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Is There Racial/Ethnic Variance in Cervical Cancer-Specific Survival of Older Women in the United States?

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Abstract

Purpose: To examine racial/ethnic differences in cervical carcinoma survival of older US women, as well as the impact of income, cell type (tumor histology), tumor stage and treatment on survival of this cohort.

Methods: A population-based cohort of women diagnosed with incident cervical carcinoma, between 1992 and 1999, in the Surveillance Epidemiology and End Results (SEER) Data was linked with Medicare to examine the impact of race/ethnicity on overall and cancer-specific survival, using Kaplan Meier survival estimates and multivariable Cox Regression model.

Results: There was no significant racial/ethnic variation in overall and cervical cancer-specific survival. However, the advanced tumor stage at diagnosis, treatment received and advanced age at tumor diagnosis were the only significant predictors of survival. Compared with no surgery, there was a significant 66% decreased risk of dying from overall cause of death (adjusted hazard ratio, AHR = 0.34, 95% Confidence Interval, CI = 0.26-0.46), and significant 51% decreased risk of dying from cervical cancer-specific cause, AHR = 0.41, 95% CI, 0.28-0.58, for women who received radical surgery. There was a dose-response effect between tumor stage at diagnosis and survival. Relative to women who were diagnosed with stage I tumor (early stage), those who were diagnosed at stage IV (late stage) were almost three times as likely to die from overall cause (AHR = 2.78, 95% CI, 2.24 – 3.45), as well as two times as likely to die from cancer-specific cause, AHR = 2.28, 95% CI, 1.76 – 2.29. The risk of dying also significantly increased with advancing age.

Conclusion: There was no racial/ethnic variance in overall and cervical cancer-specific survival among older US women but survival was significantly influenced by treatment received tumor stage at diagnosis and age at diagnosis.

Keywords: Cervical carcinoma; Race/ethnicity; Income; Histopathology; Survival.

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Introduction

In the United States, cervical carcinoma remains an important public health problem despite decline in incidence and mortality in recent years due to the introduction of Papanicoloau (Pap) testing [1]. It accounts for an estimated 2.0% of cancer incidence and 1.6% cancer mortality among women in the United States [2]. Worldwide, there is a variation in the incidence and survival, with nearly 80% cases estimated to occur in developing countries [3], and a five year survival is highest in the low risk nations [4]. The incidence and mortality vary with race; with African Americans having the higher incidence compared with Caucasians (9.2 per 100,000 versus 12.4 per 100,000) [5]. Caucasian women experience a gradual decline in incidence after age 45, while African American women show increasing incidence throughout their lifespan [6]. In addition, African Americans are less likely to be diagnosed with cervical carcinoma at a local stage compared to a regional or distant stage, and are more likely to be classified in unknown stage [7]. There is racial variation in cervical cancer mortality albeit the decline, which has been attributed to a decline among African Americans, 50 years and older [6]. However, mortality is more than two times higher in African American women compared with Caucasians (5.9 versus 2.7 per 100,000) [5].

Racial and/or socioeconomic disparity has been suggested for cervical cancer survival. Higher mortality has been associated with lower income (indicating lower socio-economic status, SES), and among women diagnosed with stage I tumor, less than 20% have lower education attainment [6,8,9,10]. Racial/ethnic disparities in cervical carcinoma have been observed for decades among United States women.

The factors accounting for incidence and survival appear to be preventable, mainly late stage cancer diagnosis, economically and socially distressed environment such as substandard housing, lower education attainment, subsistence–level employment, high unemployment, greater exposure to environmental toxin, and reduced access to health care. Overall, these conditions may affect survival from cervical cancer.

We aimed in this current study to examine the relationship between race/ethnicity and cervical cancer survival in older women, age 65 years and older, as well as to assess the impact of tumor prognostic factors on the survival of this cohort. We hypothesized that there is racial/ethnic variation in cervical cancer survival, and that tumor prognostic factors namely histology, stage and treatment are significant determinants of overall and cancer-specific survival in this cohort.

