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Factors influencing the survival of cervical cancer

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Abstract. More studies on the effect of socioeconomic (SES) factors on the survival of cervical cancer appeared while lacking comprehensive studies on both SES factors and traditional survival-influencing factors. Our study included baseline factors, SES factors, tumor features, and therapy. It thoroughly analyzed their influences and interactions on the survival of the cervical cancer population in the US. A total of 28471 cases from the Surveillance, Epidemiology, and End Results (SEER) database were adapted in our study, using the Kaplan-Meier method and log-rank test as univariate analysis and the Cox proportional hazard model as multivariate analysis. Surgery, marriage, younger age, and higher income were found to have improving effects on survival, and chemotherapy and radiotherapy did the same after adjusting baseline and SES factors. Hispanics have the best survival, while Blacks have the worst. Survival in metropolitan areas decreased as the population increased, while the opposite appeared in nonmetropolitan areas.

Keywords: Cervical cancer, survival analysis, SEER.

1. Introduction

Cervical cancer is a significant and pervasive malignancy afflicting women worldwide. According to the International Agency for Research on Cancer's latest report, the incidence and mortality rate in 2020 is 13.3% and 7.3% among women affected by cervical cancer, positioning it as the fourth leading cause of female mortality due to cancer [1]. Cervical cancer is prevalent in middle- to low-income countries, where limited access to screening and vaccines compounds its prevalence [2]. Non-genetic factors influencing cervical cancer, such as human papillomavirus (HPV) infection, smoking, C. trachomatis infection, and oral contraceptive use, have garnered attention [3]. Within all non-genetic factors, human papillomavirus infection is the predominant cause of most cervical cancer cases, with HPV 16/18 contributing 71. The most common histopathological type of cervical cancer is squamous cell carcinoma, comprising over 80% of cases, followed by adenocarcinoma, and squamous cell carcinoma is the predominant histopathological type in cervical cancer [4]. The clinical promise of alternating chemoradiotherapy for high-risk cervical cancer patients, including those with advanced nodal disease, is underscored by its effective outcomes and manageable toxicity [1].

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Besides, social factors, including race and ethnicity, socioeconomic status, access to health care, insurance status, and others, have been studied for their impacts on the incidence and prognosis of cervical cancer [3, 5, 6]. A study on area-specific economic factors found that Medicare coverage and healthcare expenditure significantly influence the surgery coverage of cervical cancer in the U.S., thus leading to differences in the incidence and mortality among different districts [7]. Black and Hispanic or Latina women were said to have a higher probability than White women of developing cervical cancer and dying from it [8]. Black women were also found to have the highest incidence rate of cervical squamous cell carcinoma and the highest mortality in adenocarcinoma, compared with the higher risk of adenocarcinoma in Hispanic and White women [9]. Patients with lower education, low annual household income, and window/divorce status were more likely to delay seeking medical care, leading to later stages of diagnosis [10]. A study from Brazil found fertility to be positively related to mortality [11]. Socioeconomic status (SES) is a measurement of the overall social standing of an individual, including social factors such as income, education, and occupation; lower SES was associated with poorer outcomes in cancers [12]. Disparities in cervical cancer survival related to health insurance coverage and SES were discovered [5]. Individuals with lower economic status and living in regions with less healthcare expenditure were less likely to access HPV vaccines, causing higher exposure to cervical cancer [13]. Lower insurance status also caused less access to outcome-improving therapies such as brachytherapy [14]. Briefly, social factors have a confounding influence on different aspects of the whole procedure of cervical cancer, including screening, diagnosis, treatment, and prognosis.

In recent years, increasing studies have attempted to include the analysis of lacking social datasets [15]. A study from 2006 on the importance of SES for survival after cervical cancer is diagnosed and a combined conceptual model of social factors(combining SES indicator, healthcare provider factors, individual factors, and shorter cervical cancer survival time) is used in the study to comprehensively analyze the impact of social factors [10]. Our study referred to the conceptual model but used more recent data (until 2020). However, studies like this often completely shifted their focus to the aspect of social or socioeconomic factors and overlooked the importance of keeping the original approach to analyzing cervical cancer. This trend of focusing on one group of factors with similar characteristics or employing the simple standard analysis of cervical cancer fails to contribute to a new nuanced understanding of survival rates of cervical cancer among women on a national basis.

This article takes a comprehensive approach to observing the relationships between cervical cancer and various determinants of different risk levels. The study's principal objective is to conduct a survival analysis to determine how a combination of factors could influence the risks of cervical cancer and women's health. Specifically, the scope of the data analyzed encompasses a wide range of potential social factors, epidemiological factors, and tumor characteristics identified. Our findings will provide a basis for additional considerations for various determinants leading to a better understanding of women's health.

2. Methodology

2.1. Study population and data selection

Data from the Surveillance, Epidemiology, and End Results (SEER) registries were used for cervical cancer analysis. SEER compiles and releases data on cancer occurrence and survival rates obtained from cancer registries among the U.S. population. The datasets are gathered for each instance of cancer reported across 22 geographical regions in the U.S. (SEER). The database selected for this study is the Incidence – SEER Research Data from 17 registries (SEER 17) in the years ranging from 2000 to 2020. According to the 2020 census, SEER 17 covers approximately 26.5% of the U.S. population [16].

To ensure the specificity and significance of the results, only cases signifying “Cervix Uteri” according to the site recode ICD-O-3 with complete records of survival months, cause of death classifications, and follow-up details were included. The cases diagnostic confirmation is only limited to positive histology, and cases reported without autopsy or death certificate were excluded. After

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excluding every case with missing records in each covariate and under 15 in age, 28471 cases were included in our research.

