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Survival disparities in non-Hispanic Black and White cervical cancer patients vary by histology and are largely explained by modifiable factors

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Presentations

Preliminary results of this study were presented in abstract form and a poster presentation at the SCO Winter Meeting in Jan. 17–19,2019, at Resort at Squaw Creek, Lake Tahoe, CA, USA. The current results were presented in abstract form and a poster presentation on February 3, 2023, at the SCO Winter Meeting in Whistler, British Columbia, Canada.

CRediT authorship contribution statement

Calen W. Kucera: Investigation, Writing – original draft. Writing – review & editing. **Nicole P. Chappell:** Conceptualization, Writing – original draft. Writing – review & editing. **Chunqiao Tian:** Conceptualization, Data curation. Formal analysis. Investigation, Visualization, Writing – original draft. Writing – review & editing. **Michael T. Richardson:** Investigation, Writing – review & editing. **Christopher M. Tarney:** Investigation, Supervision, Writing – review & editing. **Chad A. Hamilton:** Investigation, Writing – review & editing. Funding acquisition. **John K. Chan:** Investigation, Writing – review & editing. **Daniel S. Kapp:** Investigation, Writing – review & editing. **Charles A. Leath:** Investigation, Writing – review & editing. **Yovanni Casablanca:** Funding acquisition. Resources, Supervision, Writing – original draft. Writing – review & editing. **Christine Rojas:** Investigation, Writing – original draft. Writing – review & editing. **Collin A. Sitler:** Investigation, Writing-review & editing. **Lari Wenzel:** Investigation, Writing – review & editing. **Ann Klopp:** Investigation, Writing – review & editing. **Nathaniel L. Jones:** Investigation, Writing – review & editing. **Rodney P. Rocconi:** Investigation, Writing – review & editing. **John H. Farley:** Investigation, Writing – review & editing. **Timothy D. O'Connor:** Investigation, Writing – review & editing. **Craig D. Shriver:** Funding acquisition. Investigation, Writing – review & editing. **Nicholas W. Bateman:** Investigation, Writing – review & editing. **Thomas P. Conrads:** Investigation, Writing – review & editing. **Neil T. Phippen:** Funding acquisition. Investigation, Resources, Supervision, Writing – review & editing. **G. Larry Maxwell:** Funding acquisition. Investigation, Supervision, Writing – review & editing. **Kathleen M. Darcy:** Conceptualization, Investigation, Project administration. Resources, Supervision, Writing – original draft. Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.02.005.

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Abstract

Purpose.—We investigated racial disparities in survival by histology in cervical cancer and examined the factors contributing to these disparities.

Methods.—Non-Hispanic Black and non-Hispanic White (hereafter known as Black and White) patients with stage I-IV cervical carcinoma diagnosed between 2004 and 2017 in the National Cancer Database were studied. Survival differences were compared using Cox modeling to

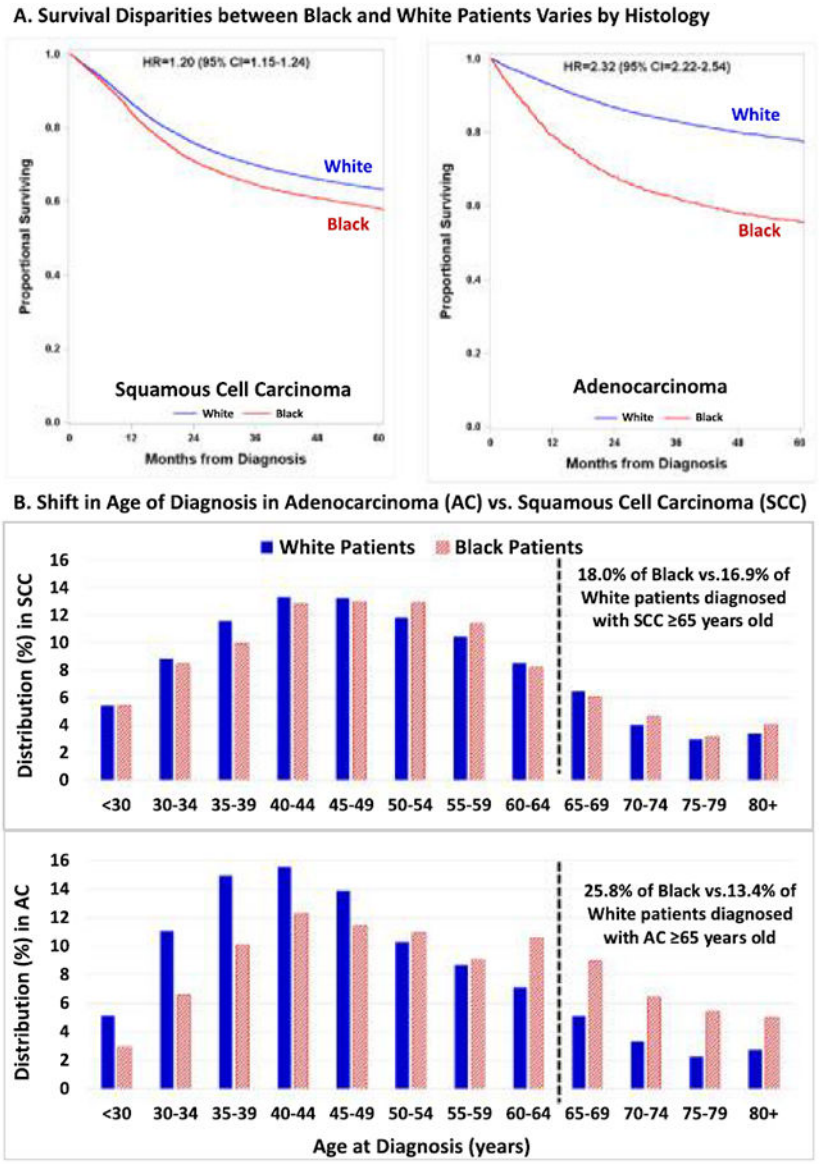
estimate hazard ratio (HR) or adjusted HR (AHR) and 95% confidence interval (Cl). The contribution of demographic, socioeconomic and clinical factors to the Black vs White differences in survival was estimated after applying propensity score weighting in patients with squamous cell carcinoma (SCC) or adenocarcinoma (AC).

Results.—This study included 10,111 Black and 43,252 White patients with cervical cancer. Black patients had worse survival than White cervical cancer patients (HR = 1.40, 95% CI = 135–1.45). Survival disparities between Black and White patients varied significantly by histology (HR = 1.20, 95% CI = 1.15–1.24 for SCC; HR = 232, 95% CI = 2.12–2.54 for AC, interaction $p < 0.0001$). After balancing the selected demographic, socioeconomic and clinical factors, survival in Black vs. White patients was no longer different in those with SCC (AHR = 1.01, 95% CI 0.97–1.06) or AC (AHR = 1.09, 95% CI = 0.96–1.24). In SCC, the largest contributors to survival disparities were neighborhood income and insurance. In AC, age was the most significant contributor followed by neighborhood income, insurance, and stage. Diagnosis of AC (but not SCC) at ≥65 years old was more common in Black vs. White patients (26% vs. 13%, respectively).

Conclusions.—Histology matters in survival disparities and diagnosis at ≥65 years old between Black and White cervical cancer patients. These disparities were largely explained by modifiable factors.