Methods

After an Institutional Review Board approval from relevant institutions, we performed a retrospective cohort study, utilizing time-to-an-event analysis to determine racial/ethnic variance in overall and cervical cancer-specific survival in older US women diagnosed with cervical carcinoma, as well as to examine the effect of prognostic factors of survival.

Study population

The study subjects were women (n=1,426) diagnosed with incident cervical neoplasm between 1992 and 1999 and followed up for 10 years. Participants were 65 years and older, and were of the main racial/ethnic groups in the US: (a) Caucasians (n=977, (68.51%), (b) African Americans (n=293, 16.76%), (c) Hispanics (n=50, 3.51%) and (d) others who are mainly Asian Americans (n=160, 11.22%).

Data source

The Surveillance Epidemiology End Result (SEER)-Medicare linked data were used to examine the hypotheses in this study. These dataset represents an estimated 14% of the

total US population, and are considered a representative sample for community-based cancer study. These data sources are described elsewhere [12].

Variable ascertainment

The following variables were examined:

Outcome variable: This is the time (in months) from diagnosis until death from any cause, including cervical cancer. A 10 year survival analysis was based on 10-year follow-up [13].

Race/ethnicity and age: Race/ethnicity referred to the major racial/ethnic groups of the women in the United States namely Caucasians, African Americans, Hispanics and others (American Indian/Alaskan Native and Asian/Pacific Islander) in the United States. The age (years) at diagnosis was categorized into 65-69 (reference group), 70-74, 75-79 and 80-102.

Income: This was used as the proxy for socioeconomic status and was based on the 1999 census tract level annual household income in US dollars. The income status was further categorized into quartiles, with the 1st quartile representing the lowest economic level or lowest socioeconomic status (SES), while the 4th quartile represented the highest quartile (wealthiest SES group).

Histology: The cervical cancer cell types were classified as epithelial cell, squamous cell, adenoma and others (adenosquamous, adenocarcinoma), with the majority being squamous cell carcinoma.

Tumor stage: This was classified as stages I to IV, with stage I identified as localized and well differentiated, while stage IV was distant and poorly differentiated.

Treatment: Surgical intervention following diagnosis was classified as: (a) no surgery, (b) biopsy, (c) less extensive surgery and, (d) radical surgery.

Vital status and causes of death: Individuals in the study group were described as alive or dead. Death from all causes other than cervical cancer and death from cervical cancer only were classified as failure [13].

Data analysis

Chi square test was used to examine the association between race and the distribution of the other socio-demographic (age at diagnosis, income) and clinicopathalogic parameters (eg. tumor stage, histologic cell type, treatment received). Fisher's exact test was used when small numbers were encountered in the contingency tables, for instance, the expected frequency of any cell less than two [14]. Race and overall/cancer-specific survival were analyzed using Kaplan Meier Survival estimates. The log-rank test was used to test the equality of survival by race/ethnicity, income and cell type and the proportionality assumption was checked [13]. Multivariable analyses based on Cox Proportional Hazards regression model was used to examine the effect of the various covariates on survival. Finally, analyses were adjusted for race, using covariates of age, tumor stage, histology, income and treatment that were statistically or biologically significant in the Cox Regression Univariable model. All tests were two tailed and the significance level was less than 0.05. All analyses were performed using Stata Statistical package, version 10.0 (StataCorp, College Station, TX 77845).

Results

Table 1 presents the distribution of demographic variables, treatment type and tumor histology by race/ethnicity. African Americans and Caucasians did not significantly differ by age (χ^2=12.20, df=9, ρ=0.20). African Americans were more likely to be in the lowest quartile of income level

compared to Caucasians (56.49% versus 18.63%), and less likely to be in the highest income quartile (5.02% versus 29.27%). Compared with Caucasian women, African American women were more likely to receive no surgery following diagnosis (12.97% versus 8.29%), but less likely to receive radical surgery (21.34% versus 27.53%). There was no significant difference in the tumor cell type by race/ethnicity. However, compared to Caucasian women, African American women were slightly more likely to present with squamous cell type at diagnosis, 10.4% versus 7.78%, while Caucasian women were slightly more likely to present with adenomas at diagnosis (18.22% versus 15.48%). Table 1 also presents the distribution of tumor stage at diagnosis, vital status and causes of death by race. There was no significant difference in the distribution of tumor stage by race/ethnicity (χ^2 = 17.90, df=12, ρ=0.11). Compared to Caucasians, African Americans were more likely to die from cervical cancer (43.93% versus 41.76%).

