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Authors

Cooley, Julianne JP
Maguire, Frances B
Morris, Cyllene R
et al.

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Cervical cancer stage at diagnosis and survival among women 65 years in California

Julianne J. P. Cooley[1], **Frances B. Maguire**[1], **Cyllene R. Morris**[1], **Arti Parikh-Patel**[1], **Renata Abrahão**[2,3], **Hui A. Chen**[4], **Theresa H. M. Keegan**[2]

[1]California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Comprehensive Cancer Center, Sacramento, California

[2]Center for Oncology Hematology Outcomes Research and Training (COHORT), University of California Davis Comprehensive Cancer Center, Sacramento, CA

[3]Center for Healthcare Policy and Research, University of California Davis Health, Sacramento, CA

[4]University of California Davis Comprehensive Cancer Center, Department of Gynecology Oncology

Abstract

Background: Through adequate screening and follow-up, cervical cancer can be prevented or detected at early-stage (stage I), which is related to excellent survival. Current guidelines recommend discontinuing screening for women 65 with history of normal Pap and/or HPV tests, potentially leaving this age group vulnerable. This study examined late-stage disease in a population-based cohort.

Methods: Using California Cancer Registry data, we identified 12,442 patients aged 21 years with a first primary cervical cancer diagnosed during 2009–2018. Proportions of late-stage disease (stages II-IV) and early and late-stage 5-year relative survival are presented by age group. Among patients aged 65 years, multivariable logistic regression estimated associations of sociodemographic and clinical characteristics with late-stage cervical cancer.

Results: Nearly one-fifth of patients (n=2,171, 17.4%) were 65 years. More women aged 65 (71%) presented with late-stage disease than younger women (48% in patients aged <65). Late-stage 5-year relative survival was lower for women 65 (23.2%–36.8%) compared to patients <65 (41.5%–51.5%). Characteristics associated with late-stage cervical cancer in women 65 included older age (odds ratio (OR)=1.02, 95% confidence interval (CI) 1.01–1.04; each year), non-adenocarcinoma histologic subtypes, and comorbidities (OR=1.59, CI 1.21–2.08).

Conclusions: There remains a significant burden of advanced cervical cancer in women 65.

Corresponding Author: Juliane J. P. Cooley, 1631 Alhambra Blvd., Suite 200, Sacramento, CA 95816, Phone: 916-731-2507; Fax: 916-454-1538, jjpcooley@ucdavis.edu.

Impact: Efforts should be made to better understand how the current screening paradigm is failing women 65 years and older. Future work should focus on determining past screening history, lapses in follow-up care, and non-invasive testing approaches.

Introduction:

Although effective screening for cervical cancer exists and can detect pre-malignant lesions and early-stage (stage I) disease (1,2), many women in the United States (US) present with late-stage disease (stages II-IV) (3). Following the introduction and widespread adoption of the Papanicolaou (Pap) smear test in the 1940's, cervical cancer incidence and mortality have fallen significantly(4,5). However, incidence rates have plateaued since 2012, and rates of invasive cervical cancer have actually increased in recent decades (5). Furthermore, from 2015–2019, nearly half of cervical cancers in the United States were diagnosed late-stage (6). Prior research suggests that women 65 had a greater burden of cervical cancer with higher incidence and more late-stage diagnoses (7–10).

The American Cancer Society (ACS), the US Preventive Services Task Force, and the American College of Obstetricians and Gynecologists all recommend that cervical cancer screening end for women >65 years with adequate negative prior screening (3 consecutive normal Pap tests, two consecutive negative HPV tests, or two consecutive negative cotests with Pap and HPV within the prior 10 years, with the most recent screening occurring within the previous five years, and no diagnosis of a precancerous lesion in the past 25 years) (1,11,12). However, 23.2% of women in the U.S. 18 are not up-to-date on recommended cervical cancer screening (13). For example, disadvantaged subgroups in the US, including uninsured women and those of lower socioeconomic status were the least likely to report being up to date with cervical cancer screening compared to women of higher educational attainment (13,14). Additionally, screening adherence may decrease as women approach 65, thereby increasing the likelihood that women have not been adequately screened prior to the upper age cutoff (15). As many as 58% of women 64 to 66 years old in a national database failed to meet the criteria to exit screening (16).