Graphical Abstract

Survival disparities between Black and White patients with squamous cell carcinoma of the cervix or adenocarcinoma of the cervix with inserts displaying hazard ratio (HR) and 95% confidence interval (Q) for risk of death for Black vs. White patients with cervical squamous cell carcinoma or adenocarcinoma, respectively (A). Shift in age at diagnosis in Black vs. White patients with squamous cell carcinoma (SCC) of the cervix or adenocarcinoma (AC) of the cervix (B).



Keywords

Cervical cancer; Racial disparities; Propensity score analysis; Adenocarcinoma; Squamous cell carcinoma; NCDB

1. Introduction

In the United States (U.S.), 13,820 new cervical cancer cases and 4360 deaths are anticipated in 2024 [1]. This disease disproportionately impacts Black and Hispanic patients and those with Medicaid or no insurance emphasizing the need for intentional strategies to mitigate inequities [1-11]. Improvements in prevention, screening, early detection and treatment of cervical cancer have reduced the burden of cervical cancer, but vaccine hesitancy delays the eradication of this disease, and disparities in incidence,

mortality and survival are associated with differences in ancestry, geography, neighborhood, socioeconomic status, insurance, lifestyle, exposures, social inequities, as well as stage and histology. [2-38]

Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two most common histologic subtypes of cervical cancer accounting for approximately 70% and 25% of all the cases, respectively [35]. AC can be challenging to diagnose with occult disease deep within the endocervical canal and is associated with a worse prognosis than SCC histology [5,13,15,16,21,22,26,34,35]. Reports by Castellsague et al. [34] and by Gien et al. [35] also indicate distinctions in HPV etiologic variants, genetic alterations and pathologic features between SCC and AC of the cervix. This study investigates racial disparities and prognostic factors in cervical cancer, whether racial differences in survival in cervical cancer vary by histology and ranks the factors contributing to the survival disparities in these patients.

2. Methods

2.1. Study population

This observational study utilized data from the National Cancer Database (NCDB) [39] and received an exempt determination under Protocol 14–1679 by the Western Copernicus Group (WCG) Institutional Review Board. Non-Hispanic Black and non-Hispanic White (hereafter known as Black and White) patients were required to have a single primary stage I-IV invasive cervical cancer diagnosis (International Classification of Diseases (ICD)-IO codes C530-C539) between 2004 and 2017. The primary clinical endpoint for this study was overall survival. Survival time was calculated from the date of diagnosis to date of death for an event or date of last contact for patients who were alive (censored). Black and White patients were selected using the self-reported race and Hispanic/Spanish ethnicity variables coded by the NCDB. The other covariates for this study included baseline factors, including age and year at diagnosis, patient health and socioeconomic variables (comorbidity score, neighborhood-derived income, and insurance status), tumor characteristics (stage, histologic subtype, and tumor grade), and first-line treatment (surgery, radiation, or chemotherapy). See the footnotes in Table 1 for additional details regarding the covariates. Patients with multiple malignancies, in situ tumors, other/unknown race, Hispanic ethnicity, missing survival data or unknown covariate data were excluded (eFig. 1).

2.2. Statistical analyses

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) in September 2022 in all cervical cancer patients and then separately in patients with SCC or AC, with patient follow-up data through December 2020. This study was reported following STROBE guidelines. Covariate differences between Black and White patients were evaluated using *t*-test for age at diagnosis or *Chi*-square test for categorical variables. Overall survival was estimated using Kaplan-Meier method and compared using log-rank test. Risk of death was evaluated using univariable and multivariable Cox proportional hazards modeling. An interaction test was performed to determine whether the hazard ratio (HR) for the risk of death in Black vs. White patients varied between SCC and AC histology. Inverse probability weighting using propensity score was applied to sequentially balance the covariates that

varied by race, and then estimate the contribution of each factor to the racial disparity in survival as referenced by Kucera et al. [40] A logistic regression model estimated the propensity score of a patient being Black conditional on the covariates. The quality of balance was examined using the standardized mean difference (SMD), with SMD <10% considered to be well-balanced. Adjusted HR (AHR) for the risk of death in Black vs. White patients was estimated from weighted Cox models in each of the sequentially balanced cohorts, with 95% confidence interval (Cl) calculated using a robust sandwich method. Total excess relative risk (ERR) of death in Black vs. White women was calculated by subtracting one from the unadjusted HR. The proportion of the total ERR explained by each factor was then derived based on the reduction in HR at each step in the sequential propensity score balancing procedure adding age at diagnosis during step 1, comorbidity score during step 2, neighborhood income during step 3, insurance status during step 4, stage during step 5, grade during step 6, and treatment during step 7. This sequence covariates at birth followed by modifiable factors like patient health, neighborhood income and insurance leading to the clinical diagnosis and then by first-line treatment

3. Results

3.1. Cervical cancer cohort

There were 53,363 women diagnosed with stage I-IV cervical cancer between 2004 and 2017 in the NCDB who met study eligibility criteria, including43,252 White and 10,111 Black patients (eFig. 1). Table 1 summarizes the characteristics for the study population. Overall, the mean age at diagnosis was 50.0 years old (standard deviation: 14.5, median: 48, interquartile range [IQR]: 39–60, range: 18–90 years old). Fifteen percent of patients had a comorbidity score ≥ 1,25% were from a low-income neighborhood, 21% had Medicaid insurance, and 7% were uninsured. Thirty-seven percent were diagnosed with stage III/IV disease, 67% with SCC, and 24% with AC. As first-line treatment, patients received surgery, radiation and/or chemotherapy as a component in 57%, 61%, and 53%, respectively.

3.2. Clinical covariates that vary by race and histology

Table 1 displays the clinical characteristics for this study. Fig. 1 high-lights the significant racial differences observed in patients with cervical SCC or AC Fig. 1A shows that the mean age at diagnosis of Black and White patients with SCC was similar (50.1 vs. 50.8 years old) but was approximately 6 years older in Black compared with White patients with AC (53.9 vs. 48.0 years old). Black patients with SCC or AC were more likely than White patients to have a higher comorbidity score (Fig. 1B), live in a lower-income neighborhood (Fig. 1C) and have no insurance or use Medicaid service (Fig. 1D). In SCC the proportion diagnosed at advanced stage or with high grade differed minimally by race. In contrast. Black patients with AC were significantly more likely than White patients to present with stage III/IV (Fig. 1E, 38.1% vs. 22.4%) or grade 3 (Fig. 1F, 43.7% vs. 25.2%). Racial differences in treatment utilization also varied in patients with SCC and/or AC Surgical treatment was less common in Black vs. White patients with stage I, II or III SCC or with stage I, III or IV AC (Fig. 1G, each $p < 0.0001$). Radiation treatment was more frequent in Black vs. White patients (Fig. 1H) with stage I SCC ($p < 0.0001$) or stage I AC ($p < 0.0001$). Fig. 1I shows that chemotherapy treatment in Black vs White patients was more common in stage I SCC (p <

0.0001) or stage I AC ($p < 0.0001$) and less frequent in stage III SCC ($p = 0.0003$), stage IV SCC ($p < 0.0001$) or stage IV AC ($p < 0.0001$). Five-year survival was 64% overall in cervical cancer patients and was 58% vs. 63% in Black vs. White patients with SCC compared with 56% vs. 78% in Black vs. White patients with AC, respectively (Fig. 1J, $p < 0.0001$).