2.2. Cervical cancer survival outcome

The main survival outcome of this study is the survival class data that combines both SEER 17 cause-specific death classifications and survival months. Cause-specific death classifications represent cases' survival status, with dying from cervical cancer as positive results and other as negative. Individuals with negative cause-specific death classifications were treated as censored data points. Survival months are calculated as those measured after cancer diagnosis until death or last follow-up up to December in 2020 [17].

2.3. Covariates

Median household income and rural-urban continuum code were chosen as SES factors available in the SEER database. The county attribute variables are computed utilizing the 5-year data files of the American Community Survey (ACS). Detailed technical documentation for the ACS files during this period is available for access through the United States Census Bureau [18].

Other factors relevant to the influence of cervical cancer survival analysis are grouped into three categories based on characteristics: the therapy group, the tumor feature group, and the baseline factors group. The therapy group includes radiation recode, chemotherapy recode, and surgery recode. Utilization of each therapy was identified as yes or no. The tumor feature group consists of the histology recode of the tumor (adenocarcinoma(ADC), squamous cell carcinoma(SCC), epithelial, other types), primary site (Endocervix, Exocervix, Overlapping lesion of cervix uteri, Cervix uteri), combined summary stage (Distant, In situ, Localized, Regional, Unknown/unstaged), grade recode (Grade I/II/III/IV), and record number record(1, 2, equal or more than 3). The baseline group contains age code, race, and origin recode (Hispanic, American Indian/Alaska Native, Asian or Pacific Islander, Black, White), and marital status at diagnosis (Divorced, Married including common law, Separated, Single never married, Widowed).

For each covariate treated as a categorical variable, groups with the most numbers were chosen as reference groups while studying, like White for race, married including common law for marital status, ADC for histology, and Cervix uteri for primary site, except for Counties in metropolitan areas ge 1 million pop for continuum code, Grade I for grade, and no for each therapy.

2.4. Statistical analysis:

Univariate analysis was conducted by using the Kaplan-Meier method to estimate the survival condition and assess the impact on survival of each covariate. Kaplan-Meier curves were generated to show the changes in survival over time, and 1-, 3- and 5-year survival rates were calculated. The log-rank test was used to compare the differences between distant groups in each covariate. Cox regression model was also used to identify the influence of each covariate on survival.

Covariates statistically significant in the univariate cox regression model were included in multivariate analysis. The Cox proportional hazard model was employed to analyze the net impact on survival of all covariates included separately, and adjusting different factors to find the relationship between each factor: adjusted the baseline (age, marital status at diagnosis, race) individually and respectively with socioeconomic (median household income, rural-urban continuum code), histology recode, grade and stage, tumor feature, therapy; adjusted both baseline and socioeconomic respectively with histology, grade and feature, tumor features, and therapies; and we have adjusted all factors into one Cox proportional hazard model to examine the net relationship of all factors. The hazard ratio (HR) was calculated in every Cox model. All the statistical computations mentioned above were executed using R statistical software (version 3.6.1, http://www.R-project.org/). A less than 0.05 in p-value was denoted as statistically significant in this study.

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3. Results

Table 1. Counts and percentages of each group of the 28471 cervical cancer patients included from the SEER 17 database from 2000 to 2020.

Characteristic	N=28,471
Year of diagnosis	2,011.0 (2,007.0, 2,014.0)
Age recode with <1 year olds and 90+	16 (<0.1%)
15-19 years	
20-24 years	230 (0.8%)
25-29 years	1,181 (4.1%)
30-34 years	2,501 (8.8%)
35-39 years	3,392 (12%)
40-44 years	3,842 (13%)
45-49 years	3,667 (13%)
50-54 years	3,299 (12%)
55-59 years	2,791 (9.8%)
60-64 years	2,347 (8.2%)
65-69 years	1,796 (6.3%)
70-74 years	1,261 (4.4%)
75-79 years	940 (3.3%)
80-84 years	645 (2.3%)
85-89 years	383 (1.3%)
90+ years	180 (0.6%)
Race and Origin Recode NHW, NHB, NHAIAN, NHAPI, Hispanic	
Hispanic All Races	6,652 (23%)
Non-Hispanic Asian or Pacific Islander	210 (0.7%)
Non-Hispanic Asian or Pacific Islander	2,665 (9.4%)
Non-Hispanic Black	3,639 (13%)
Non-Hispanic White	15,305 (54%)
Marital Status at Diagnosis	
Divorced	3,556 (12%)
Married Including Common Law	12,807 (45%)
Separated	645 (2.3%)
Single Never Married	8,499 (30%)
Unmarried or Domestic Partner	113 (0.4%)
Widowed	2,851 (10%)
Median Household Income Inflation adj to 2021	
< $35,000	335 (1.2%)
$35,000-$39,000	565 (2.0%)
$40,000-$44,999	986 (3.5%)
$45,000-$49,999	1,591 (5.6%)
$50,000-$54,999	1,638 (5.8%)
$55,000-$59,999	2,469 (8.7%)
$60,000-$64,999	2,815 (9.9%)
$65,000-$69,999	5,724 (20%)
$70,000-$74,999	2,970 (10%)
$74,999+	9,358 (33%)
Rural-Urban Continuum Code	
Counties in metropolitan areas ge 1 million pop	17,186 (60%)

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Table 1. (continued).

