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Incidence and Survival of Oral Tongue Cancers among Adult Women in the US; 1973-2010

By

Lindsay J. Joseph
Master of Public Health
in
Global Epidemiology

Michael Goodman, MD, MPH
Committee Chair

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Lindsay J. Joseph

B.A., Brown University, 2009

Faculty Thesis Advisor: Michael Goodman, MD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2014

Abstract

Incidence and Survival of Oral Tongue Cancers among Adult Women in the US; 1973-2010

Lindsay J. Joseph, MPH candidate

Background: The incidence of oral tongue cancer (OTC) in the United States is reported to be increasing in women. To better understand this phenomenon, we sought to examine the time trends and racial disparities in incidence and survival in this population.

Methods: We identified 6,199 women diagnosed with OTC who were reported to the Surveillance, Epidemiology and End Results (SEER) Program from 1973 to 2010. Cases were categorized by age, race, year of diagnosis and residential setting. The incidence rates were compared across various demographic categories by calculating rate ratios (RRs) with the corresponding 95% confidence intervals (CIs). We also examined temporal variations in incidence of OTC across racial groups using joinpoint analyses to evaluate changes since 1973. Racial differences in survival were examined using Cox regression models after controlling for age, stage, and type of treatment received.

Results: OTC incidence in white females demonstrated a statistically significant increase with 0.53 annual percentage change (APC) between 1973 and 2010. For African-American (AA) females, on the other hand, the incidence has decreased by -2.79 APC since 1973. Overall incidence was higher among white women (1.30 cases per 100,000/year) compared to AA women (0.67 cases per 100,000/year). Survival of AA women was significantly lower than that among white OTC patients. The racial disparity in survival was less pronounced after controlling for age, stage, and treatment. Other significant predictors of poor survival were advanced age and stage. Better survival was associated with tumor directed surgery, and radical removal and examination of neck lymph nodes, but not radiation therapy.

Conclusions: The increase in OTC incidence among women over the last four decades is limited to whites. Identifying the demographic characteristics of this group may lead to a better understanding of the causes behind this increase. The racial disparity in survival is pronounced, but appears to be explained in large part by differences in stage at diagnosis, and receipt of care.

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INTRODUCTION

Each year about 11 out of 100,000 adults are diagnosed with cancer of the oral cavity **[1]**. The category of ”oral cancers” includes malignant tumors of the vermilion, and the internal mucosa-lined surfaces of the lips, cheeks gums, floor of the mouth and the palate , as well as the front two-thirds of the tongue **[2]**. Over 90 percent of these cancers are squamous cell carcinomas **[2, 3, 4]**. According to the National Cancer Institute (NCI), cancers of the oral cavity and pharynx rank 8th out of the top 17 cancers for males and 14th out of the top 18 cancers in females **[2,5]**. Oral cavity cancers are more commonly found in males with an incidence rate of 16.06 per 100,000 as compared to a rate of 6.16 per 100,000 for females **[6]**.

The known risk factors for oral cavity cancers include consumption of all forms of tobacco, excessive alcohol drinking and human papilloma virus (HPV) infections. In the United States the overall incidence of oral cavity cancers has been declining due largely in part to the success of national smoking cessation programs **[7]**. However, more recent data from the Surveillance Epidemiology and End Results (SEER) program suggest that this trend in declining incidence is reversed in some population groups. In particular, incidence of malignant tumors of the anterior tongue, termed oral tongue cancers (OTC) has increased over the past three decades among women **[3, 8-10].** From 1975 to 2007, incidence of OTC in women has increased by 16.8% (annual percent change: +0.6; p-value <0.05) **[11]**.

