Racial Disparity in Primary Hepatocellular Carcinoma: Tumor Stage at Presentation, Surgical Treatment and Survival

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Objectives: The incidence and mortality rates from primary hepatocellular carcinoma (HCC) are higher in black Americans compared to whites. The goal of this study was to determine if there are racial disparities in HCC stage at diagnosis and treatment.

Methods: We compared patient age, tumor stage, rates of surgical intervention and survival in black (n=1,718) and white (n=9,752) HCC cases between 1992 and 2001 in the Surveillance, Epidemiology and End Results (SEER)-11 + Alaska database.

Results: Black HCC cases were significantly younger at diagnosis ($p<0.0001$). Black cases were more likely to have regional and distant metastasis at presentation ($p<0.0005$) and were less likely to have surgery performed ($p<0.001$). The racial difference in surgery treatment was significant among patients with localized ($p=0.001$) and regional ($p=0.012$) HCC, but not with distant HCC. Overall survival rates were lower in blacks ($p=0.0033$). Survival was similar in blacks and whites with regional and distant disease. Yet, among patients with localized HCC, survival rates were lower in blacks ($p=0.0030$).

Conclusions: Black HCC patients have more advanced tumor stage at diagnosis and lower rates of both surgical intervention and survival. The racial disparities in surgical treatment utilization and survival were most striking between black and white HCC patients with localized HCC.

Key words: hepatocellular carcinoma ■ racial disparity

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INTRODUCTION

Primary liver cancer is the fifth most common malignancy in the world and accounts for up to 1 million deaths per year worldwide. The incidence of hepatocellular carcinoma (HCC) has been rising in the United States over the past 20 years.[1,2] The age-adjusted incidence for HCC in the United States increased from 1.4 per 100,000 in 1975–1977 to 3.0 per 100,000 in 1996–1998. There was a concurrent rise in HCC mortality from 1.7 per 100,000 to 2.4 per 100,000 during 1991–1995. The increased incidence of HCC has been attributed, in part, to an increase in the prevalence of end-stage liver disease due to chronic hepatitis-B and -C infections.[3,4] Both the incidence and mortality rates for HCC are 2–3 times higher in black Americans than in whites.[1,2] HBV, HCV, concurrent HBV and HCV, and diabetes mellitus plus viral hepatitis were significantly more common in black HCC cases compared to white cases in the Nationwide Inpatient Sample for the year 2000.[5] Thus, differences in the prevalence of HCC risk factors may account for the racial differences in HCC incidence. However, the explanation for the higher HCC mortality rates in blacks is unknown.

Previous studies have found more advanced tumor stage at diagnosis and lower rates of surgery with curative intent for colorectal, breast, cervical and prostate cancers in black Americans relative to white Americans.[6] To better define the racial disparity in HCC in the United States, we compared the HCC tumor stage at diagnosis, utilization of surgical treatment, and survival in black and white HCC cases in the United States for 1992–2001.

METHODS

Description of Database

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program is a comprehensive source of population-based information on cancer incidence and survival in the United States.[7] We utilized data from the SEER-11 + Alaska database registry from 1992–2001. The registry includes data on

cancer cases from Atlanta, GA; Connecticut' Detroit, MI; Hawaii; Iowa; New Mexico; Los Angeles, San Jose-Monterey and San Francisco–Oakland, CA; Seattle–Puget Sound, WA; and Utah. Starting in 2001, cases from Louisiana, Kentucky, New Jersey and the remaining areas of California were also included.

Patient Characteristics and Clinical Variables

The intended cohort was all cases in the SEER database with a diagnosis of primary HCC, using ICD-9 code 155.0 (cases through 1998), and ICD-10 code C22.0 (cases from 1999 and beyond). HCC cases with race classified as either white or black were selected for this study. The following patient variables were examined: age at diagnosis, gender, tumor stage, utilization of surgical therapy and status (dead or alive). In the SEER database, tumor stage is categorized as localized, regional spread or distant spread. Localized cancer is defined as disease that is limited to the organ in which it began, without evidence of spread. Regional spread is cancer that has spread beyond the original (primary) site to nearby lymph nodes, organs and tissues. Distant spread is cancer that has extended beyond the primary site to distant organs or lymph nodes.

SEER classifies surgical interventions into several categories: surgery performed; surgery recommended, unknown if performed; surgery refused; surgery not recommended; surgery contraindicated; unknown intervention; and unknown–death certificate only. The mortality data reported by SEER are obtained from the National Center for Health Statistics.