Counties in metropolitan areas of 250,000 to 1 million pop	5,783 (20%)
Counties in metropolitan areas of It 250 thousand pop	2,170 (7.6%)
Nonmetropolitan counties adjacent to metropolitan area	1,886 (6.6%)
Nonmetropolitan counties not adjacent to a metropolitan area	1,446 (5.1%)
Behavior Recode for Analysis	
Malignant	28,471 (100%)
Histology Recode – Broad Groupings	
SCC	18,777 (66%)
ADC	6,602 (23%)
Epithelial	1,945 (6.8%)
Other Subtype	1,147 (4.0%)
Primary Site – Labeled	
C53.9-Cervix Uter	21,480 (75%)
C53.0-Endocervix	5,847 (21%)
C53.1-Exocervix	582 (2.0%)
C53.8-Overlapping lesion of cervix uteri	562 (2.0%)
Combined Summary Stage 2004+	
Distant	3,948 (14%)
Localized	12,874 (45%)
Regional	11,184 (39%)
Unknown/Unstaged	465 (1.6%)
Grade Recode thru 2017	
Well differentiated; Grade I	11,976 (42%)
Moderately differentiated; Grade II	11,432 (40%)
Poorly differentiated; Grade III	1,032 (3.6%)
Undifferentiated; anaplastic; Grade IV	4,031 (14%)
Reason No Cancer-Directed Surgery	16,889 (59%)
Radiation Recode	16,785 (59%)
Chemotherapy Recode yes, no/unk	
No/Unknown	14,039 (49%)
Yes	14,432 (51%)
Record Number Recode	
>=3	193 (0.7%)
1	26,744 (94%)
2	1,534 (5.4%)
SEER Cause-Specific Death Classification	
Alive or Dead of other Cause	19,493 (68%)
Dead Attributable to this Cancer dx	8,978 (32%)
Survival Months	61 (21, 119)
Patient ID	34,901,095 (22,091,334, 49,730,636)
[1]Median (IQR); n (%)	

Our sample size includes 28,471 cases, excluding subjects with missing information.

Table 1 shows the distribution of each covariate in our data. The data contains age, race, marital status, income, rural-urban continuum code, histology recode, cancer stage, primary sites, grade recode, record number, surgery, radiation recode, and chemotherapy recode. The categories that include the most cases of the groups are age ranging from 40 to 44 years (13%), non-Hispanic white population (54%), married including common law (45%), earning of $75,000+ (33%), counties in metropolitan areas per 1 million population (60%), SCC histology recode (66%), Cervix uteri primary site (75%),

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localized summary stage (45%), grade III recode (40%), reason no cancer-directed surgery (59%), record number 1 (94%), alive or death of other cause (68%). Among most covariates, we have very equivalent distributions among different groups.

Table 2. 1-,3-,5-year overall survival rate of the 28471 cervical cancer patients included from the SEER 17 database in percentage calculated by Kaplan-Meier method and the 95% confidence interval.

Year	Survival rate(95%CI)
1-year	0.87(0.87, 0.88)
3-year	0.74(0.73, 0.74)
5-year	0.69(0.69, 0.70)

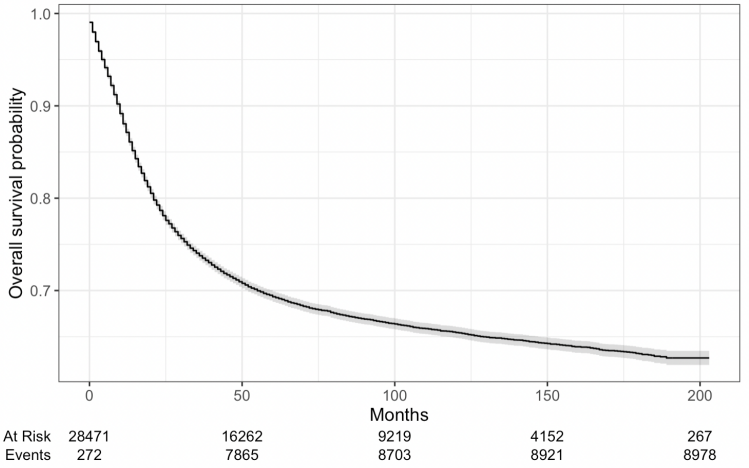

Figure 1. Overall 200-month Kaplan-Meier survival curve of the 28471 cervical cancer patients included from the SEER 17 database from 2000 to 2020.

We have calculated the survival rates for 1-year, 3-year, and 5-year shown in Table 2. We would like to note our 5-year survival rate as it is the common timeframe for survival rates. Figure 1 is the Kaplan-Meier curve for the overall survival results.

Table 3. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Age, Race, Marital Status, Income, Continuum Code, Tumor Feature, and All.

Covariates	Unadjusted model HR(95% CI)	p-value	Adjusted model race, marital status, income, continuum code HR(95% CI)	p-value	Adjusted model race, marital status, income, continuum code, tumor feature HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Age	1.33(1.31, 1.35)	<0.01	1.33(1.31, 1.35)	<0.01	1.16(1.14, 1.18)	<0.01	1.11(1.09, 1.12)	<0.01

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Table 4. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Race, Age, Marital Status, Income, Continuum Code, and All.

Covariates	Unadjusted model HR(95% CI)	p-value	Adjusted model race, marital, income, continuum code HR(95% CI)	p-value	Adjusted model race, marital, income, continuum code, tumor feature HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
White	ref	ref	ref	ref	ref	ref	ref	ref
American Indian/Alaska Native	1.11(0.88, 1.40)	0.4	1.16(0.92, 1.47)	0.2	1.14(0.90, 1.44)	0.28	1.15(0.91, 1.45)	0.25
Asian or Pacific Islander	0.94(0.87, 1.02)	0.12	0.92(0.85, 0.99)	<0.05	0.96(0.89, 1.04)	0.28	0.93(0.86, 0.95)	0.05
Black	1.47(1.38, 1.55)	<0.01	1.31(1.24, 1.39)	<0.01	1.26(1.19, 1.34)	<0.01	1.12(1.06, 1.20)	<0.01
Hispanic	0.91(0.86, 0.96)	<0.01	0.93(0.88, 0.99)	<0.01	0.94(0.89, 1.00)	<0.01	0.89(0.85, 0.95)	<0.01

Table 5. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Marital Status, Age, Race, Income, Continuum Code, and All.