We therefore sought to examine cervical cancer stage at diagnosis and relative survival in women 65. Previous studies have focused on differences in incidence, mortality, and therapeutic management for younger women (<65) diagnosed with cervical cancer vs. older groups (7,9,15). However, they have not considered adjusted sociodemographic and clinical characteristics associated with late-stage cervical cancer in women 65 or associated relative 5-year survival by stage at diagnosis compared to younger age groups within the screening criteria. Therefore, this study utilized large population-based data from the California Cancer Registry (CCR) to examine cervical cancer relative survival by stage at diagnosis and characteristics associated with late-stage disease among women 65.

Materials and Methods:

Study Population

The CCR is a state-mandated population-based cancer surveillance system that has collected cancer incidence and patient demographic, diagnostic, and treatment information since 1988. Statewide data are collected through a network of regional registries that are affiliated with the National Cancer Institute's Surveillance, Epidemiology and End Results program. The CCR has consistently met the highest national standards for data quality and completeness. We used CCR to identify all women ≥21 years who were diagnosed with a first primary cervical cancer in California from 2009–2018, the 10 most recent years for which complete data were available. Cervical cancer was identified using the SEER site recode International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) (17) code 27010 with the histologic subtypes grouped into adenocarcinoma (8098, 8140–8245, 8250–8500), squamous cell carcinoma (8050–8084), and other histologies (8000–8046, 8130, 8246, 8560, 8570, 8720–9473). Patients diagnosed posthumously (n=81) were excluded. In total, 13,485 patients were identified, including 2,420 patients ≥65 years. However, for the main analysis, 1,043 (7.7%) patients diagnosed at unknown stage were excluded; 12,442 total patients and 2,171 ≥65 years remained.

Sociodemographic and clinical characteristics

Patient demographic and clinical characteristics included stage at diagnosis, histologic subtype, comorbidity, neighborhood socioeconomic status (nSES), health insurance status, urbanicity, marital status, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, and other/unknown), age at diagnosis, and year of diagnosis. Stage at diagnosis was determined by using American Joint Committee on Cancer staging rules (18). We defined early-stage as stage I, as the International Federation of Gynecology and Obstetrics (FIGO) classifies stage I as disease confined to the organ of origin, similar to localized stage; late-stage was classified as stages II-IV as they are similar to regional and distant stages (19).

To capture patient comorbidities, we used a modified Charlson comorbidity score, a weighted index of 16 comorbid conditions, not including cancer, diagnosed from 12 months prior to 6 months following cancer diagnosis (20). Comorbidities were categorized as having none, one, ≥2, or missing comorbidity information. nSES is derived using principal components analysis of aggregated 2015–2019 block group level demographic, economic, social, and housing data collected through the American Community Survey using methods described by Yang et al. (21). nSES was categorized into tertiles (lowest, medium, highest). Health insurance was categorized as private/military (health maintenance organization (HMO), preferred provider organization (PPO), Fee-For-Service (FFS), military insurance, and Medicare with supplement), public/Medicaid (Medicaid, county-funded, Indian Health Service or other public health service, Medicare with Medicaid eligibility, Medicare without supplement, Medicaid/Medicare), uninsured, and unknown. Urbanicity was determined using the California Health Manpower Policy Commission Medical Service Study Area (MSSA) urban/rural designation (22).

Statistical Analysis

Five-year relative survival by age group (20–39, 40–59, 60–64, 65–69, 70–74, 75–79, 80) and stage at diagnosis were calculated using SEER*Stat software (23). Relative survival was calculated using the US state-county 1992–2016 life tables by SES/ geography/ race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian and Pacific Islander, non-Hispanic American Indian and Alaskan Native, Hispanic), ages 0–99. Relative survival was calculated using the Ederer II method and is a net survival measure that estimates the probability of avoiding death due to cancer in the absence of other causes of death (24). It is defined as the ratio of the observed survival rate among those who have cancer divided by the expected survival rate for people of the same sex, race/ethnicity, and age who do not have cancer, and is expressed as a percentage.

Descriptive statistics (frequencies, percentages) and chi square tests assessed unadjusted associations between cervical cancer stage (early, late) at diagnosis and age group. Among women 65 years, multivariable logistic regression was used to assess sociodemographic and clinical characteristics associated with late-stage (stages II-IV vs. I). Models were adjusted for health insurance status, race/ethnicity, nSES, comorbidities, marital status, histologic subtype, year of diagnosis, and age in years. SAS version 9.4 was used to conduct analyses. Collinearity was examined using variance inflation factors and eigenvalues. Results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CI). A two-sided P-value < 0.05 was considered statistically significant. Sensitivity analyses were conducted including unknown stage with stages II-IV because Kaplan-Meyer curves indicated that survival for those with unknown stage at diagnosis was similar to those with stage IV diagnosis and we wanted to assess the impact of excluding unknown stage at diagnosis on associations in our main analyses. All analyses were overseen by the Institutional Review Board of the University of California, Davis.