Data Analysis

The age-adjusted HCC incidence for black and white cases was determined using U.S. population data provided by SEER, and compared using the Kruskal-Wallis test. The Chi square with post hoc cell analysis, and observed versus expected cases were used to compare the age distributions of HCC, tumor stages and surgical treatment utilization rates between black and white cases.

Survival by race, HCC stage, age and gender were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox regression models were used to compare HCC survival by race, adjusting for age, gender, surgical procedure and HCC stage. Two-sided p values of <0.05 were considered statistically significant. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Cases with status "alive" were deemed to be uncensored, whereas those with "dead" status were deemed to be censored. Survival times were adjusted for age.

RESULTS

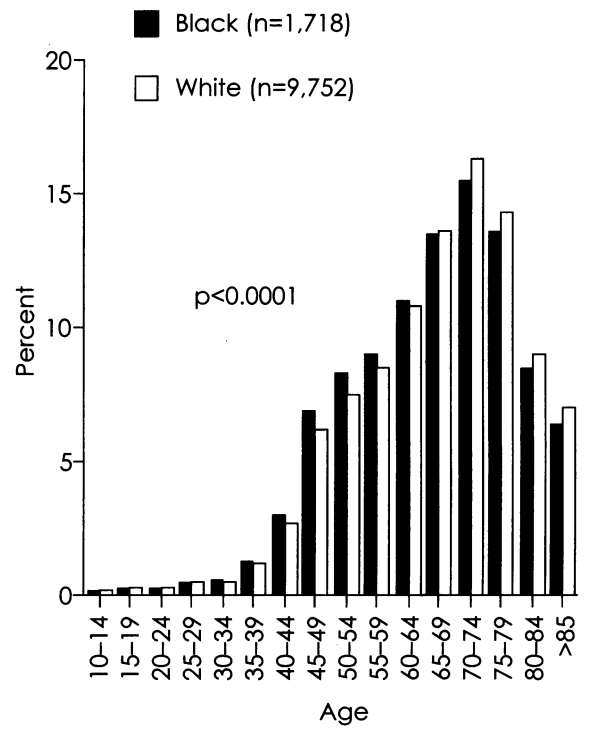
We identified 9,752 white and 1,718 black HCC cases in the SEER database between 1992 and 2001. Males accounted for 68% of both the white and black cases. The age-adjusted HCC incidence was higher in blacks than in whites (4.6 per 100,000 vs. 2.6 per 100,000, p<0.0001). In addition, both black and white males had a greater HCC incidence than black and white females (7.6 per 100,000 vs. 2.3 per 100,000 and 4.1 per 100,000 vs. 1.4 per 100,000, respectively; p<0.0001). The age distribution of HCC cases among blacks and whites is shown in Figure 1. HCC was uncommon in cases <40 years of age in both races. Compared to white cases, a greater proportion of black cases were <70 years of age, and a smaller proportion were >70 (p<0.0001). The racial difference in age distribution applied to both male (p<0.001) and female cases (p=0.02).

Tumor stages at diagnosis (Figure 2) were significantly different between black and white HCC cases overall [p<0.0005 (Chi square)] as well as within each gender (p<0.001 for males; p=0.02 for females). Black patients were more likely to have regional (27.5% vs. 22.4%) and distant (22.7 vs. 19.9%) HCC, and less likely to have localized (27% vs. 30.1%, Figure 2) and unstaged disease (22.8% vs. 27.7%). White males were more likely to have regional and distant HCC and less likely to have localized tumor than white females (p<0.0001). There was no difference, however, in HCC stage between black males and females (p=0.14).

Surgical Treatment Utilization and Patient Survival

There was a significant association between tumor stage and surgical intervention (p<0.0001) (Figure 3).

Figure 1. Age distribution of hepatocellular carcinoma cases



Surgical treatment was "not recommended" more often for patients with regional and distant HCC spread than for patients with localized and unstaged HCC (p<0.001).