Covariates	Unadjusted model HR(95% CI)	p-value	Adjusted model race, marital, income, continuum code HR(95% CI)	p-value	Adjusted model race, marital, income, continuum code, tumor feature HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Married including common law	ref	ref	ref	ref	ref	ref	ref	ref
Divorced	1.45(1.36, 1.54)	<0.01	1.28(1.20, 1.37)	<0.01	1.28(1.20, 1.37)	<0.01	1.13(1.06, 1.21)	<0.01
Separated	1.39(1.21, 1.59)	<0.01	1.38(1.20, 1.58)	<0.01	1.37(1.19, 1.57)	<0.01	1.18(1.03, 1.36)	<0.05
Single never married	1.38(1.31, 1.45)	<0.01	1.44(1.37, 1.52)	<0.01	1.44(1.37, 1.51)	<0.01	1.22(1.16, 1.28)	<0.01
Widowed	2.20(2.06, 2.34)	<0.01	1.25(1.17, 1.35)	<0.01	1.24(1.16, 1.33)	<0.01	1.20(1.12, 1.29)	<0.01

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Table 6. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Therapy, Age, Race, Marital Status, Income, Continuum Code, and All.

Covariates	Unadjusted model HR(95% CI)	p-value	Adjusted model age, race, marital status HR(95% CI)	p-value	Adjusted model age, race, income, continuum code HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Surgery(1 to 0)	0.21(0.20, 0.22)	<0.01	0.25(0.23, 0.26)	<0.01	0.25(0.23, 0.26)	<0.01	0.42(0.40. 0.44)	<0.01
Radiotherapy(1 to 0)	2.21(2.10, 2.31)	<0.01	0.80(0.75, 0.86)	<0.01	0.80(0.75, 0.85)	<0.01	0.81(0.76, 0.86)	<0.01
Chemotherapy(1 to 0)	2.27(2.17, 2.37)	<0.01	1.24(1.16, 1.32)	<0.01	1.24(1.17, 1.32)	<0.01	0.68(0.64, 0.72)	<0.01

Table 7. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Income, Age, Race, Marital Status, Continuum Code, Histology, and All.

Covariate	Unadjusted model HR(95% CI)	p-value	Adjusted model age, race, marital status HR(95% CI)	p-value	Adjusted model age, race, marital status, code, histology HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Income	0.92(0.91, 0.94)	<0.01	0.94(0.92, 0.95)	<0.01	0.92(0.90, 0.94)	<0.01	0.95(0.93, 0.97)	<0.01

Table 8. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Continuum Code, Age, Race, Marital Status, Income, and All.

Rural Urban Continuum Code	Unadjusted model HR(95% CI)	p-value	Adjusted model age, race, marital HR(95% CI)	p-value	Adjusted model age, race, marital, income HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Counties in metropolitan areas ge 1 million pop	ref	ref	ref	ref	ref	ref	ref	ref
Counties in metropolitan areas of 250,000 to 1 million pop	1.00(0.95, 1.06)	<0.01	1.02(0.97, 1.08)	<0.01	0.97(0.92, 1.03)	<0.01	0.99(0.93, 1.04)	<0.01
Counties in metropolitan areas of It 250 thousand pop	1.03(0.95, 1.11)	<0.01	1.04(0.85, 0.99)	<0.01	0.91(0.84, 1.00)	<0.01	0.90(0.82, 0.98)	<0.01

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Table 8. (continued).

Nonmetropolitan counties adjacent to metropolitan area	1.12(1.03, 1.21)	<0.01	1.10(1.01, 1.19)	<0.01	0.91(0.82, 1.00)	<0.01	0.86(0.78, 0.95)	<0.01
Nonmetropolitan counties not adjacent to a metropolitan area	1.14(1.04,1.25)	<0.01	1.15(1.95,1.26)	<0.01	0.92(0.82, 1.03)	<0.01	0.98(0.88, 1.09)	<0.01

Table 9. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Record Number Recode, Age, Race, Marital Status, Histology, Primary Site Recode, Stage Recode, Continuum Code, Grade, and All.

Covariate	**Unadjusted model HR(95% CI)**	**p-value**	**Adjusted model age, race, marital status, histology, site, stage, code, grade, records HR(95% CI)**	**p-value**	**Adjusted model all HR(95% CI)**	**p-value**
Record Number Recode	1.28(1.20, 1.37)	<0.01	1.11(1.03, 1.19)	<0.01	1.11(1.03, 1.19)	<0.01

Table 10. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Primary Site, Age, Race, Marital Status, Histology, Primary Site, Stage Recode, Grade, Record Number Recode, and All.

Primary Site	**Unadjusted model HR(95% CI)**	**p-value**	**Adjusted model age, race, marital statis, histology, site, stage, grade, records HR(95% CI)**	**p-value**	**Adjusted model race, marital, income, continuum code, tumor feature HR(95% CI)**	**p-value**	**Adjusted model all HR(95% CI)**	**p-value**
C53.9-Cervix Uter	ref	ref	ref	ref	ref	ref	ref	ref
C53.0-Endocervix	0.61(0.58,0.65)	<0.01	0.77(0.72, 1.01)	<0.01	0.78(0.73, 0.83)	<0.01	1.13(1.06, 1.21)	<0.01
C53.1-Exocervix	0.67(0.56,0.79)	<0.01	0.86(0.73,1.01)	<0.01	0.86(0.73,1.01)	<0.01	0.88(0.75,1.04)	<0.05
C53.8-Overlapping lesion of cervix uteri	0.87(0.75,1.01)	0.073	0.95(0.82,1.11)	0.53	0.95(0.82,1.11)	0.55	1.06(0.91,1.24)	0.43

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Table 11. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Histology, Age, Race, Marital Status, Primary Site, Stage, and All.