3.3. Prognostic factors in cervical cancer patients

Table 2 provides the prognostic factor analysis using a multivariate Cox model. Older age, higher comorbidity score, lower neighborhood income, uninsured or Medicaid insurance, advanced stage, higher grade, or lack of treatments were independently associated with decreased survival overall and in both the SCC and AC subtypes. There was also evidence that patients with AC vs. SCC subtype had a 10% higher adjusted risk of death after controlling for other prognostic factors (AHR = 1.10,95% CI = 1.05–1.14).

In the original cohort without adjustment for clinical covariates. Black patients had significantly worse survival than White patients with cervical cancer overall (Fig. 2A, = 1.40,95% CI = 135–1.45). The survival disparities between Black and White patients varied significantly by histology (interaction $p < 0.0001$) with smaller differences in SCC (Fig. 2B, = 1.20,95% CI = 1.15–1.24) and larger differences in AC (Fig. 2C, = 232,95% CI = 2.12–2.54).

3.4. Factors contributing to racial disparities in survival in cervical cancer patients

Further analyses of survival by race in SCC and AC subtype were performed after applying propensity score analysis to balance the covariates that varied by race in cervical cancer patients with SCC (eTable 2) or AC (eTable 3). The HR (95% CI) in Black vs. White patients with SCC dropped from 1.20 to 1.18,1.17,1.09,1.04,1.04,1.03 and 1.01 after balancing for age, comorbidity, income, insurance, stage, grade and treatment, respectively (Fig. 3A, eTable 4) indicating that the largest contributors to racial disparity in survival in the SCC subtype were neighborhood income and insurance accounting for 38.1% and 23.4% of the observed disparities, respectively. The HR (95% CI) in Black vs. White patients with AC dropped from 232 to 1.77,1.74,1.59,1.42, 1.23,1.15 and 1.09 after balancing for age, comorbidity, income, insurance, stage, grade and treatment, respectively (Fig. 3B, eTable 4) indicating that age at diagnosis was the most significant contributor to the survival disparities in Black vs. White patients with AC accounting for 41.1% of the total ERR, followed by neighborhood income, insurance and stage that accounted for 11.1%, 12.8%, and 14.7% of the ERR. Of note, treatment only explained 4.5% of the survival difference between Black and White patients with AC.

We also evaluated the impact of treatment on racial disparities using an alternate modeling strategy, with type of treatment categorized by stage according to guideline-recommended management, and consideration of volume of treatment facility. eTable 5 shows the independent prognostic value of these two factors with the other clinical covariates in all cervical cancer patients and the subset with SCC or AC eTable 6 displays the proportions by type of treatment and volume of treatment facility in the original cohort and after applying PSM. Type of treatment and volume of treatment facility did not impact the more

modest survival disparities between Black and White patients with SCC after adjusting for first adjusting for age, comorbidity, income, insurance, stage, and grade (eTable 7). In AC patients, neither the type of treatment nor the volume of treatment facility significantly mediated the racial disparity in survival (eTable 7) with 2.9% associated with type of treatment categorized by stage and guideline-recommendations and 1.7% associated with the volume of the treatment facility in Black compared with White patients with AC.

3.5. Age at diagnosis of cervical squamous cell carcinoma and adenocarcinoma by race

Fig. 4A illustrates the distribution of age at diagnosis of SCC approximating a bell-shaped curve in both Black and White patients. This distribution matches the median [IQR] age at diagnosis of SCC reported in Table 1 of 50 [40–60] years old in Black patients vs. 49 [39–60] years old in White patients. There were 18.0% of Black patients and 16.9% of White patients diagnosed with SCC ≥65 years old. Fig. 4B displays the shift with older age in the diagnosis of AC in Black vs. White patients. The median [IQR] age of AC diagnosis was 52 [42–65] years old compared with 46 [37–57] years old in White patients (Table 1). There were 25.8% of Black patients and 13.4% of White patients diagnosed with AC at ≥65 years old (Fig. 4B).

4. Discussion

This study provides a novel extension to prior studies reporting racial disparities in survival and mortality in cervical cancer. Herein, we demonstrate that Black patients with cervical AC were more than twice as likely to die as White patients (HR = 23) while survival disparity between Black and White patients with SCC was less pronounced (HR = 1.2). Next, we showed that age was the largest contributor to survival disparities in Black vs. White patients with AC Neighborhood income and insurance were additional potentially modifiable factors contributing to some of the racial disparities in survival in both SCC and AC Stage at diagnosis explained the remaining survival disparities between Black and White patients with AC Finally, the proportion of Black vs. White patients diagnosed at ≥65 years old with AC was 26% vs. 13%, and with SCC was 18% vs. 17%, respectively, suggesting the need to extend standard cervical cancer screening beyond 65 years old. In addition. Black vs. White patients with AC were more likely to have stage III or IV disease when diagnosed with AC (38% vs. 22%, respectively) or with SCC (43% vs. 40%), indicating a need to prioritize more effective screening strategies and early detection to reduce the proportion of cervical cancers diagnosed with locally advanced or metastatic disease and subsequently improve survival.

Studies have described differences in follow up of abnormal tests, screening effectiveness, screening guideline adoption, utilization of preventative services, and HPV vaccinations as sources of disparities [2,14,25,27-33]. For example, Ford et al [29] analyzed National Health Interview Survey data and delineated gaps in follow-up of abnormal tests between Black and White women. Lichter et al. [25] accessed SEER-Medicare data and demonstrated that most women >65 years old with cervical cancer were diagnosed with locally advanced or metastatic disease and 15% did not receive treatment highlighting the need to re-evaluate screening and treatment in women >65 years, who make up an increasing proportion of the

U.S. population. Cooley et al. [27] documented that 20% of cervical cancers in California were diagnosed in women ≥65 years old and a majority had advanced stage supporting the importance of tracking past screening history, reducing lapses in follow up care, and using non-invasive screening methods in older women. Tranberg et al. [38] demonstrated the value of catch-up HPV testing in women ≥65 years old in a Danish population-based non-randomized intervention study to improve cervical cancer prevention in older women. Sokale et al. [30] evaluated cervical cancer screening using the Behavioral Risk Factor Surveillance System and found lower screening rates in older patients or in Black patients. Gradissimo et al. [32] reported on a new and more sensitive detection method and advocate its use to improve screening and detection of AC Fuzzel et al. [31] highlight reasons for low screening participation among subgroups in the U.S., discussing the challenges, barriers and potential solutions for under-screened groups, including racial and ethnic minorities, rural residents, individuals with sexual/gender minority status, limited English proficiency, specific religious beliefs, and various health conditions. Vadaparampil et al. [33] evaluated results from a cross-sectional survey of clinician characteristics, practices and attitudes associated with adoption of the 2019 ASCCP guidelines indicating that few clinicians followed the updated national guidelines for the management of abnormal cervical cancer screening test results, which results in unnecessary invasive testing in low-risk patients and inadequate surveillance testing in high-risk patients, and that patterns of nonadherence varied by specialty. The complexity of cervical cancer screening algorithms also contributes to suboptimal utilization of preventive programs, an issue which may become a greater challenge given the poor adoption of ASCCP guidelines. Spencer et al. [14] performed a meta-analysis in over 100 studies and showed that racial and ethnic minorities were more likely to initiate HPV vaccination but less likely to follow-through with HPV vaccination. Together these factors may lead to delays in diagnosis, lower detection of AC by cytology alone, late stage diagnosis, and worse mortality and survival.