Overall survival

In the univariate Cox regression model (not shown on table), there were no significant racial/ethnic differences in the ten-year all cause survival. Compared to Caucasians, African Americans and Hispanics had 12% unadjusted Hazard ratio (HR=0.88, 95% CI= 0.82-1.17), and 36% (HR=0.64, 95% CI= 0.43-0.95) reduction in all cause mortality, respectively. Income was a significant factor in all cause mortality and was directly proportional to survival. Thus, women in the highest income level (highest quartile) had 23% reduction in mortality compared with the women in the lowest quartile (HR=0.77, 95% CI=0.64-0.93). Cervical cancer cell type was a significant factor in all cause mortality. Compared with the tumor located within the epithelia, there was a 56% reduction in all cause mortality (HR=0.44, 95% CI=0.35-0.55) associated with squamous cell tumor and 52% reduction in all cause mortality with adenoma (HR, 0.48, 95% CI=0.37-0.62).

Cancer-specific survival

The univariable Cox regression model for the ten-year cervical cancer-specific mortality showed an insignificant association between race/ethnicity and survival in women with cervical cancer. Compared with their Caucasian counterparts, African American women were 8% more likely to die from cervical cancer (HR=1.08, 95% CI=0.87-1.34) while Hispanic women showed a 31% insignificant increase in survival (HR=0.69, 95% CI=0.42-1.12). Survival was significantly associated with cervical cancer cell type. Relative to women diagnosed with epithelial cell cervical carcinoma, those diagnosed with squamous cell type had a significant 51% improvement in survival, (HR=0.49, 95% CI=0.36-0.66) while those with adenoma had a significant 37% improved survival (HR=0.63, 95% CI=0.45-0.89). Income level significantly influenced cervical cancer–specific survival. Compared with women diagnosed with cervical cancer in the lowest income quartile, women in the highest quartile experienced 30% increase in survival (HR=0.70, 95% CI=0.56-0.89). Age was inversely proportional to survivability among these participants. Compared with women in age group 65 to 69 years, women diagnosed with cervical cancer at age 80 years were three times as likely to experience mortality from cervical cancer (HR=3.35, 95% CI=2.66-4.23). There was a significant association between tumor stage and cervical cancer–specific survival. Compared with stage I (well differentiated) women with stage IV (poorly differentiated) were four times as likely to die from cervical cancer (HR-3.90, 95% CI=3.06-4.94, data not shown).

Overall/all-cause survival – adjusted model

Table 2 presents Cox regression in the multivariable model. This model simultaneously adjusted for all the biologically and statistically significant variables. There was no significant difference in survival with