Histology	Unadjusted model HR(95% CI)	p-value	Adjusted model age, marital statis, histology HR(95% CI)	p-value	Adjusted model, age, race, marital status, histology, site, stage HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
ADC	ref	ref	ref	ref	ref	ref	ref	ref
SCC	0.69(0.66,0.73)	<0.01	0.79(0.75,0.83)	<0.01	1.18(1.11,1.26)	<0.01	1.26(1.18,1.34)	<0.01
Epithelia	1.63(1.52,1.75)	<0.01	1.76(1.64,1.89)	<0.01	1.35(1.25,1.45)	<0.01	1.41(1.31,1.52)	<0.01
Other Subtypes	1.23(1.12,1.35)	<0.01	1.27(1.15,1.40)	<0.01	1.46(1.32,1.61)	<0.01	1.88(1.70,2.08)	<0.01

Table 12. Univariable and Multivariable Hazard Ratio Analyses for Associations Between Grade Recode, Age, Martial Status, Stage Recode, Histology, Primary Site, Record Number, and All.

Grade Recode Thru 2017	Unadjusted model HR(95% CI)	p-value	Adjusted model age, marital statis, grade, stage HR(95% CI)	p-value	Adjusted model, age, marital status, grade, stage, histology, stie, records HR(95% CI)	p-value	Adjusted model all HR(95% CI)	p-value
Well differentiated; Grade I	ref	ref	ref	ref	ref	ref	ref	ref
Moderately differentiated; Grade II	2.32(2.11,2.54)	<0.01	14.65(13.67,15.69)	<0.01	1.43(1.3,1.58)	<0.01	1.48(1.34,1.63)	<0.01
Poorly differentiated; Grade III	4.12(3.76,4.51)	<0.01	4.18(3.92,4.45)	<0.01	1.93(1.75,2.12)	<0.01	1.97(1.79,2.17)	<0.01
Undifferentiated; anaplastic; Grade IV	5.46(4.83,6.18)	<0.01	5.68(4.90,6.59)	<0.01	1.99(1.76,2.26)	<0.01	2.06(1.81,2.34)	<0.01

Age had a significant effect on survival under either adjustment ($p<0.01$); the older the worse the prognosis (Table 3).

Across all adjustments, Hispanics had the best survival, and HR(<1) is almost unaffected by various adjustments. Black consistently had the worst survival, but HR(>1) gradually decreased with the increase of adjustment. After adjusting for age and marital status, Asian or Pacific Islander was significantly better than White, but this advantage disappeared after further adjustment for SES (Table 4).

Survival of different marital status are significantly different ($p<0.01$). Among them, the survival status of married, including common law, was significantly better than others under all adjustments. Without any adjustment, the survival of the divorced group was significantly worse than that of the other

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groups (HR=2.20) but was similar to that of the other non-married groups after adjusting for age. There was no significant change in the separated and divorced group after age, race, and SES were adjusted. HR decreased in all groups after balancing tumor features and therapy (Table 5).

All therapy factors significantly affected survival ($p<0.01$). Patients who underwent surgery had significantly better survival than those who did not (HR=0.21), but HR(<1) increased slightly after further adjusting the tumor feature. Before any adjustment, radiotherapy had a significant negative effect on survival (HR=2.21). However, it changed to a positive effect after balancing baseline (HR=0.80), and there was no significant difference after further balancing SES and tumor features. Chemotherapy had a significant negative effect on survival before any adjustment (HR=2.27) and after balancing baseline and SES (HR=1.24), but the effect became positive after balancing tumor features (HR=0.68)(table 6).

According to Table 7, after adjustments, high income's positive influence on survival decreases. After additionally adjusting code and histology, high income's advantage in survival then increased.

Table 8 shows no notable distinctions in the survival rates of Counties in metropolitan areas of 1 million population and Counties in metropolitan areas of 250,000 to 1 million population under, regardless of any adjustments made. Incorporating income data and implementing additional modifications result in improved survival rates for counties in metropolitan areas with a population of 250 thousand. (<0.05). Nonmetropolitan counties adjacent to a metropolitan area have an advantage in survival over Counties in metropolitan areas of 1 million population, except when income and adjustments(age, race, marital status) are considered.

According to Table 9, after adjustments, the negative impact of the record number recode decreases since it is a sequential number of individuals' submissions within SEER.

According to Table 10, there are no statistical differences examined for the C53.8-Overlapping lesion of cervix uteri ($p>0.01$), while the others do in all scenarios ($p<0.01$). C53.9-Cervix uteri has the greatest negative impact on survival (HR<1 for all other factors). The negative impact of the primary site increases while adjusting more factors, but there are no significant differences as more factors are adjusted.

According to Table 11, the Histology Recode significantly impacts survival in all adjustment scenarios (<0.001), while acc has the most negligible negative impact on survival under all scenarios. Epithelia has the worst survival before adjusting more factors, but its survival improves after adjustments. The survival of the subtype gets worse compared to the adc while adjusting more factors. The survival overall decreases as more factors are considered for histology to recode.