Figure 2. HCC tumor stage

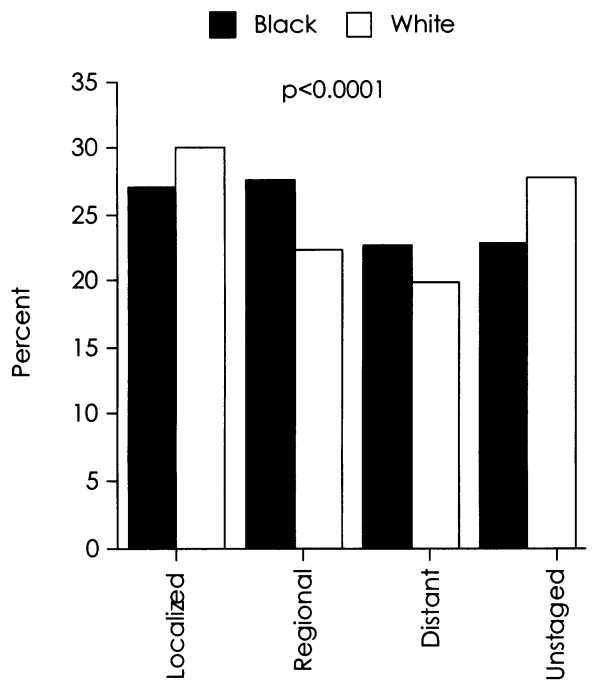
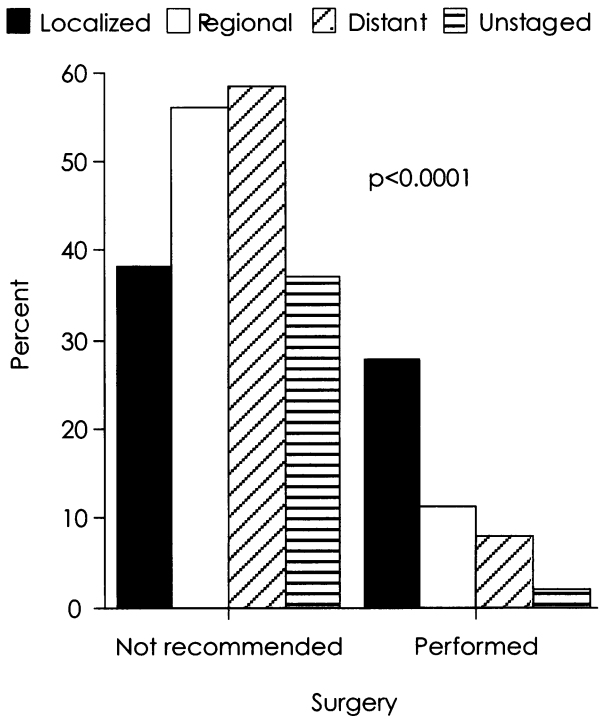


Figure 3. Surgical treatment by HCC stage



Conversely, surgery was performed more often for patients with localized HCC and less often for patients with regional, distant and unstaged HCC. There were also significant differences in other surgical intervention categories based on HCC stage. Cases with distant spread had contraindications more often than cases with localized and regional spread, whereas the unstaged cases were less likely to have contraindications. Unstaged HCC cases tended to refuse surgical intervention more often and were more likely to be categorized as "intervention unknown" and "unknown–death certificate." There were no differences by stage in the percentage of cases classified as "surgery recommended but unknown if done."

There was also a significant difference in surgical treatment between black and white patients (p<0.0001). Assuming race and surgery were independent variables, 795 blacks were expected to have "surgery not recommended," and 223 were expected to have "surgery performed." The observed numbers were 898 and 160, respectively. A similar percentage of blacks and whites were classified as: surgery contraindicated (7.4% vs. 6.6%); surgery refused (1.6% vs. 1.5%); surgery recommended, with unknown outcome (0.5% each); unknown intervention (26.3% vs. 27.5%); and, unknown–death certificate only (3.5% vs. 4.8%). Analysis of post hoc cell contributions indicated that the racial disparity explained the "surgery not recommended" and "surgery performed" categories. Thus, when the Chi-squared analysis was restricted to these two categories, black patients were still significantly more likely to have "surgery not recommended" and less likely to have "surgery performed" than white patients (p<0.0001). A comparison of the proportions of "surgery not recommended" and "surgery performed" by race and HCC stage showed racial differences only in localized (p=0.001) and regional (p=0.012) HCC cases (Figure 4). blacks with localized (Figure 4A) and regional (Figure 4B) spread were more likely to have "surgery not recommended" and, subsequently, were less likely to have surgery performed. There were no differences in surgical intervention between black and white cases with distant (Figure 4C) and unstaged (Figure 4A) disease.