Racial and ethnic disparities in incidence, mortality and survival in cervical cancer in the U.S. have been reported by a number of groups [4-13,15-25,27], For example, Singh and Jemal [9] reported higher mortality in Blacks than Whites with an array of cancers including cervical cancer and this inequity in outcome was associated with more deprived neighborhoods and may reflect differences in smoking, obesity, physical inactivity, diet, alcohol intake, screening and treatment Yoo et al. [10] identified Black race and age as key risk factors mediating the increased cervical cancer incidence and mortality in the U.S. South region. Cohen et al. [11] used data from SEER to document age- and hysterectomy-adjusted incidence rates, survival and mortality for patients with SCC or AC stratified by stage and show that Black patients were less likely to be diagnosed with AC of the cervix compared with all other racial and ethnic groups but experienced the highest mortality rate likely attributable to the higher diagnosis of regional and distant AC in Black patients. Markt et al. [12] also used the SEER data to show that insurance status and treatment were key contributors to racial disparities in mortality in cervical cancer patients. In our study, we used the NCDB and propensity score analysis to demonstrate that the 2-fold worse survival in Black vs. White patients with AC histology was largely attributed to Black patients being diagnosed at older age and advanced stage. Social determinants of health such as barriers to

care, exposures and lifestyle may explain at least some of the disparities in survival observed between Black vs. White patients with AC in our study.

A number of groups have documented differences between cervical SCC and AC [5,16,21,22,26,34,35]. Our study design allowed us to examine age as an independent factor and measure its contribution to survival disparities for both SCC and AC. While only 11% of the excess relative risk was attributed to age for SCC, 41% of the survival disparity in AC was attributed to age. We found this observation to be novel, surprising and in need of further study. It is important to investigate why Black patients were more likely than White patients to be diagnosed with AC but not with SCC at an older age. While stage at diagnosis is directly related to screening protocols and early detection, screening disparities in cervical cancer are unlikely to explain the age differences among racial groups with AC. AC is less likely to be detected on a single screening test than SCC and may require stricter adherence to screening and diagnostic protocols. If Black patients are less likely to strictly adhere to screening and diagnostic protocols this may explain the higher proportion diagnosed at older age. Differences in environmental exposures, structural determinants of health, high-risk HPV infection and variations in genetic ancestry may also contribute to the higher proportion of AC and/or stage III-IV disease in patients diagnosed at ≥65 years old.

The Cancer Genome Atlas (TCGA) analysis of cervical cancer high-lighted the association between differential genomic features corresponding to different HPV types [37], No significant survival difference was noted across the three major clusters (keratin-low squamous, keratin-high squamous, and adenocarcinoma-rich). Unfortunately, the TCGA cervical cancer samples were not sufficiently representative with only 8.9% of the tumor samples obtained from Black women. Given that Black patients represent nearly 30% of the South region population, and approximately 12% of the total U5. population, racial diversity is an important component of future genomic and molecular cervical cancer studies.

The contributory magnitude of social determinants of health to racial disparities in cervical cancer survival based on histology has not been well described. Prior studies have identified the impact of geographic, socioeconomic status, demographics, insurance and healthcare access on cervical cancer screening, incidence and outcomes [2-13,15-31,36]. Specifically in the Mississippi Delta region, a federally designated, socioeconomically disadvantaged region of the U.S., mortality rate in Black women is nearly three-fold higher compared to White women diagnosed with cervical cancer [20]. In our hospital-based NCDB study, the role of community and neighborhood largely mediates the racial disparity in survival for Black women with SCC and partly mediates it for AC Prior studies have identified the effect of insurance status to cervical cancer survival in Black women, with worse outcomes in those with Medicaid or no insurance associated with late-stage diagnosis and a lower likelihood of receiving standard of care treatments [3,4,6,7,12,15]. For example, Markt et al. [12] used data from SEER to estimate the proportion of excess cervical cancer mortality for NHB vs. NHW women as mediated by insurance status in 18.6% of cases, but did not report on the difference by histology. Additionally, Holt et al. [7] assessed the proportion of observed racial differences in the stage at diagnosis that were mediated by health insurance status using SEER patients between 2006 and 2016 and found 513% of inequities of advanced stage diagnosis were mediated by insurance status. Underrepresented

population groups are at higher risk of early cervical cancer detection failure, screening noncompliance, and lack of follow up in part due to reliance on subsidized clinics, which often have fewer services and staffing [3]. Thus, insurance status may represent a surrogate for structural determinants of health and healthcare access. Addressing barriers such as available clinics to get screened at, regular primary care, outreach to remind patients to get screened, support services to be able to complete standard of care treatment in timely fashion, are likely needed to reduce at least some of disparities between Black and White patients with cervical cancer.

Strengths of our study include the statistical power to perform sub-group analyses within the large, well known and commonly deployed NCDB. Limitations include those inherent to retrospective database centered analyses with errors and omissions in abstracted data possibly confounding results. While the NCDB represents approximately 70% of incident cancer diagnoses in the U.S., it does not represent patients who did not have access to care at a Commission on Cancer accredited cancer program. This study did not include other racial and ethnic groups or country of origin subgroups which also deserve attention. Caution should be exercised to avoid over-generalization of the conclusions. We were also unable to control for adjuvant chemotherapy details including agent names and cycles or for treatment after relapse for recurrent, metastatic, or progressive disease. This database also does not capture the cancer-specific survival which has been shown to correlate closely with overall survival in advanced cervical cancer but may not with early-stage disease. The association between age or income and life expectancy in the U.S. my distort the contribution of age or neighborhood income on survival. The differential relationship between AC vs. SCC on survival is complex and this study was not able to account for the impact of unmeasured covariates and modifiable risk factors, including smoking, diet, exercise, marriage, receipt of guideline-based care, health facility volume, treatment details for up front, recurrent or progressive disease, social determinants of health, ancestral admixture or molecular alterations related to the measured covariates that largely explained the disparities. We also acknowledge the heterogeneity and inadequacies of the common racial and ethnic categorizations used by the National Cancer Database. White and Black are highly simplified classifications for a multitude of variations with intersections between ancestry and sociocultural factors as discussed and referenced by Kucera et al. [40] This simplification can inevitably lead to overgeneralization and false conclusions, which we caution against

This study evaluated identifiable factors that contributed to racial disparities in cervical cancer by histology and provides a more detailed landscape of factors and the social determinants linked to this finding. These data suggest that comprehensive safety-net efforts are needed to ensure improved care coordination, resource allocation, and social support for Black patients with cervical cancer. It is essential for policymakers and researchers to acknowledge that the explained contributors to racial disparities in survival in cervical cancer are largely modifiable with overlap and distinctions for patients with SCC vs. AC Furthermore, socioeconomic variables including being uninsured and age at diagnosis, coupled with stage accounted for nearly 80% of the excess relative risk of death in the Black AC cohort Future racial disparity investigations should consider measuring both the individual-level and community-level factors associated with cancer health outcomes. In

particular, the interaction between age and race among patients with cervical AC should be further explored. Cervical cancer is almost completely preventable and despite decades of population-level interventions vaccine hesitancy, inconsistent adherence to screening guidelines and guidelines that focus on screening through 65 years old prevent eradication of this disease. The explained factors presented in our study can serve to promote evidence-based actions that are meaningful to survival and health equity in cervical cancer. We must also acknowledge that there may be factors that contribute to the racial disparity that are not included in our study such as implicit bias and systemic racism. A multidisciplinary approach that collectively incorporates a broader understanding of etiology, ancestry, exposures, lifestyle, structural determinants of health, access to healthcare services, and health care policy is needed to create health equity among our country's cervical cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

Chad A. Hamilton reported personal fees from GlaxoSmithKline outside the submitted work. Yovanni Casablanca cited personal fees from AstraZeneca outside the submitted work. John K. Chan reported personal fees from Agenus, AstraZeneca, Eisai, Genmab, GlaxoSmithKline, Immunogen, Mersana, Molecular Targeting Technologies, Myriad, Roche, and Seagen outside the submitted work. Thomas P. Conrads is a ThermoFisher Scientific, Inc. SAB member and receives research funding from AbbVie outside the submitted work. Charles A. Leath, III received funding from the NIH UG1 CA23330 and P50 CA098252, contracted research with Agenus and Seattle Genetics, and served on a scientific advisory board for Seattle Genetics, all outside of the submitted work. The other authors have no conflicts of interest to disclose.