Previous population based studies evaluating gender-specific trends in incidence and survival of tongue cancers in the US focused primarily on comparisons between men and women. These studies often included OTC together with cancers originating in the base of tongue and the tonsils, which represent a very different group of malignancies with respect to both etiology and prognosis. Several studies have examined possible rural-urban disparities and stage at diagnosis, but the findings have been mixed **[12-15]**. However, little has been done to examine the association between residential settings and specifically OTC incidence or prognosis in women. With these knowledge gaps in mind, the objective of the current study was to analyze the 1973–2010 SEER data to explore trends in OTC rates among women and to examine demographic characteristics and determinants of survival in this patient population.

METHODS

The study was exempt from review by the Emory Institutional Review Board. We are conducting a secondary analysis of an existing de-identified dataset.

Study subjects

We obtained information on newly diagnosed OTC cases among women reported to the SEER program between 1973 and 2010. The SEER program collects data from 18 population-based cancer registries that account for approximately 26% of the US population. For this analysis, we selected all squamous cell carcinoma cases that were diagnosed among women during the study period and had International Classification of Disease-Oncology (ICD-O) primary site codes of 'C02.0-Dorsal surface of tongue, NOS', 'C02.1-Border of tongue','C02.2-Ventral surface of tongue, NOS','C02.3-Anterior 2/3 of tongue, NOS', and 'C02.8-Overlapping lesion of tongue.' Cancers of the base of tongue and lingual tonsil were excluded because they belong in the etiologically and prognostically distinct group of oropharyngeal malignancies.

Our primary independent variable of interest, race/ethnicity, was categorized into three groups “African-American (AA)”, “White”, and “Other”; with the last category comprised of American Indians/Alaska Natives and Asians/Pacific Islanders. Residential settings, the secondary exposure variable of interest, were categorized using the 2003 Rural-Urban Continuum Codes developed by the United States Department of Agriculture. Rural-Urban Continuum Codes are a classification tool used to distinguish metropolitan counties based on population size and nonmetropolitan (urban and rural) counties by adjacency to metro areas and degree of urbanization **[16,17]**. Cases were grouped according to county RUCC values 1 to 3, 4 to 6, and 7 to 9 for metropolitan, urban and rural settings respectively.

Each eligible case was further categorized according to disease stage at diagnosis, age, marital status, and type of surgical and radiation treatment received. In SEER, all variables refer to the patients' status at the time of diagnosis.

Statistical analysis

Descriptive data analyses were performed using SEER*Stat software version 8.1.2, and Joinpoint Regression Program version 4.0.4 (both available from NCI, Bethesda, MD). Multivariable analyses were carried out using SAS statistical software 9.3 (Cary, North Carolina). The cut-point for statistical significance was a two-sided alpha error of 0.05 for all analyses.

We estimated incidence rates (IR) as the number of new cases per 100,000 person-years; rates were age-adjusted to the 2000 US standard population. The rates among whites were compared to those in AA and in persons of other racial groups, which included primarily Asians/Pacific Islanders (A/PI) but also a few American Indians/Alaska Natives (AI/AN). The comparisons were carried out by calculating crude and age-adjusted rate ratios (RRs) and the corresponding 95% confidence intervals (CIs) as described by Tiwari et al **[18]**. To assess trends over time, we calculated the annual percent change (APC) for the period 1973-2010 for each racial group by fitting a weighted least-squares regression line to the natural logarithm of the rates where the regressor variable was the calendar year **[8,19]**.

The survival of OTC patients was analyzed using several methods with a total follow up extended to 10 years (120 months) post-diagnosis. First, we calculated relative survival (RS), which is obtained by dividing observed overall survival among cancer patients by the expected survival in the general population with the same age, race, and gender characteristics. The one-, three-, five- and ten-year RS estimates and were calculated separately by race. These survival calculations were based on the actuarial life table method. Following RS calculations, we constructed Kaplan-Meier curves with corresponding log-rank tests for statistical significance to examine patient survival according to race and type of residence. In addition, we used multivariable Cox proportional hazards models to examine the association between survival and race while controlling for age, residence type, stage, marital status and treatment received. Treatment was characterized using three binary (yes. vs. no) variables reflecting receipt of radical surgery of primary site, radiation, and neck dissection. The results of multivariable survival analyses were expressed as adjusted hazard ratios (HRs) and reported along with the corresponding 95% CIs. Proportional hazard assumptions were tested by examining log minus log plots for each variable in the model **[20]**. In addition, all models were examined for interactions and co linearity among covariates.