Table 12 shows that the grade recode significantly influences survival in all adjustment scenarios ($p<0.01$), and Moderately differentiated; Grade II, Poorly differentiated; Grade III and Undifferentiated; anaplastic; Grade IV have a significantly more significant impact than Well differentiated; Grade I. Grade 4 has the most significant negative impact on survival before adjustment, and grade 2 has an extremely large negative impact on survival (HR=14.56) while adjusting to age, marital status, and stage.

4. Discussion

Age was a significant factor affecting the survival of cervical cancer patients, and survival decreased with increasing age. This is similar to past research by Beavis, and found that Black women's incidence rises as their age increases [19]. Cohen et al. observed age-specific incidence rate differences in their study of racial and pathological differences in the US cervical cancer population using the SEER database, whose incidence was exceptionally high among people above 65-year-old, presumably due to a lack of screening during the past decade [9]. The effect of age on survival is likely to be achieved by influencing other factors, such as older people are more likely to have an advanced stage at diagnosis. For example, in our study, HR changed from 1.33 to 1.16 after adjusting tumor features; and young people are less likely to have their independent insurance [20].

There has always been a great difference in the incidence and mortality of cervical cancer among different races, with one of the largest Black-White mortality gap [21]. A significant racial difference was also observed in our study, with Hispanics having the best survival (HR=0.91) and Blacks having

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the worst (HR=1.47) compared to Whites. This is consistent with previous studies [13, 20]. Cohen et al. found that Hispanics had the highest 5-year survival but also a high incidence, speculating that nativity contributed to the difference in survival among Hispanics [9]. Gomez et al. found that foreign-born Hispanics had a survival advantage over the US-born in the study of the Hispanic cervical cancer population, which may be related to cultural preference [22]. Black people are consistently reported to have the highest mortality rates [8, 23], but a relatively lower incidence rate at present [9]. The reason for the high mortality rate of Black people may be related to insurance-related disparities and insufficient follow-up of abnormal pap test [23, 24], and possibly access to treatment (like Brachytherapy) [14]. In fact, in our study, as every additional part of adjustment is added, Black's HR will produce a certain change. Cohen et. al found in their study that [9] API had the lowest mortality rates. However, interestingly in our study, a similar trend only appeared when balancing the baseline factors, and it disappeared after balancing the SES factors, inferring that it is mainly influenced by SES factors. Observation of changes in HR also suggests that SES is an important factor affecting the disparities of mortality in different races.

We found that people who married in common law had the best survival. This is consistent with previous studies, suggesting that marriage is a factor that promotes the prognosis of cervical cancer [25]. Many studies have shown that unmarried patients are often at later stages when diagnosed [26], which might be related to the higher acceptance of screening in married group [27]. Married patients also have higher treatment compliance, are more willing to accept radical treatment, such as surgery, and are more likely to receive chemotherapy than unmarried patients [25]. The survival advantage in married groups may also come from the emotional and economic support from their children and spouses [28]. In our study, widowed women have the worst living conditions (HR = 2.20), but after the adjustment of age and race, no significant difference was left; this trend also appeared in the divorced group, suggesting the survival disadvantage in these two groups might be mainly related to age. Some studies also proposed that marital status may be affected by cultural background and social status of different races, but more than present evidence is needed to support this conclusion [26]. It is worth mentioning that there was no significant difference in survival between each group before and after adjustment for SES factors, but there was a significant decline after adjustment for tumor feature and therapy, suggesting that the survival advantage of marriage may be more attributed to the latter than to economic status.

In general, it is shown that higher income levels correlate to better survival, even when other variables like continuum code and histology are considered. Previous research, such as the one on socioeconomic status and survival following cervical cancer, has also examined this trend. Rising income level enables higher levels of education, which may explain the variations in survival among cervical cancer patients [6].

Socioeconomic factors such as income and continuum code play significant roles in the survival of patients. Patients in nonmetropolitan areas may experience poorer survival rates initially, but the tendency is reversed with further adjustments, most likely due to the influence of income. Other studies regarding rural and urban areas' effects on cervical cancer make contrasting conclusions. Research on rural–urban and racial/ethnic disparities in invasive cervical cancer incidence in the United States stated that rural counties had a higher incidence of cervical cancer than urban counties at every stage. The comparisons between cervical cancer frequency and age-adjusted incidence are made. However, the amount of adjustment factors put into consideration is limited. Lulu Yu and the team utilized the comparisons between cervical cancer frequency and age-adjusted incidence [29]. Our approach differs as much more comprehensive factors, such as age, marital status, tumor features, therapy, income, and histology, are adjusted to test whether they influence the continuum code's effects on survival. Areas with lower populations and higher income levels may have greater access to healthcare services and treatments. Patients with higher salaries may also be able to afford better treatments, leading to better survival rates. The affordability of healthcare may be a problem in areas with higher populations and lower average income [30].

Nonmetropolitan areas might have poorer survival rates with the possibility of fewer people having access to Medicare, which prevents screening [31]. Because of this, most cases are at an advanced stage

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at the time of diagnosis. After adjusting for tumor features, this disadvantage disappears [32]. This differs from the studies that only included age for adjustments since they will not detect other insights from multiple factors. Metropolitan locations are more likely to have advanced medical facilities and specialists, leading to rapid diagnosis [33]. This could result in more cases being detected at earlier stages, allowing for more effective treatment and improved survival rates. The advantage is evident when tumor characteristics are taken into account for adjustment [34]. Lower SES often correlates with reduced access to public healthcare, including proper cervical cancer screening and timely treatment, leading to increasing HR values after tumor features are adjusted to the Cox regression [15]. Age is associated with both the marital status of females and the affordability of individuals for their treatments, leading to an increasing HR after adjusting age to tumor features [35]. The significance of tumor feature factors (histology recode, primary site, grade recode) was indicated by an increasing HR value after adjusting to SES. The increases in HR values also suggest a significant association between considered histology type and survival month of cervical cancer. The increasing HR value implies that the histology type has an independent and significant influence on the survival month. Biologically, the histological type of the tumor determines how the cancer behaves and responds to different types of treatments [36]. Our research shows that the advanced histology types of epithelia and squamous cell neoplasms may be more resistant to considered treatments like radiation therapy and surgery, causing failure and reduced survival rates [37]. These histologic types are relatively more challenging to detect in an early stage since they are less responsive to screening tests such as Pap smears or do not produce obvious symptoms [38].