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HIGHLIGHTS

- Survival disparities between Black and White patients with cervical cancer varied by histology.
- Cervical adenocarcinoma subtype dominated the survival disparities between Black and White patients with cervical cancer.
- Age, income, insurance, and stage were the largest contributors to the 2.3-fold disparities in survival in adenocarcinoma.
- Neighborhood income and insurance were the largest contributors to the 20% survival disparities in squamous cell carcinoma.
- 26% of all adenocarcinoma cases in Black patients were diagnosed >65 years beyond the standard cervical screening guidelines.

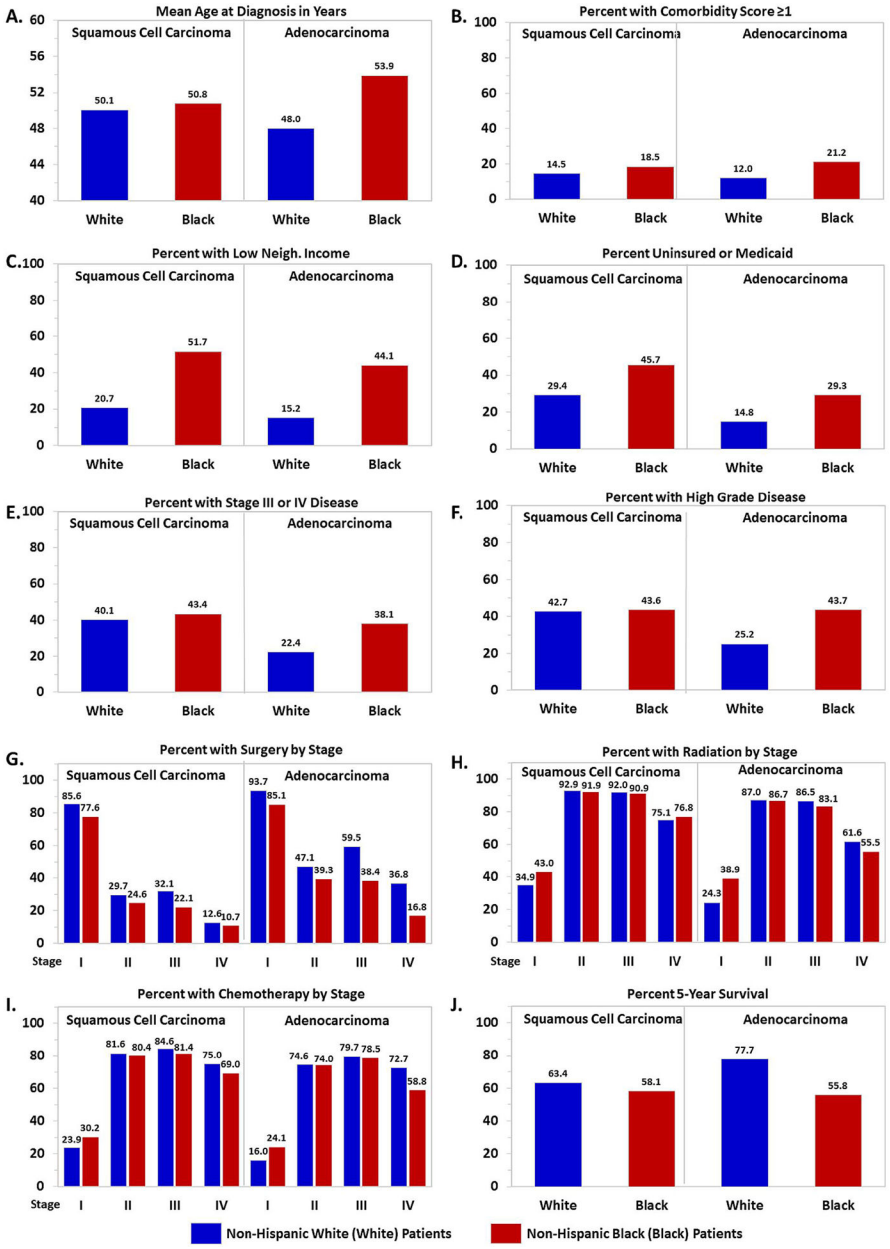


Fig. 1.

Disparities in patient characteristics and outcome in Black vs. White patients with cervical squamous cell carcinoma (SCC) or adenocarcinoma (AC), including mean age at diagnosis (A), and percent with comorbidity score ≥ 1 (B), low neighborhood income (C), uninsured or with Medicaid insurance (D), stage III or IV disease (E), high grade (F), treated with surgery by stage (G), treated with radiation by stage (H), treated with chemotherapy by stage (I) or five-year survival (J).