RESULTS

A total of 6,199 cases were reported to SEER between 1973 and 2010. However, patients diagnosed prior to 1987 were excluded from the survival analysis due to unknown and otherwise ambiguous reporting for prior therapies and surgical procedures including lymph node dissection. Additionally, our inclusion criteria for survival analysis omitted all cases with death certificate only, autopsy only and cases that were alive with no survival time. After exclusions, 3443 cases were considered for survival analysis. At the time of diagnosis, 80.0% of those cases (N=2,755) were over 50 years of age. As shown in Table 1, 89.8% (N=3,086) of the total cases reside in metro areas while 9.2% (N=316) and 1.1% (N=36) of cases were from urban and rural areas, respectively. The total study group consisted of 2,873 (83.4%) white females, 183 (5.3%) AA females and 387 (11.2%) were American Indians/Alaska Natives (AI/AN) or Asians/Pacific Islanders (A/PI). Just under one-half of the patients were married (47.5%; N=1,636) approximately one-third (30.5%) were diagnosed with localized or regional disease.

Incidence Rates

Incidence rates were highest among women residing in metropolitan areas (IR=1.26), followed by women in urban areas (IR=1.16), then women in rural areas (IR=1.03), but the differences across residential settings were not statistically significant. With respect to race, incidence rates were highest among whites, followed closely by AI/AN & A/PI and lowest among AA women with IR estimates of 1.30, 1.29 and 0.67, respectively. Only the difference between white and AA women was statistically significant (RR=0.52; 95% CI: 0.44, 0.61).

Overall, white females have demonstrated a statistically significant increase with 0.53 annual percentage change (APC) between 1973 and 2010. Conversely, for AA females, the incidence has decreased significantly by -2.79 APC since 1973. The APC for the AI/AN & A/PI females decreased by -0.21 APC, however, the decrease was not statistically significant. As shown by the joinpoint regression analysis, (Figure 1a), the decrease in incidence for AA women was particularly pronounced prior to 2000 (APC= -3.18; 95% CI: -5.0, -1.3). As shown in Figure 1b, the trend among white women has been increasing since the early 1990s (APC= 1.13; 95% CI: 0.4, 1.8). The trend for AI/AN & A/PI women, as shown in Figure 1c, revealed no significant changes over time.

Survival Analysis

The 1-, 3-, 5- and 10-year RS estimates for all women with OTC were 85%, 67%, 63% and 53%, respectively. When stratified on race, as shown in Table 3, the corresponding 1-, 3-, 5- and 10-year RS estimates were 86%, 68%, 63% and 54% for white women, 76%, 50%, 46% and 33% for AA women, and 85%, 69%, 66%, and 62% for AI/AN & A/PI women.

The Kaplan-Meier curves in Figure 2 show that survival was significantly different across the 3 racial groups (log-rank p-value <0.001) –lowest among AA and highest among AI/AN & A/PI women. Similar Kaplan-Meier survival curves by residential setting in Figure 4 demonstrated no statistically significant difference (log-rank p-value = 0.76).

While performing Cox proportional hazards models to assess the association between survival and race and other covariates, it was determined that two variables, race and Rural-Urban Continuum Codes, did not meet the proportional hazards assumption. In order to keep race in the model and because there was no discernable difference between white and AI/AN & A/PI women, race was recoded into a dichotomous variable whereby whites and AI/AN & A/PI were included into a single category. The race variable in the final Cox model was categorized as AA vs. non-AA. The model was stratified on RUCC to account for PH assumption violation, and for this reason the HR estimate for type of residency is not reported.