Table 1: Study size and demographic Information by race/ethnicity

Covariates	Caucasians (n, %)	African Americans (n, %)	Hispanics (n, %)	Others (n, %)	χ^2, df, ρ value
Sample size	977 (68.51)	293 (16.76)	50 (3.51)	160 (11.22)	
Age (yr)					12.20, 9, 0.203
65-69	257 (26.31)	62(25.94)	20(40.0)	41(25.62)	
70-74	247(25.28)	44(18.41)	10 (20.00)	42 (26.26)	
75-79	213 (21.80)	55 (23.01)	7 (14.00)	35 (21.88)	
80+	260 (26.61)	78 (32.64)	13 (26.00)	42 (26.25)	
Income (Quartile)					192.20, 9, 0.001
1st (Lowest)	182 (18.63)	135 (56.49)	15 (30.0)	25 (15.63)	
2nd (50th percentile)	230 (23.54)	63 (26.36)	14 (28.00)	49(30.63)	
3rd (75th percentile)	279(28.56)	29(12.13)	14(28.00)	35(21.88)	
4th (Highest)	286 (29.27)	12 (5.02)	7 (14.00)	51(31.87)	
Treatment					27.06, 9, 0.001
No surgery	81 (8.29)	31(12.97)	0 (0.00)	7(4.38)	
Biopsy	490 (50.15)	124(51.88)	25(50.00)	90 (56.25)	
Less extensive surgery	137 (14.02)	33 (13.81)	4(8.00)	13 (8.13)	
Radical surgery	269 (27.53)	51(21.34)	21(42.00)	51(31.25)	
Histology					15.93, 9, 0.068
Epithelial	76 (7.78)	24(10.04)	2 (4.00)	10 (6.25)	
Squamous cells	631(64.59)	160(66.95)	37(74.00)	125(78.13)	
Adenomas	178(18.22)	37(15.48)	7(14.00)	16(10.00)	
Others	92 (9.42)	18(7.53)	4(8.00)	9(5.63)	
Tumor Stage					17.90, 12, 0.119
I	349(35.72)	84(35.15)	16(32.00)	45(28.13)	
II	175(17.91)	51(21.34)	14(28.00)	36(22.50)	
III	171(17.50)	33(13.81)	11(22.00)	38(23.75)	
IV	164(16.79)	41(17.15)	5(10.00)	18(11.25)	
Unknown	118(12.08)	30(12.55)	4(8.00)	23(14.37)	
Vital status					10.25, 3, 0.017
Alive	301(30.81)	81(33.89)	24(48.00)	63(39.38)	
Death	676(69.19)	158(66.11)	26(52.00)	97(60.62)	
Cause of death					12.63, 6, 0.049
Alive	301(30.81)	81(33.89)	24(48.00)	63(39.38)	
Death (overall causes)	268(27.43)	53(22.18)	9(18.00)	53(25.00)	
Cervical cancer death only	408(41.76)	105(43.93)	17(34.00)	57(35.63)	

respect to race/ethnicity. Also, there was no significant difference in all cause survival with respect to income and cervical cancer cell type. However, there was a statistically significant difference in survival with respect to histology, and squamous cell cervical tumor compared to epithelia cell type showed survival advantage (adjusted Hazard ratio, AHR=0.66, 95% CI=0.52-0.87). Age was statistically significantly associated with survival, and was inversely proportional. Thus compared to age group, 65 to 69, women age 80 years and older were two times as likely to die from all causes (AHR= 2.18, 95% CI=1.81-2.63). Likewise, survival was significantly associated with the type of treatment received. In this model, women receiving radical surgery compared to those

without treatment were 66% more likely to survive all cause mortality (AHR=0.34, 95% CI=0.26-0.46). The stage of the tumor at diagnosis was a significant predictor of survival from all cause mortality in women diagnosed with cervical cancer. Compared to stage one, women diagnosed at stage IV, experienced poorer survival, and were almost three times as likely to die (all-cause mortality, AHR=2.78, 95% CI=2.24-3.45).

Cancer-specific survival – adjusted model

In this model, after adjustment for all the covariates including age, the significant association between survival and income disappeared. Again, there was no significant racial/ethnic difference in cervical cancer-specific survival. Cancer cell type was not significantly associated with cervical cancer survival. But the type of treatment received was significantly related to cervical cancer survival. Therefore, compared to women who did not receive treatment following cancer diagnosis, women who received radical surgery, had 60% decreased risk of dying (AHR=0.41, 95% CI=0.28-0.58). Survival was significantly associated with the stage of tumor at diagnosis. Remarkably, there was a dose-response relationship, with the risk of dying directly proportional to the stage of tumor at diagnosis. Thus compared with women in stage 1, women diagnosed at stage II were 28%, and III were 61% more likely to die from cervical cancer (AHR=1.28, 95% CI=1.00-1.65), and (AHR=1.61, 95% CI=1.24-2.10), respectively; while women diagnosed with stage IV tumor were two times as likely to die from cervical cancer (AHR=2.28, 95% CI=1.75-2.97). Advanced age at diagnosis increased the risk of dying. Relative to the youngest age group (65-69 years), women 80 years and above were almost three times as likely to die from cervical cancer (AHR=2.78, 95% CI=2.19-3.54).