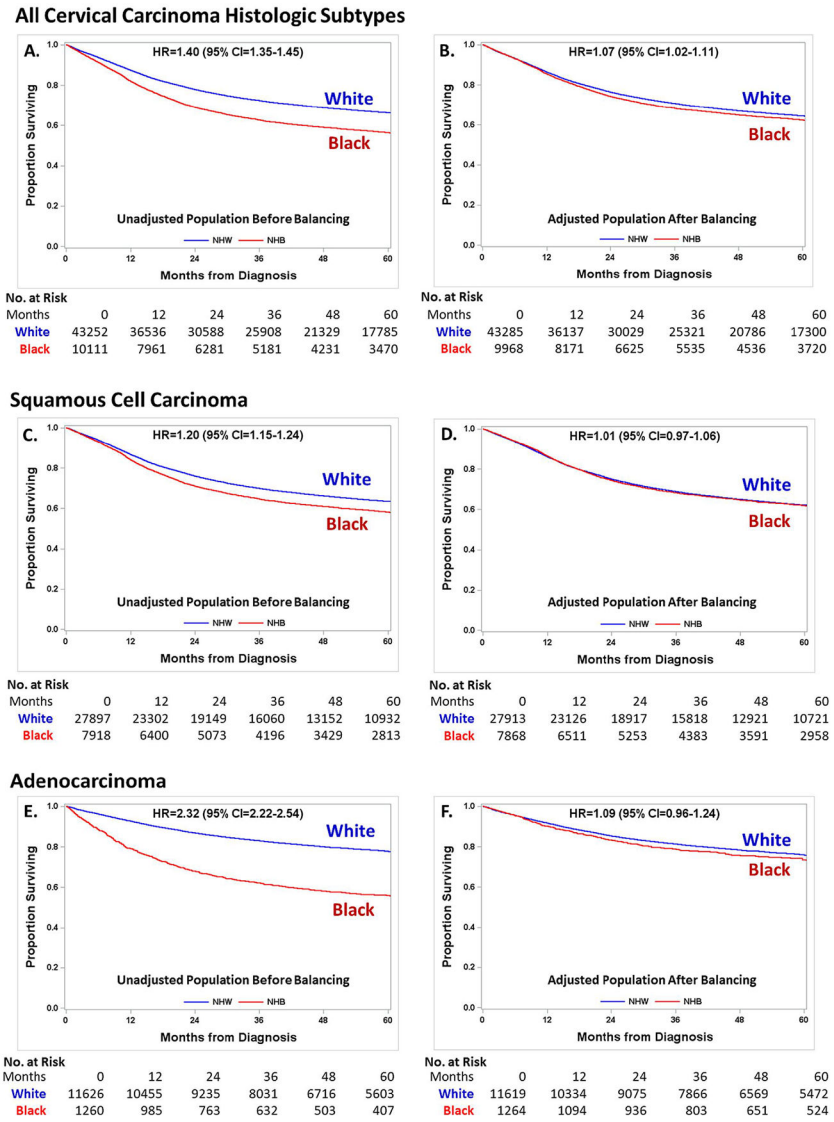


Fig. 2.

Survival in Black vs. White patients with cervical cancer (A, B), squamous cell carcinoma (SCC) of the cervix (C, D) or adenocarcinoma (AC) of the cervix (E, F) before propensity score balancing (A, C, E) or after propensity-score balancing for demographic, socioeconomic and clinical factors (B, D, F).

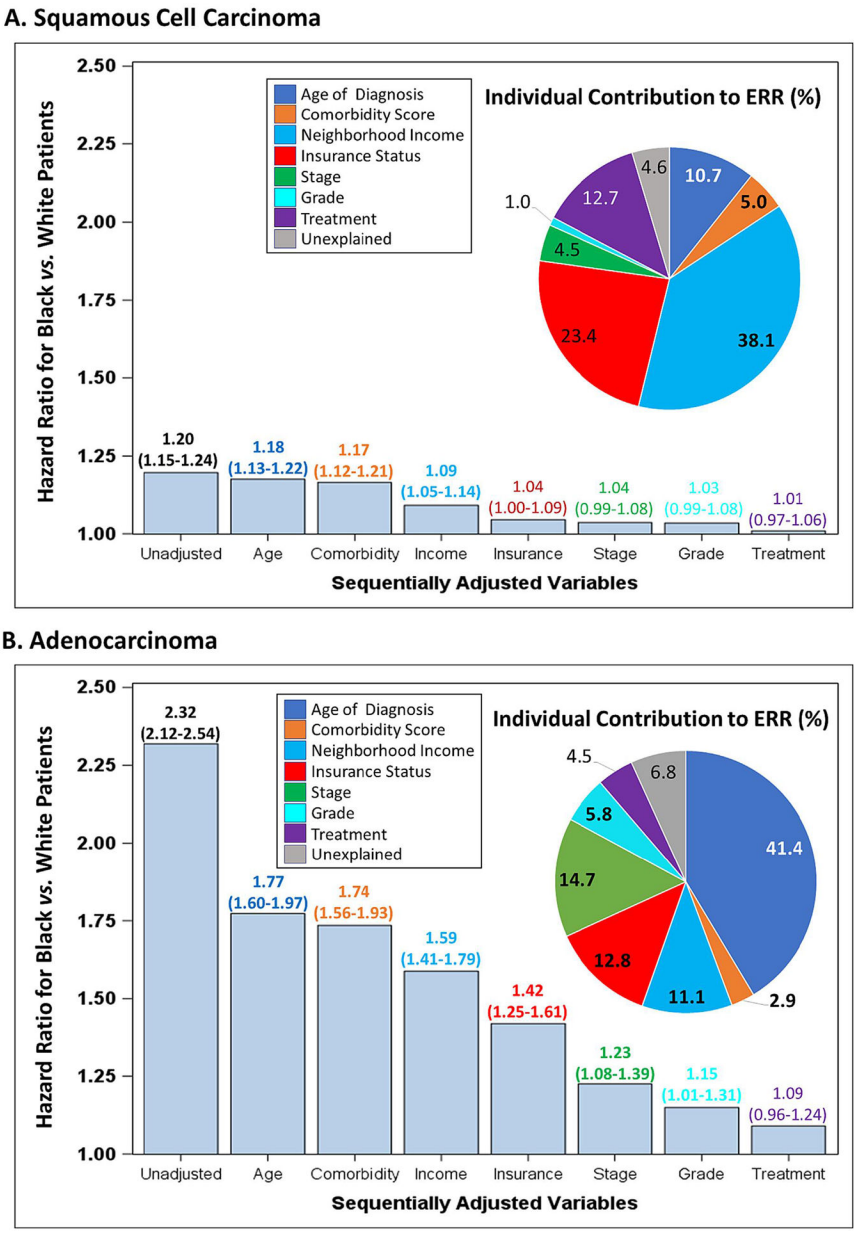
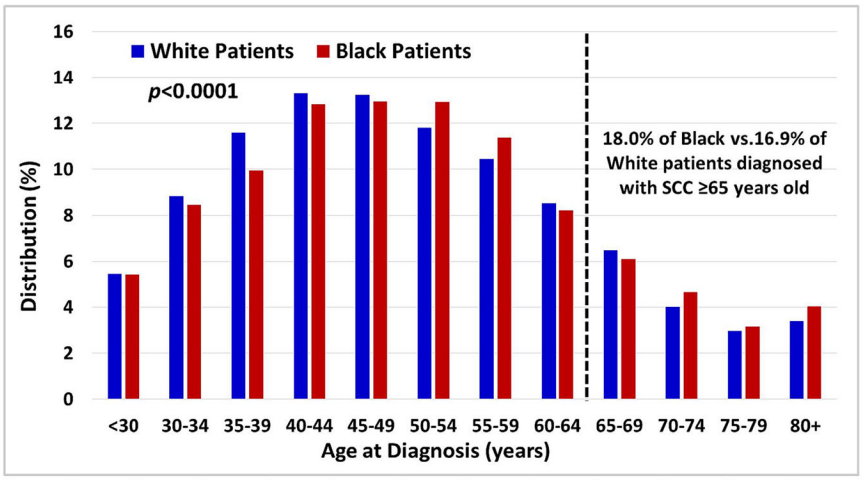


Fig. 3.