The results from the multivariable survival analysis are shown in Table 4. AA women experienced higher mortality than “non-AA” women (HR= 1. 22; 95% CI: 0.99, 1.49). Women ages 70 and older as well as women with advanced or “distant” disease experienced significantly higher mortality with HR (95% CI) estimates of 2.76 (2.35, 3.24) and 2.91 (2.44, 3.47), respectively). Married women experienced lower mortality than their single and unmarried counterparts (HR= 0.75; 95% CI: 0.67, 0.84). With respect to treatment received, surgery of the primary site reduced mortality significantly by approximately 35% (HR= 0.65; 95% CI: 0.58, 0.74) while radical regional lymph node dissection (excluding biopsy or aspiration only) reduced mortality by approximately 23% (HR= 0.77; 95% CI: 0.67, 0.89). In contrast, cases that underwent radiation therapy experienced higher mortality (HR= 1.47; 95% CI: 1.30, 1.65).

DISCUSSION

In this study, we analyzed oral tongue cancer incidence among women by race and residential settings. Despite the overall decrease in oral cavity squamous cell carcinoma incidence in the US over the past 30 years, our study demonstrates an upward trend for OTC in women. This increase however appeared to be limited to whites.

There were no significant differences in incidence or survival across the metropolitan, urban and rural residential settings. On the other hand, the racial disparities were quite pronounced when AA women were compared to their counterparts in all other racial groups. While incidence of OTC in AA women was declining and on average was about one half of that in whites and A/PI or AI/AN, prognosis of AA OTC patients was clearly worse. This disparity in survival was attenuated, however, and after controlling for age, marital status and, likely most importantly, treatment and stage. As in previous studies, early stage diagnosis and surgical procedures (both radical tumor excisions and neck dissections) remained significant predictors of survival. Also consistent with previous reports receipt of radiotherapy in our data was associated with worse prognosis **[4,22]**. Generally, low survival rates are associated with late stage diagnoses, however, poor survival outcomes have even been documented even among stage I/II oral cancer patients **[21,22]**.

Similar to other recent population-based studies, we found that OTC rates were increasing more rapidly among white women than women of other races. Patel et al analyzed the SEER 9 Registry from 1975 to 2007 and observed decrease of squamous cell OTC incidence in men with a concurrent increase in incidence in women particularly those between 20 and years of age **[11]**. In a more recent study, Brown and colleagues reported that an increase in OTC incidence was limited to white women, ages 25-44 years. **[23]**. By employing joinpoint regression technique, we confirmed that OTC incidence was increasing only for white women, and also observed that this increase seemed to have accelerated since the 1990s.

Our findings of substantial disparities in survival by race are also in agreement with the previously published results for oral cancers using both national and state data**[24,25]**. It has been reported that AA oral cancer patients in general are more likely to be diagnosed with advanced stage; though many have found that the racial disparity in survival remained after controlling for stage at diagnosis **[21,24,25].** Our results confirm these findings specifically for OTC among women.

Low socioeconomic status coupled with residential area deprivation is believed to be a strong determinant of cancer incidence, stage at diagnosis, and patient survival **[14]**. However, our study did not reveal any significant differences in either incidence or overall survival by residential setting. This may indicate that the risk factors for OTC and the likelihood of survival following OTC diagnosis are distributed roughly evenly in metro urban and rural areas. The racial disparities in OTC incidence and prognosis may be related to differential distribution of and perhaps susceptibility to traditional risk factors in white and AA women **[26]**. As SEER registries do not collect information on known risk factors, further examination of the reasons for the observed disparities and time trends in OTC incidence would not be possible with these data. Similarly, racial disparities in survival, although partially explained by stage and treatment, remained statistically significant in the multivariable models indicating the need to examine other patient-, disease and provider-related factors.