Figures 1 presents the unadjusted Kaplan Meier survival estimates for race/ethnicity. The curve indicates the crossing of hazards, indicating that the proportional hazard PH assumption was not met by race/ethnicity. This assumption states that the Hazard ratio is constant over time, meaning that the hazard for one individual is proportional to the hazard for any other individual, where the proportionality constant is dependent on time. The Hispanics demonstrated the best survival in the unadjusted survival estimate, while African Americans showed the worst survival, but this was not significant, log rank ($p > 0.05$). Figure 2 presents the survival function curve for race/ethnicity adjusted for income, histology, tumor stage at diagnosis, age at diagnosis, and treatment received, log rank ($p > 0.05$).

Discussion

Whereas racial/ethnic disparities have been shown in cancer survival, such remained to be shown in cervical cancer among community-based older women in the United States. There are some relevant findings from our study: (1) There was no racial/ethnic disparities in overall and cancer-specific survival of older women diagnosed with cervical cancer and treated for the disease, and (2) treatment received, tumor stage and age at diagnosis were the significant factors associated with survival. Remarkably, there was a dose-response relationship between survival and the age at tumor diagnosis.

Racial/ethnic and socioeconomic disparities have been suggested for cervical cancer survival [6,8,9,10]. Since tumor stage at diagnosis and treatment variation had been associated with survival differences [5,15,16], we explored the association between tumor stage and treatment and survival. We found that in both univariable and multivariable models used to examine these relationships, race/ethnicity was not significantly associated with survival in all cause and cervical cancer-specific. However, there was a significant association between income and cervical cancer cell type and survival, all cause and cervical cancer-specific, but these associations disappeared

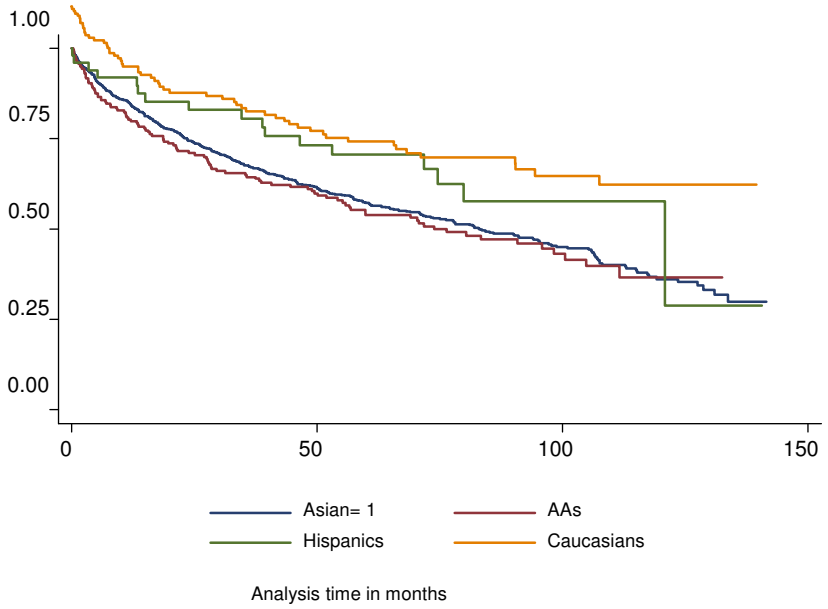

Figure 1: Kaplan-Meier survival estimates by race/ethnicity.
Note and abbreviations: *The curve indicates the crossing of hazards, meaning that there is not significant difference in survival by race/ethnicity. Because the PH is not met, these curves must be interpreted with caution. AAS = African Americans.*