Black cases had significantly lower overall survival (p=0.0033) (Figure 5A). Survival among black male cases was significantly lower than for white male cases (p=0.02). There was no difference in survival between black and white female HCC cases. When compared by age category, the racial disparity in survival was statistically significant only for ages 20–45 (p<0.0001) and 46–69 (p=0.0012) years. Survival in both races was also related to HCC stage, with the longest survival in localized HCC cases followed by regional, distant and unstaged cases (p<0.0001) (Figure 5B). Comparison of survival by race and tumor stage demonstrated significantly lower survival in blacks compared with whites with localized HCC (p=0.003; Figure 6A); there was no

difference in survival between black and white cases with regional (Figure 6B), distant (Figure 6C) and unstaged HCC (Figure 6D). Survival among black HCC cases was lower [p=0.002; 95% hazard ratio confidence interval (CI) 1.041–1.20] after adjusting for age, gender, tumor stage and surgical treatment intervention using Cox regression analysis.

DISCUSSION

Black HCC cases in our study tended to be younger and to have more advanced tumor stage. In addition, black cases were less likely to have surgery recommended and, consequently, less likely to have surgery performed. However, the lower surgical and patient survival rates among black patients were not explained solely by racial differences in tumor stage.

Previous studies have reported more-advanced tumor stages and lower rates of surgery with curative intent in black Americans with colorectal, breast, lung and head/neck cancers relative to white Americans.[6,8-10] In an analysis of SEER data from 1973–1998, Shavers and Brown found lower five-year survival rates for African Americans than for whites for all the major cancer sites.[9] In addition, their study revealed racial disparities in cancer treatment, including treatment with primary and adjuvant chemotherapy, as well as surgery with curative intent. Our study found similar disparities between black and white HCC patients in tumor stage at presentation, surgical treatment and survival.

The more advanced HCC stage at diagnosis may certainly account for the lower rate of surgical treatment with curative intent and for lower survival in black patients. A clinical decision against either surgical resection or liver transplantation is appropriate for many patients with localized HCC and all patients with regional and distant HCC. However, several findings in the current study suggest that the racial disparities in surgical treatment and patient survival are not completely explained by differences in tumor stage at diagnosis. First, the most striking disparities in surgical treatment and survival were found in patients with HCC localized to the liver. Providers tended to recommend against surgery more often—and surgery was thus performed less often—in blacks with localized and regional HCC spread. In addition, blacks with localized HCC had a significantly lower overall survival time. Patients of both races who had surgery had significantly longer survival than patients for whom surgery was not recommended. Yet, among the patients who survived, black patients were recommended for surgical therapy 50% less often than their white counterparts.

Issues of socioeconomic disparity and racial differences in access to care may certainly play a role in these observations. However, SEER does not contain data pertaining to income or insurance status. Other investigators have identified racial inequities in access to care, average