In our study, survival was significantly affected by implementing every treatment, including surgery, radiotherapy, and chemotherapy. Surgery was the most significant contributor to survival in multivariate analysis (HR=0.42), consistent with the previous study [19]. For cervical cancer at its early stages, radical surgery is the most recommended treatment, and there are always great benefits for stage I and II, so early detection is a very important [39]. As surgery can only be performed at the early stage, the specific effect of surgery on prognosis will be interfered with by the stage at diagnosis; in our study, the promoting effect of surgery decreases after balancing tumor features. Although there was no significant change in the effect of surgery before and after adjusting baseline factors in our study, some studies have shown that there are differences in the performance of surgery by race like blacks are more likely to receive radiotherapy than surgery [8], and the difference in survival between races before adjusting Hysterectomy is vastly underestimated [19].

Interestingly, chemotherapy and radiotherapy were found to hurt survival without any adjustment. After balancing the baseline factors, radiotherapy changed to have a positive effect, and after further balancing tumor feature, chemotherapy changed to a positive effect. This suggests that both chemotherapy and radiotherapy actually had a positive effect on survival, and radiotherapy is mainly affected by baseline factor, while chemotherapy is mainly affected by tumor feature. Care should be taken to balance these confounding factors while studying the effects of therapy on cervical cancer. Although we found no influence of SES factors on the effect of the therapy, studies have shown that Medicare coverage, health care expenditure, and insurance greatly impact surgery coverage [7, 23]. Advanced-stage concurrent chemotherapy with radiotherapy is the best treatment [37], but in low-middle-income areas the capacity of radiotherapy is limited, leading to the decline of radiotherapy utilization rate and the deterioration of prognosis of cervical cancer patients in these areas [7].

There are several limitations in our study. We had some missing data among many of our covariate groups; some cases have been removed during the final model analysis process, which may lead to bias in the results. Further covariates such as education level and poverty were not included in this model due to lack of access. Furthermore, the changes in the record pattern of the SEER database from 2000 to 2020 might cause differences in results, such as the “unmarried or domestic partner” group in marital status, which refers to other single conditions such as homosexual partners, was only started to be recorded after 2010, so we included it into the “single never married” group in the final analysis. Insurance is also a factor frequently mentioned to influence the survival of cervical cancer [5, 8], but a database containing records of individual insurance conditions additional to other essential basic factors

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(like covariates studied in this study) is hard to found. Further study on a more comprehensive scale is expected.

5. Conclusion

Overall, we examined the relationships between baseline factors, SES factors, tumor features, and therapy and their impact on the survival month in cervical cancer with a large and representative sample size of 28,471 subjects. The distribution of covariates (age, race, marital status, income, rural-urban continuum code, histology recode, cancer stage, primary site, grade recode, record number, surgery, radiation recode, and chemotherapy recode) was assessed within different groupings. Age emerged as a significant factor impacting survival, with older individuals experiencing worse prognosis. The influence of race on survival months was pronounced, with Hispanics showing the best overall survival rate and Black individuals facing the worst rate. Patients who underwent surgery indicated a notably higher survival rate than those who did not. Examining covariates like rural-urban continuum code, record number recode, primary site, and histology recode relationships with the survival month. This study provides valuable insights into the complicated nature of cervical cancer survival, displaying the significance of considering more comprehensive factors. Further cohort studies are expected to verify the results.

References

[1] Singh, D., et al., Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health, 2023. 11(2): p. e197-e206.

[2] Hull, R., et al., Cervical cancer in low and middle-income countries. Oncol Lett, 2020. 20(3): p. 2058-2074.

[3] Li, X.Y., et al., Non-Genetic Factors and Risk of Cervical Cancer: An Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies. Int J Public Health, 2023. 68: p. 1605198.

[4] Pfaendler, K.S., et al., Disparities in Adherence to National Comprehensive Cancer Network Treatment Guidelines and Survival for Stage IB-IIA Cervical Cancer in California. Obstet Gynecol, 2018. 131(5): p. 899-908.

[5] Chayo, I., et al., The impact of health insurance affiliation and socioeconomic status on cervical cancer survival in Bucaramanga, Colombia. Cancer Epidemiol, 2023. 85: p. 102375.

[6] Bolormaa, E., et al., Income-based disparities in the risk of distant-stage cervical cancer and 5-year mortality after the introduction of a National Cancer Screening Program in Korea. Epidemiol Health, 2022. 44: p. e2022066.

[7] Li, Z., et al., Area-specific economic status should be regarded as a vital factor affecting the occurrence, development and outcome of cervical cancer. Sci Rep, 2020. 10(1): p. 4759.

[8] Markt, S.C., et al., Insurance status and cancer treatment mediate the association between race/ethnicity and cervical cancer survival. PLoS One, 2018. 13(2): p. e0193047.

[9] Cohen, C.M., et al., Racial and Ethnic Disparities in Cervical Cancer Incidence, Survival, and Mortality by Histologic Subtype. J Clin Oncol, 2023. 41(5): p. 1059-1068.