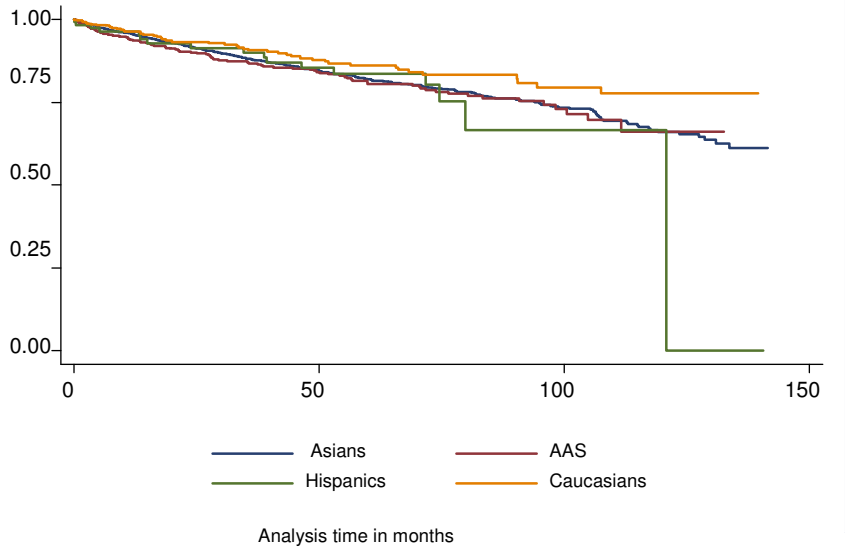

Figure 2: Adjusted Kaplan-Meier survival estimates - adjusted for income, age, histology, tumor, and treatment.
Note: *The curve indicates the crossing of hazards, meaning that there is not significant difference in survival by race/ethnicity. Survival improved in African Americans (AAS) after adjustment. Because the PH is not met, these curves must be interpreted with caution.*

Table 2: Mortality associated with race/ethnicity and other factors in older United States women diagnosed with cervical cancer, 1992-1999

Covariates	Adjusted Hazard ratio and 95% confidence interval (CI)			
	All cause mortality		Cervical cancer specific mortality	
	Hazard ratio (AHR)	95% CI	Hazard ratio (AHR)	95% CI
Race/ethnicity				
Caucasian	1.0	Reference	1.0	Reference
African Americans	0.85	(0.70,1.03)	0.91	(0.72,1.20)
Hispanics	0.68	(0.46,1.01)	0.73	(0.44,1.19)
Others	0.87	(0.70, 1.09)	0.83	(0.63,1.11)
Age				
65-69	1.0	Reference	1.0	Reference
70-74	1.18	(0.97, 1.44)	1.22	(0.94,1.59)
75-79	1.55	(1.27, 1.89)	1.66	(1.28,2.15)
80+	2.18	(1.81, 2.63)	2.78	(2.19, 3.54)
Income				
Lowest Quartile	1.0	Reference	1.0	Reference
2nd Quartile	0.83	(0.69, 1.00)	0.84	(0.66,1.06)
3rd Quartile	1.02	(0.85, 1.24)	1.00	(0.79,1.28)
Highest Quartile	0.88	(0.72, 1.07)	0.85	(0.66,1.09)
Treatment				
No surgery	1.0	Reference	1.0	Reference
Biopsy	0.92	(0.74, 1.16)	0.98	(0.73,1.33)
Less extensive surgery	0.56	(0.42, 0.74)	0.57	(0.40,0.83)
Radical surgery	0.34	(0.26, 0.46)	0.41	(0.28, 0.58)
Histologic type				
Epithelial cells	1.0	Reference	1.0	Reference
Squasmous cell	0.66	(0.52, 0.84)	0.73	(0.53, 1.01)
Adenoma	0.84	(0.64, 1.10)	1.11	(0.78,1.58)
Others	0.97	(0.72, 1.32)	1.15	(0.77, 1.73)
Tumor Stage				
I	1.0	Reference	1.0	Reference
II	1.52	(1.23, 1.88)	1.28	(1.00, 1.65)
III	2.13	(1.72, 2.63)	1.61	(1.24, 2.10)
IV	2.78	(2.24, 3.45)	2.28	(1.76, 2.96)
Unknown	6.36	(5.09, 7.95)	4.33	(3.22, 5.83)

after adjusting for other tumor prognostic factors and treatment received. Further, in both models and in all cause and cervical cancer-specific mortality, we demon-strated a significant association between type of treatment received and tumor stage at diagnosis. Therefore, in this cohort of older women with cervical cancer, race/ethnicity was not a significant predictor of survival but treatment, age at tumor diagnosis and the tumor stage at diagnosis were.