The interpretation of our findings requires understanding of the strengths and limitations of the SEER data. As we previously noted elsewhere [**27-28**], the large sample size enables SEER-based studies to study even rare cancers, allows sufficient power for detecting relatively moderate associations, and permits a variety of multivariable analyses. The population-based, as opposed to institution-based, identification of cases increases the generalizability of findings and the active follow-up of cases improves the accuracy of survival analyses. While institutional studies often have more detailed information about each patient, those studies usually are confined to major referral centers and may not be representative of the cases treated in community hospitals and clinics.

The main limitations of this study pertain to the lack of data on certain important clinical and demographic variables. While SEER data on surgery and radiation are reasonably complete, the information pertaining to systemic treatment such as chemotherapy is usually missing and is not included the public use files **[28]**. In addition, SEER data do not contain information on such important predictors of survival as health insurance and socioeconomic status all of which may determine access to and utilization of health care. Another important data item that may need to be considered is the effect of provider- and facility-related characteristics, which cannot be addressed in the context of SEER-based research, but may be critical determinants of diagnostic (including pathology) quality. For all of the above reasons, both cancer registry-based and institution-based studies provide useful non-overlapping information that contributes to the evidence despite their strengths and limitations **[28]**.

CONCLUSION

The findings of this analysis add to the earlier evidence that OTC incidence increased among women over the last four decades. It is notable that this increase is limited to whites, and has become particularly evident in the 1990s. These observations underscore the need for further research to identify which risk factors may explain the observed difference in incidence trends. The racial disparity in survival is quite pronounced, but may, in large part, be attributable to the differences in stage at diagnosis as well as access to and the receipt of care. Health interventions promoting early detection through routine oral screening exams, primarily targeting high risk populations and women with limited access to medical care services may help reduce the disparities in OTC prognosis.

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TABLES

Table 1: Selected Characteristics of Tongue Cancer Cases included in the Survival analyses: SEER 1988-2010

Case Characteristics	All Cases (n=3,443)	
	N	%
RUCC[1]		
Metro	3,086	89.8%
Urban	316	9.2%
Rural	36	1.1%
Age at Diagnosis		
30-49	688	20.0%
50-69	1,462	42.5%
70+	1,293	37.5%
Race		
White	2,873	83.4%
AA	183	5.3%
Other[2]	387	11.3%
Marital Status		
Married	1,636	47.5%
Single	456	13.2%
Divorced/Separated/Widowed	1,193	34.7%
Unknown	158	4.6%
SEER Historic Stage		
Localized/Regional	1,889	30.5%
Distant	180	2.9%
Unstaged	378	6.1%

[1] Using 2003 Rural-Urban Continuum Codes
[2] American Indian/Alaska Native or Asian/Pacific Islander

Table 2: Incidence of tongue cancers by race and residential settings: SEER 1973-2010

	Incidence Rate[1]	RR	95% CI Lower	95% CI Upper
RUCC[2]				
Metro	1.26	1.00	Reference	
Urban	1.16	0.92	0.83	1.03
Rural	1.03	0.81	0.58	1.12
Race				
White	1.30	1.00	Reference	
AA	0.67	0.52	0.44	0.61
Other[3]	1.29	1.00	0.88	1.13

[1] Per 100,000 and age adjusted to 2000 US-Standard Population
[2] Using 2003 Rural-Urban Continuum Codes
[3] This category includes Asians/Pacific Islanders (A/PI), and American Indians/Alaska Natives (AI/AN)

Table 3: Relative Survival of tongue cancer cases by race

Time post-diagnosis	Whites (n=2,873)			African-Americans (n=183)			Other* (n=387)		
	RS	95% CI		RS	95% CI		RS	95% CI	
1 year	85.5%	84.2%	86.6%	76.3%	70.3%	81.3%	84.5%	80.6%	87.7%
3 years	68.3%	66.6%	70.0%	50.2%	43.2%	56.7%	68.7%	63.7%	73.1%
5 years	63.4%	61.5%	65.2%	46.0%	38.8%	52.9%	66.3%	61.0%	71.1%
10 years	53.5%	51.0%	55.9%	33.2%	25.3%	41.3%	61.9%	55.1%	68.0%