[10] Ma, J., et al., Effect of socio-economic factors on delayed access to health care among Chinese cervical cancer patients with late rectal complications after radiotherapy. Gynecol Oncol, 2012. 124(3): p. 395-8.

[11] Vale, D.B., et al., Correlation of Cervical Cancer Mortality with Fertility, Access to Health Care and Socioeconomic Indicators. Rev Bras Ginecol Obstet, 2019. 41(4): p. 249-255.

[12] Woods, L.M., B. Rachet, and M.P. Coleman, Origins of socio-economic inequalities in cancer survival: a review. Ann Oncol, 2006. 17(1): p. 5-19.

[13] Jeudin, P., et al., Race, ethnicity, and income factors impacting human papillomavirus vaccination rates. Clin Ther, 2014. 36(1): p. 24-37.

[14] Boyce-Fappiano, D., et al., Socioeconomic and Racial Determinants of Brachytherapy Utilization for Cervical Cancer: Concerns for Widening Disparities. JCO Oncol Pract, 2021. 17(12): p. e1958-e1967.
[15] Coker, A.L., et al., Ethnic disparities in cervical cancer survival among Medicare eligible women in a multiethnic population. Int J Gynecol Cancer, 2009. 19(1): p. 13-20.
[16] SEER. Number of persons by race and Hispanic ethnicity for Seer Participants - seer registries. 2020; Available from: https://seer.cancer.gov/registries/data.html.
[17] SEER. Months survived based on complete dates. 2013; Available from: https://seer.cancer.gov/survivaltime/.
[18] SEER. Static County attributes. 2020; Available from: https://seer.cancer.gov/seerstat/variables/countyattribs/static.html.
[19] Beavis, A.L., P.E. Gravitt, and A.F. Rositch, Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. Cancer, 2017. 123(6): p. 1044-1050.
[20] Alimena, S., et al., Race- and Age-Related Disparities in Cervical Cancer Mortality. J Natl Compr Canc Netw, 2021. 19(7): p. 789-795.
[21] Doll, K.M., Investigating Black-White disparities in gynecologic oncology: Theories, conceptual models, and applications. Gynecol Oncol, 2018. 149(1): p. 78-83.
[22] Gomez, N., et al., Nativity and neighborhood characteristics and cervical cancer stage at diagnosis and survival outcomes among Hispanic women in California. Am J Public Health, 2015. 105(3): p. 538-45.
[23] Holt, H.K., et al., Mediation of Racial and Ethnic Inequities in the Diagnosis of Advanced-Stage Cervical Cancer by Insurance Status. JAMA Netw Open, 2023. 6(3): p. e232985.
[24] Ford, S., et al., Differences in cervical cancer screening and follow-up for black and white women in the United States. Gynecol Oncol, 2021. 160(2): p. 369-374.
[25] Huynh-Le, M.P., et al., Impact of marital status on receipt of brachytherapy and survival outcomes in locally advanced cervical cancer. Brachytherapy, 2019. 18(5): p. 612-619.
[26] Yuan, R., et al., The impact of marital status on stage at diagnosis and survival of female patients with breast and gynecologic cancers: A meta-analysis. Gynecol Oncol, 2021. 162(3): p. 778-787.
[27] Moore de Peralta, A., B. Holaday, and J.R. McDonell, Factors Affecting Hispanic Women's Participation in Screening for Cervical Cancer. J Immigr Minor Health, 2015. 17(3): p. 684-95.
[28] Ali, R., A. Mathew, and B. Rajan, Effects of socio-economic and demographic factors in delayed reporting and late-stage presentation among patients with breast cancer in a major cancer hospital in South India. Asian Pac J Cancer Prev, 2008. 9(4): p. 703-7.
[29] Yu, L., S.A. Sabatino, and M.C. White, Rural-Urban and Racial/Ethnic Disparities in Invasive Cervical Cancer Incidence in the United States, 2010-2014. Prev Chronic Dis, 2019. 16: p. E70.
[30] McMaughan, D.J., O. Oloruntoba, and M.L. Smith, Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. Front Public Health, 2020. 8: p. 231.
[31] Kilbourne, A.M., Care without Coverage: Too Little, Too Late. Journal of The National Medical Association, 2005. 97: p. 1578.
[32] Rural Health Information Hub. Healthcare Access in Rural Communities. 2022; Available from: https://www.ruralhealthinfo.org/topics/healthcare-access.
[33] Cyr, M.E., et al., Access to specialty healthcare in urban versus rural US populations: a systematic literature review. BMC Health Serv Res, 2019. 19(1): p. 974.
[34] Pimple, S.A. and G.A. Mishra, Global strategies for cervical cancer prevention and screening. Minerva Ginecol, 2019. 71(4): p. 313-320.
[35] Zhou, D., et al., Marital status is an independent prognostic factor for cervical adenocarcinoma: A population-based study. Medicine (Baltimore), 2023. 102(16): p. e33597.

DOI: 10.54254/2753-8818/46/20240520

[36] Shen, S., et al., Potential role of microRNAs in the treatment and diagnosis of cervical cancer. Cancer Genet, 2020. 248-249: p. 25-30.
[37] Gopu, P., et al., Updates on systemic therapy for cervical cancer. Indian J Med Res, 2021. 154(2): p. 293-302.
[38] Bedell, S.L., et al., Cervical Cancer Screening: Past, Present, and Future. Sex Med Rev, 2020. 8(1): p. 28-37.
[39] Poddar, P. and A. Maheshwari, Surgery for cervical cancer: consensus & controversies. Indian J Med Res, 2021. 154(2): p. 284-292.