Figure 4. Surgical intervention by stage

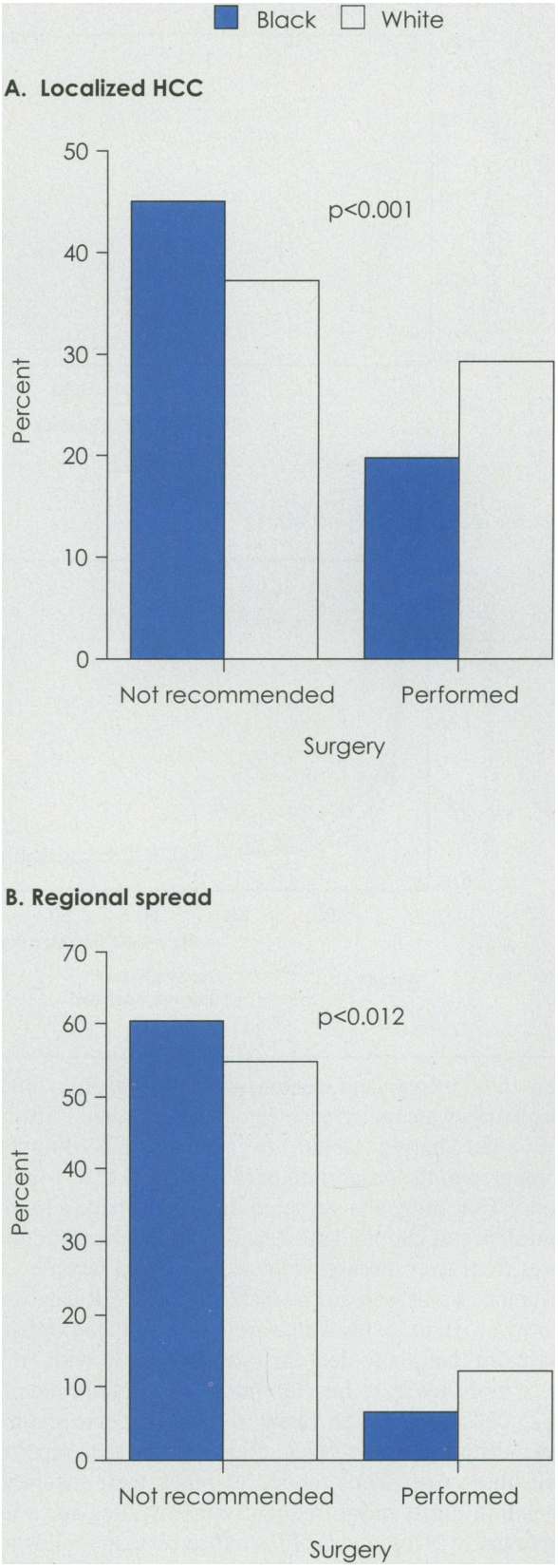
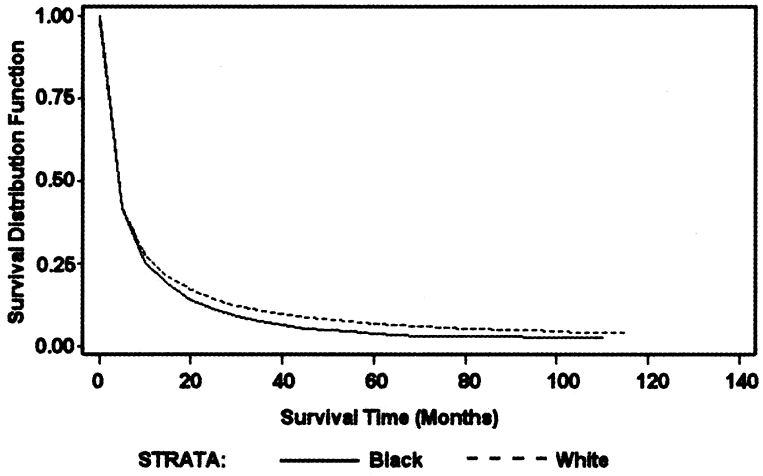
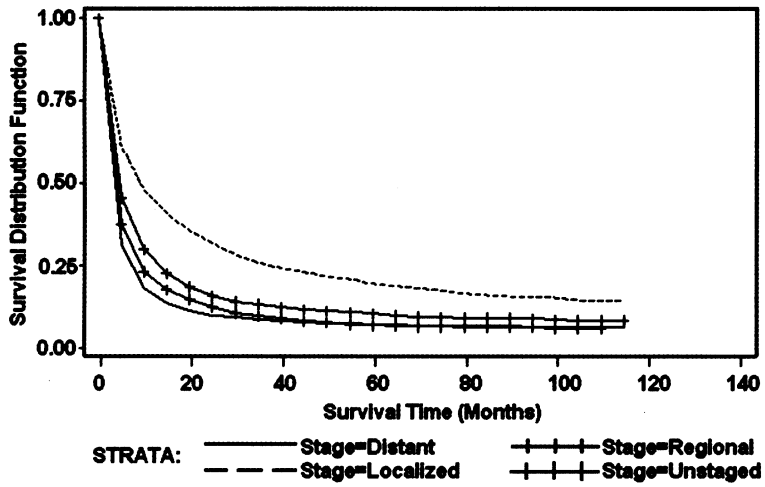


Figure 5. Patient survival

A. By race (p=0.0033)



B. By HCC stage (p<0.0001)



household income and insurance status. Reid et al. found that blacks were underrepresented on the United Network for Organ Sharing (UNOS) liver transplant waiting list, compared to the proportion of blacks in the U.S. population.[11] That study also revealed that blacks have a higher prevalence of chronic viral hepatitis and higher mortality rates from liver disease. Data on household income and insurance status were not available in the SEER database. However, Yu et al. used data from the 2000 Nationwide Inpatient Sample to demonstrate that blacks with HCC were more likely to have an annual household income <$25,000 and were less likely to have Medicare and private healthcare payers.[5] In addition, Guidry et al. reported that black Americans tended to reach their insurance spending limits more frequently than whites and were more likely to lose medical insurance coverage following a cancer diagnosis.[12] Thus, differences in healthcare payers between blacks and whites could contribute to unequal access to healthcare for HCC screening and treatment, and delayed referral for surgery.