Racial and ethnic differences in cervical cancer survival had been reported to have declined [6]. Unlike previous findings, this study found no significant association between ethnicity and overall or cervical cancer-specific survival. Age of elderly women of the study population, where race/ethnicity may be more difficult to define in the biologic or non-biologic pathway to disparities [17], is a possible explanation for this current finding. However, the association between race/ethnicity and survival may be explained by income status. In the univariate

model, this study found a significant association between income and survival, which disappeared after adjustment for other covariates. Our univariable or unadjusted finding confirms previously published studies on socioeconomic status as predictor of cervical cancer survival [6,8,9,10]. In analysis reporting significant racial disparities in survival, adjustment for socio-economic variables substantially reduced such variability [18].

The racial variation between African American and Caucasian women in cancer survival has been explained by racial variation in the tumor stage at diagnosis. Studies that report racial variation in survival also report significant racial variation in tumor stage at diagnosis [10]. Our study found significant difference in survival by the tumor stage at diagnosis. Survival was favored by early stage of tumor (stage I), while stage IV compared to stage I was associated with nearly three times overall and cervical cancer-specific mortality. However there was no significant ethnic/racial difference in the tumor stage at diagnosis, $\rho=0.12$. Therefore since tumor stage was independently associated with overall and cervical cancer-specific survival, and there was no significant difference among race/ethnic groups, there is strong plausibility to support the observed statistically insignificant racial/ethnic variation in overall and cervical cancer-specific survival in this population. Further, our study indicated no significant difference in survival by tumor histopathology in the adjusted model. However our findings on the distribution of adenoma by race/ethnicity, which is observed most in Caucasian women (18.22% versus 15.48%), confirms previous reports [20].

Income level was significantly associated with overall and cervical cancer-specific survival in the univariable Cox regression model, but was not significant after adjusting for the covariates in the multivariable model. Unlike race/ethnicity, income was a significant predictor at the unadjusted model for overall and cervical cancer-specific survival. Though the association between race /ethnicity and survival was insignificant, the adjustment for income in the multivariable model further diminished the race-survival relationship. Our finding in this vein supports previous literature on this perspective [6,8,9,10].

Despite the strengths of our study, there are some limitations. First, although we attempted in this analysis to adjust for several possible confounders of cervical cancer survival outcome, information on several confounders such as comorbidity, marital status, other forms of treatment received, residence (geographic locale) and education attainment, was not available. Second, we used census tract–level indicators of SES, since individual level was not available; measures of the latter type might minimize misclassification and allow more precise estimates of income level [19]. Third, confining our analysis to the Medicare population (patients age 65 and older) limits generalizability to younger patients who are increasingly being more diagnosed with cervical neoplasm compared to older females. Fourth, like all epidemiologic studies, our results may be in part influenced by unmeasured and residual confounding since no matter how sophisticated the statistical model used, confounding cannot be completely removed from the data [21]. Finally, the assignment of a racial classification encompasses a multitude of social, environmental, dietary, and life style factors that may affect response to specific treatments, none which can be completely controlled in a statistical model [21].

Conclusion

There was no racial/ethnic variance in overall and cervical cancer specific survival among older US women. Tumor stage, age at diagnosis and treatment received were the significant predictors of survival in this cohort of older US women diagnosed with cervical cancer and followed for the disease. Further investigation may be needed to address

whether these results are similar in the younger population who may have different risk, treatment and possibly different survival outcomes.

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