* This category includes Asians/Pacific Islanders (A/PI), and American Indians/Alaska Natives (AI/AN)

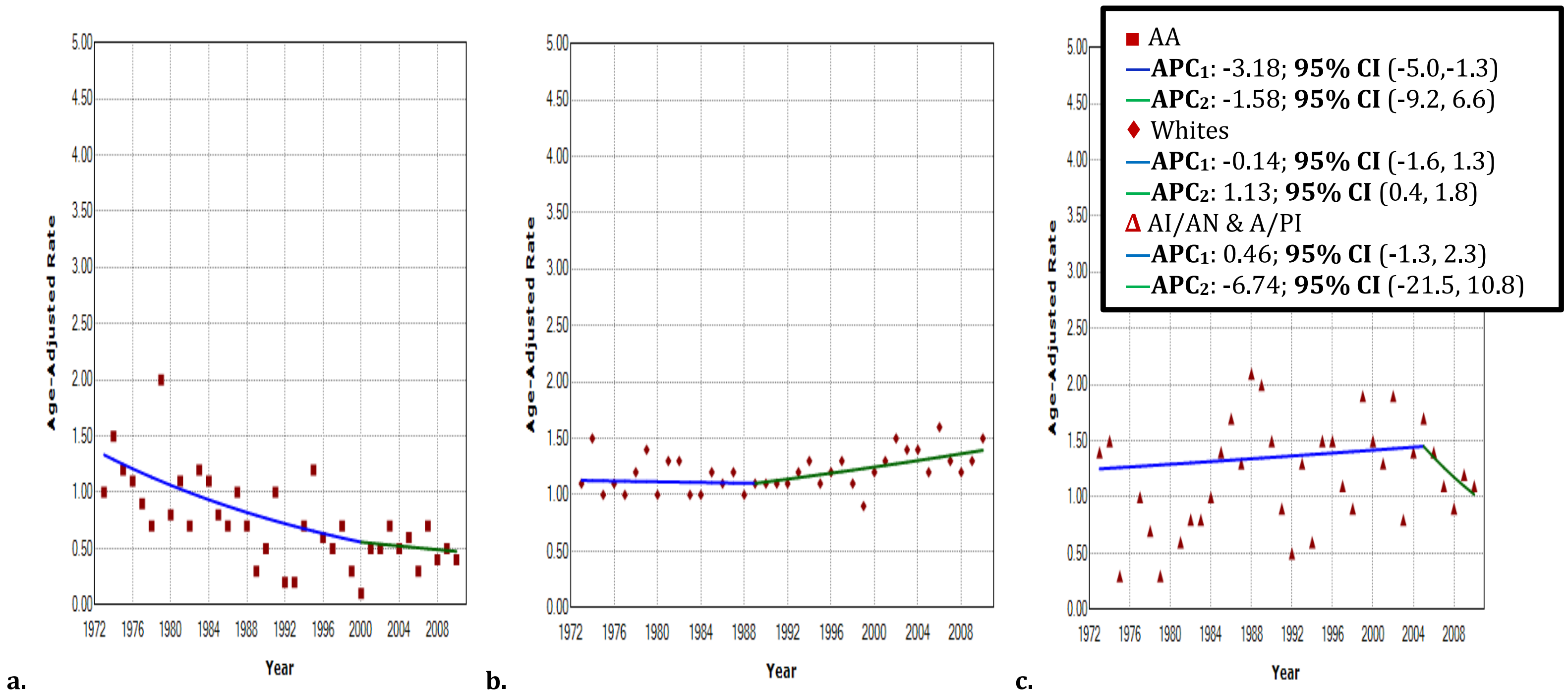
Table 4: Cox Regression Analyses for Race, Residence, Stage, Age, Marital Status and Treatment