This study has a few limitations. The SEER database includes only certain geographic regions. Thus, this cohort might not be completely representative of national black and white HCC cases. Second, decisions concerning surgical treatment for HCC localized to the liver typically take into consideration the size of the tumor, the number of tumor nodules and the distribution of HCC inside the liver. Thus, the broader criteria for localized tumor stage used by the SEER program could obscure potential differences in staging that would have been identified using more conventional criteria, such as the TMN, Milan or Okuda system. Third, because SEER includes all-cause mortality, it is not possible to determine HCC-related deaths from other causes for mortality. Moreover, as previously mentioned, we were not able to examine other factors that might influence the tumor stage at presentation, such as racial differences in healthcare payers, health-seeking behavior and tumor behavior.

Given our findings of racial disparity in surgical treatment and survival for HCC patients, we suggest that future studies address the importance of healthcare system, healthcare provider and patient factors that lead to racial disparities in HCC treatment utilization.

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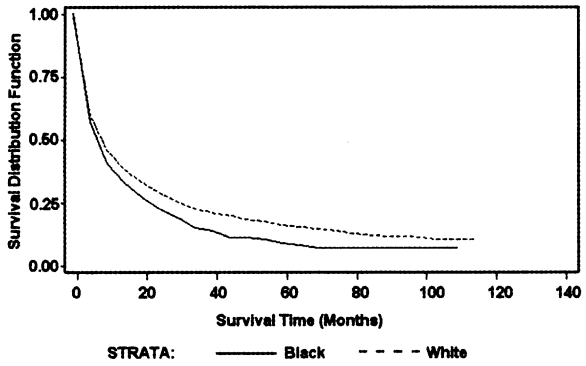
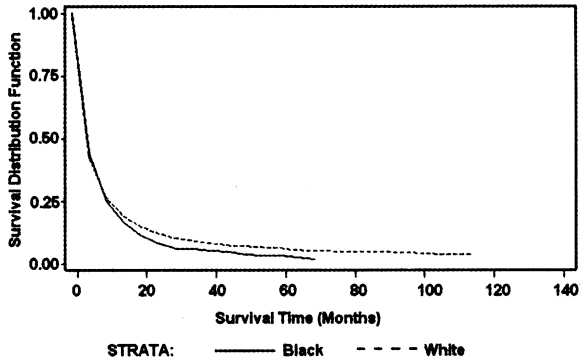
Figure 6. HCC survival by race and stage

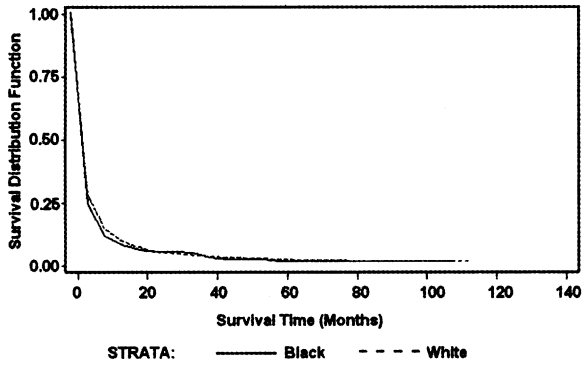
A. By race and localized stage (p=0.2321)



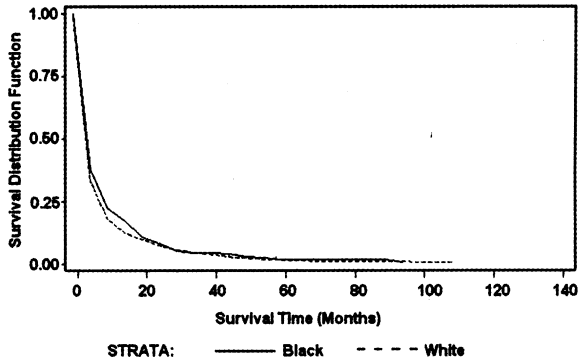
B. By race and regional stage (p=0.0030)



C. By race and distant stage (p=0.1922)



D. By race and unstaged disease (p=0.2452)



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