Hazard ratio for the risk of death in Black vs. White patients following sequential adjustment for demographic, socioeconomic and clinical factors from propensity score analysis, and the estimated contribution of these factors to racial disparities in survival in patients with squamous cell carcinoma (SCC) of the cervix (A) or adenocarcinoma (AC) of the cervix (B). The adjusted risk of death was 20% higher in Black vs. White patients with SCC but lost statistical significance after stepwise balancing for age, comorbidity, income, insurance, stage, grade, and treatment (A) indicating that the largest contributors to racial disparity in survival in the SCC subtype were neighborhood income and insurance accounting for 38.1% and 23.4% of the observed disparities, respectively. The adjusted risk of death was 230% higher in Black vs. White patients with AC but also lost statistical

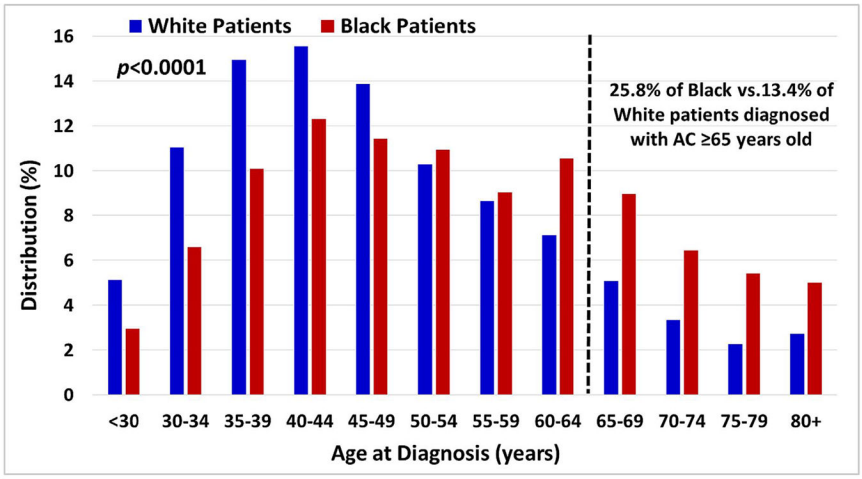
significance after stepwise balancing for age, comorbidity, income, insurance, stage, grade and treatment (B) indicating that age at diagnosis was the most significant contributor to the survival disparities in Black vs. White patients with AC accounting for 41.1% of the total excess relative risk (ERR), followed by neighborhood income, insurance and stage that accounted for 11.1%, 12.8%, and 14.7% of the ERR.

A. Squamous Cell Carcinoma (SCC)



Age	<30	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
White	5.4	8.8	11.6	13.3	13.2	11.8	10.4	8.5	6.5	4.0	3.0	3.4
Black	5.4	8.5	10.0	12.8	13.0	12.9	11.4	8.2	6.1	4.7	3.2	4.0

B. Adenocarcinoma (AC)



Age	<30	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+
White	5.1	11.1	15.0	15.5	13.9	10.3	8.7	7.1	5.1	3.3	2.3	2.7
Black	2.9	6.6	10.1	12.3	11.4	11.0	9.1	10.6	9.0	6.4	5.4	5.0

Fig. 4.

Distribution of age at diagnosis in Black vs. White patients with squamous cell carcinoma (SCC) of the cervix (A) or adenocarcinoma (AC) of the cervix (B).

Table 1

The characteristics for cervical cancer patients overall and in self-reported non-Hispanic Black (Black) versus non-Hispanic White (White) patients with invasive cervical cancer or within the subset with cervical squamous cell carcinoma or adenocarcinoma.

	All patients			**Squamous cell carcinoma**		**Adenocarcinoma**	
	Total	**White**[k]	**Black**[k]	**White**[k]	**Black**[k]	**White**[k]	**Black**[k]
	***N* = 53,363**	***N* = 43,252**	***N* = 10,111**	***N* = 27,897**	***N* = 7918**	***N* = 11,626**	***N* = 1260**
Age at Diagnosis							
Mean [SD] in years	50.0 [14.5]	49.6 [14.3]	51.6 [14.9]	50.1 [14.3]	50.8 [14.6]	48.0 [13.8]	53.9 [15.1]
Comorbidity Score[a]							
0	45,422 (85.1)	37,243 (86.1)	8179 (80.9)	23,865 (85.6)	6454 (81.5)	10,235 (88.0)	993 (78.8)
≥1	7941 (15.0)	6009 (13.9)	1932 (19.1)	4032 (14.5)	1464 (18.5)	1391 (12.0)	267 (21.2)
Neighborhood Income[b]							
≥$63,333	15,010 (28.1)	13,598 (31.4)	1412 (14.0)	7782 (27.9)	1020 (12.9)	4556 (39.2)	224 (17.8)
$50,354–$63,332	11,869 (22.2)	10,430 (24.1)	1439 (14.2)	6830 (24.5)	1114 (14.1)	2728 (23.5)	200 (15.9)
$40,227–$50,353	13,180 (24.7)	11,018 (25.5)	2162 (21.4)	7512 (26.9)	1687 (21.3)	2580 (22.2)	280 (22.2)
<$40,227	13,304 (24.9)	8206 (19.0)	5098 (50.4)	5773 (20.7)	4097 (51.7)	1762 (15.2)	556 (44.1)
Insurance Status[c]							
Private	28,464 (53.3)	24,774 (57.3)	3690 (36.5)	14,422 (51.7)	2766 (34.9)	8205 (70.6)	579 (46.0)
Medicare	9901 (18.6)	7794 (18.0)	2107 (20.8)	5287 (19.0)	1537 (19.4)	1702 (14.6)	312 (24.8)
Medicaid	11,169 (20.9)	7970 (18.4)	3199 (31.6)	6138 (22.0)	2700 (34.1)	1263 (10.9)	249 (19.8)
Uninsured	3829 (7.2)	2714 (6.3)	1115 (11.0)	2050 (7.4)	915 (11.6)	456 (3.9)	120 (9.5)
Stage[d]							
I	25,252 (47.3)	21,359 (49.4)	3893 (38.5)	11,962 (42.9)	2984 (37.7)	7900 (68.0)	630 (50.0)
II	8148 (15.3)	6350 (14.7)	1798 (17.8)	4761 (17.1)	1498 (18.9)	1118 (9.6)	150 (11.9)
III	12,440 (23.3)	9713 (22.5)	2727 (27.0)	7295 (26.2)	2249 (28.4)	1568 (13.5)	242 (19.2)
IV	7523 (14.1)	5830 (13.5)	1693 (16.7)	3879 (13.9)	1187 (15.0)	1040 (9.0)	238 (18.9)
Histologic Subtype[e]							
Squamous ceil	35,815 (67.1)	27,897 (64.5)	7918 (78.3)	27,897 (100)	7918 (100)	–	–
Adenocarcinoma	12,866 (24.2)	11,626 (26.9)	1260 (12.5)	–	–	11,625 (100)	1260 (100)
Other Subtypes[f]	4662 (8.7)	3729 (8.6)	933 (9.2)	–	–	–	–

	All patients			Squamous cell carcinoma		Adenocarcinoma	
	Total	White[k]	Black[k]	White[k]	Black[k]	White[k]	Black[k]
	N = 53,363	*N* = 43,252	*N* = 10,111	*N* = 27,897	*N* = 7918	*N* = 11,626	*N* = 1260
Tumor Grade[g]							
Grade 1	7417 (14.0)	6571 (15.0)	848 (8.4)	2420 (8.7)	561 (7.1)	3924 (33.8)	265 (21.0)
Grade 2	23,294 (43.9)	18,953 (43.8)	4474 (44.3)	13,554 (48.6)	3906 (49.3)	4770 (41.0)	444 (35.2)
Grade 3	22,326 (42.1)	17,828 (41.2)	4789 (47.4)	11,923 (42.7)	3451 (43.6)	2932 (25.2)	551 (43.7)
Surgery[h]							
Yes	30,257 (56.7)	25,619 (59.7)	4438 (43.9)	14,483 (51.9)	3308 (41.8)	9246 (79.5)	728 (57.8)
No	23,106 (43.3)	17,433 (40.3)	5673 (56.1)	13,414 (48.1)	4610 (58.2)	2380 (20.5)	532 (42.2)
Radiation[i]							
Yes	32,365 (60.7)	25,423 (58.8)	6942 (68.7)	18,224 (65.3)	5614 (70.9)	4894 (42.1)	708 (56.2)
No	20,998 (39.4)	17,829 (41.2)	3169 (31.3)	9673 (34.7)	2304 (29.1)	6732 (57.9)	552 (43.8)
Chemotherapy[i]							
Yes	28,111 (52.7)	22,184 (51.3)	5927 (58.6)	15,822 (56.7)	4755 (60.1)	4102 (35.3)	593 (47.1)
No	25,252 (47.3)	21,068 (48.7)	4184 (41.4)	12,075 (43.3)	3163 (40.0)	7524 (64.7)	667 (52.9)

[a]Comorbidity score was code by the National Cancer Database (NCDB) using the Charlson-Deyo index system and for this study was categorized as 0 or ≥ 1.

