adult; RMS = rhabdomyosarcoma