	Hazard Ratio	95% CI Lower	Upper
Race			
Non-AA[1]	1.00	Referent	
AA	1.22	0.99	1.49
Marital Status			
Not Married	1.00	Referent	
Married	0.75	0.67	0.84
Age, y			
30-49	1.00	Referent	
50-69	1.48	1.25	1.74
70+	2.76	2.35	3.24
SEER Historic Stage A			
Localized	1.00	Referent	
Regional	2.51	2.21	2.86
Distant	2.91	2.44	3.47
Surgery			
No	1.00	Referent	
Yes	0.65	0.58	0.74
Lymph node dissection			
No	1.00	Referent	
Yes	0.77	0.67	0.89
Radiotherapy			
No	1.00	Referent	
Yes	1.46	1.30	1.65

[1] Non-AA category consists of whites, American Indians/Alaska Natives and Asians/Pacific Islanders

FIGURES

Figure 1: Joinpoint analyses: Annual Percent Change for African-American (AA), White and AI/AN & A/PI females



Note: In Figure 1c, APC for the year 1976 could not be calculated as the incidence rate was zero among this racial group.

Figure 2. Kaplan-Meier Curves by Race

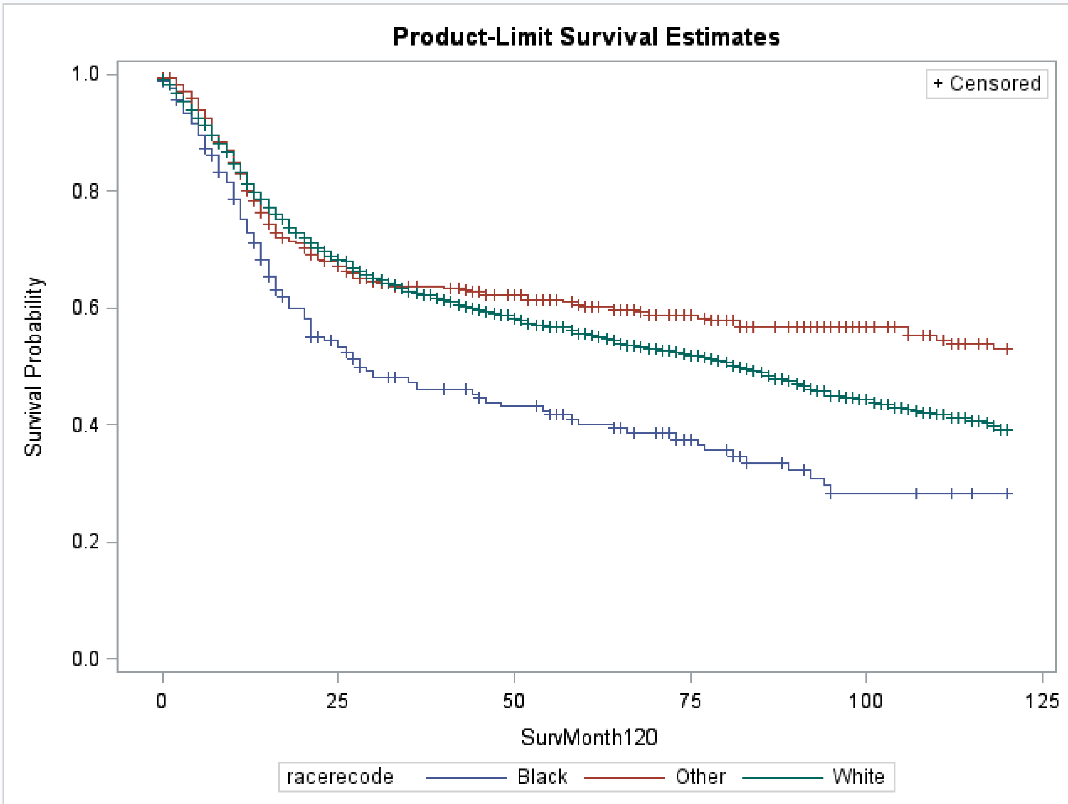


Figure 3. Kaplan-Meier Curves by Residential Setting