[b]Neighborhood income was measured using the median household income for each patients area of residence estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from the 2016 *American Community Survey* data and categorized as quartiles based on equally proportioned income ranges among ail US zip codes: < $40,227, $40,227–$50,353, $50354–$63,332 or ≥ $63333.

[c]Insurance was classified by the NCDB as uninsured, Medicaid, Medicare, or private insurance.

[d]Stage was determined by the NCDB using American Joint Committee on Cancer (AJCC) criteria and was categorized as I, II, III or IV.

[e]Histologic subtype was evaluated using the ICD for Oncology, third edition (ICD-O-3). SCC were represented by codes 8052, 8070–8078. AC was captured using codes 8140–8141, 8143, 8147, 8255, 8260–8263, 8310, 8323, 8380, 8384, 8430 and 8480–8482. The remaining heterogenous collection of histologic subtypes were integrated into other histologic subtypes (see eTable 1 for a manifest by ICD-O-3 code).

[f]This included 1937 cases with adenosquamous carcinomas identified using ICD-O-3 code of 8560,8570,8574,8572 and 8575. There were also 860 cases with carcinoma not otherwise specified with ICD-O-3 code 8010 and 409 cases with small cell carcinoma with ICD-O-3 code 8041. The remaining 1456 patients were distributed across 45 ICD-O-3 codes.

[g]Tumor grade was categorized by the NCDB as grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated or undifferentiated).

[h]Surgery (yes/no) to the primary site.

[i]Radiation (yes/no) to the primary site or any metastatic site.

[j] Chemotherapy (yes/no) as administration of single- or multi-agent chemotherapy during the first treatment course.

[k] Non-Hispanic Black (Black) and non-Hispanic White (White) were classified as coded by the NCDB using the self-reported race variable (Black vs. White) and the Hispanic/Spanish ethnicity variable (No). Patients with Hispanic/Spanish ethnicity were excluded.

Table 2

The adjusted risk of death for the demographic, patient health, socioeconomic and clinical variable in cervical cancer patients overall and then patients with cervical squamous cell carcinoma or adenocarcinoma.

	All patients		Squamous cell carcinoma		Adenocarcinoma	
	AHR (95% CI)[b]	***P* value**	**AHR (95% CI)[b]**	***P* value**	**AHR (95% CI)[b]**	***P* value**
Race/Ethnicity						
White[a]	Reference		Reference		Reference	
Black[a]	1.02 (0.98–1.05)	0.404	0.98 (0.94–1.02)	0.411	1.18 (1.07–1.30)	0.001
Age at Diagnosis						
Per 5-year increase	1.08 (1.07–1.09)	<0.0001	1.07 (1.06–1.08)	<0.0001	1.15 (1.13–1.17)	<0.0001
Comorbidity Score						
0	Reference		Reference		Reference	
≥1	1.38 (1.33–1.43)	<0.0001	1.37 (1.31–1.43)	<0.0001	1.41 (1.29–1.54)	<0.0001
Neighborhood Income						
≥$63,333	Reference		Reference		Reference	
$50,354–$63,332	1.06 (1.01–1.10)	0.009	1.06 (1.01–1.12)	0.027	0.99 (0.90–1.09)	0.800
$40,227–$50,353	1.10 (1.05–1.14)	<0.0001	1.11 (1.06–1.17)	<0.0001	1.09 (0.99–1.19)	0.086
<$40,227	1.17 (1.12–1.22)	<0.0001	1.18 (1.12–1.24)	<0.0001	1.16 (1.06–1.29)	0.003
Insurance Status						
Private	Reference		Reference		Reference	
Medicare	1.41 (1.35–1.47)	<0.0001	1.47 (1.39–1.55)	<0.0001	1.36 (1.23–1.51)	<0.0001
Medicaid	1.36 (1.31–1.41)	<0.0001	1.34 (1.28–1.40)	<0.0001	1.52 (1.36–1.68)	<0.0001
Uninsured	1.36 (1.29–1.43)	<0.0001	1.34 (1.26–1.42)	<0.0001	1.41 (1.21–1.63)	<0.0001
AJCC Stage						
I	Reference		Reference		Reference	
II	2.03 (1.92–2.15)	<0.0001	1.92 (1.80–2.05)	<0.0001	2.22 (1.96–2.52)	<0.0001
III	3.53 (3.36–3.71)	<0.0001	3.30 (3.11–3.50)	<0.0001	4.00 (3.58–4.46)	<0.0001
IV	8.45 (8.03–8.89)	<0.0001	7.97 (7.49–8.49)	<0.0001	9.27 (8.28–10.38)	<0.0001
Histologic Subtype						
Squamous Ceil	Reference					
Adenocarcinoma	1.10 (1.05–1.14)	<0.0001	–	–	–	–

	All patients		Squamous cell carcinoma		Adenocarcinoma	
	AHR (95% CI)[b]	***P* value**	**AHR (95% CI)[b]**	***P* value**	**AHR (95% CI)[b]**	***P* value**
Other subtypes	1.41 (1.35-1.48)	<0.0001	–	–	–	–
Grade						
Grade 1	Reference		Reference		Reference	
Grade 2	1.40 (1.31–1.49)	<0.0001	1.18 (1.09–1.28)	<0.0001	1.50 (1.34–1.68)	<0.0001
Grade 3	1.78 (1.67–1.90)	<0.0001	1.40 (1.29–1.52)	<0.0001	2.20 (1.97–2.46)	<0.0001
Surgery						
Yes	Reference		Reference		Reference	
No	2.14 (2.06–2.23)	<0.0001	2.14 (2.04–2.25)	<0.0001	2.15 (1.98–2.34)	<0.0001
Radiation						
Yes	Reference		Reference		Reference	
No	1.07 (1.03–1.12)	0.001	1.11 (1.05–1.18)	0.0001	0.92 (0.84–1.01)	0.094
Chemotherapy						
Yes	Reference		Reference		Reference	
No	1.51 (1.45–1.57)	<0.0001	1.49 (1.43–1.56)	<0.0001	1.33 (1.21–1.45)	<0.0001

[a]Non-Hispanic Black and non-Hispanic White patients were known as Black and White, respectively.

[b]Adjusted Hazard ratio (AHR) and 95% confidence interval (Q) were estimated from multivariate Cox model adjusted for ail the listed covariates. Multivariate analysis was conducted on ail patients, patients with cervical squamous cell carcinoma or patients with adenocarcinoma, respectively. AHR for risk of death in Back vs. White patients was further evaluated using propensity-score analysis (eTable 4).