Data Availability:

The data analyzed in this study are available from the California Cancer Registry. Access is granted through an application process by the management or data custodians (https:// www.ccrcal.org/retrieve-data/).

Results:

Among 12,442 women diagnosed from 2009–2018 with a first primary cervical cancer, 17.4% (2,171) were aged 65 years (Table 1). The proportion of women diagnosed late stage increased with increasing age through age 75 to 79 (Figure 1). Among women 65 years, the proportion diagnosed late stage ranged from 60.2% to 70.6% compared to 33.5% to 58.7% for those ages 21 to 64 years. Among women diagnosed with early-stage disease, 5-year relative survival was lowest for women 80 years and older at 51.6%. For those 20–39, 40–59, 60–64, 65–69, 70–74, and 75–79, 5-year relative survival was 93.6%, 92.9%, 89.3% 81.5%, 86.2%, and 72.0% respectively. Likewise, among those with late-stage cervical cancer, 5-year relative survival was lowest for women 80 years and older at only 23.2%. For those 20–39, 40–59, 60–64, 65–69, 70–74, and 75–79, 5-year relative survival was 51.5%, 47.5%, 41.5%, 36.8%, 39.1%, and 30.8% respectively (Figure 2).

Of 2,171 women 65, most patients were aged 65–69 (34.6%) followed by 70–74 (24.7%), 80 plus (23.1%) and 75–79 (17.5%). More women with early-stage disease at diagnosis were younger (65.7% 65–74 years and 34.3% ages 75 years and older) compared to women with lates-stage disease at diagnosis (56.7% 65–74 years and 43.3% ages75 years and older). The most common histologic subtype for both early-stage and late-stage diagnoses was squamous cell carcinoma (67.0% early-stage; 69.3% late-stage), followed by adenocarcinoma (27.1% early-stage; 19.3% late-stage), and other subtypes (5.9% early-stage; 11.3% late-stage) (Table 1). Compared to patients diagnosed at early-stage, those diagnosed at late-stage had 2 comorbidities, were unmarried, and had non-adenocarcinoma histologic subtypes.

In multivariable logistic regression models, among patients 65, factors associated with late-stage included older age at diagnosis (increase with each additional year of age, OR 1.02; CI, 1.01, 1.04), 2 comorbidities (vs. no comorbidities: OR, 1.59; CI, 1.21, 2.08), squamous cell carcinoma histology (OR, 1.38; CI 1.10, 1.74), or other subtypes (OR, 2.52; CI 1.68, 3.79) vs. adenocarcinoma (Table 2). Women of Hispanic ethnicity were less likely to be diagnosed with late-stage disease (OR 0.76; CI 0.60, 0.97) compared to non-Hispanic White women. Year of diagnosis, marital status, health insurance status, nSES, and urbanicity were not shown to be significantly associated with late-stage cervical cancer.

In sensitivity analyses including unknown stage at diagnosis with late-stage, unmarried women were more likely to be diagnosed late-stage (OR 1.27; CI 1.04, 1.56) (Table S1). Late-stage disease was associated with older age, comorbidity, non-adenocarcinoma histology and less associated with Hispanic ethnicity, consistent with the main analysis that excluded unknown stage.

Discussion

In our large population-based study in California, nearly 1 in 5 new cervical cancer cases diagnosed from 2009–2018 were in women 65, and these older women had lower 5-year relative survival for both early- and late-stage diagnoses than younger women, with women 80 years and older having the lowest survival of all age groups. We also observed that the proportions of late-stage diagnoses increased up to age 79 years. Among women 65, those who were older, had non-adenocarcinoma histology, and had comorbidities were more likely to be diagnosed with late-stage disease.

Our study confirms findings from prior US-based studies that have noted substantial burden of cervical cancer, high rates of late-stage disease, and worse survival in women 65 (7–10,15). However, to our knowledge, prior studies have not examined cervical cancer 5-year relative survival by age group and stage at diagnosis. Our study found worsening 5-year relative survival with each increasing age grouping category for both early and late-stage diagnoses.

While we cannot determine the reason for these age disparities with our data, several factors may contribute. More late-stage diagnoses may be due to inadequate screening in women approaching 65 as noted previously (15). Some reasons cited for forgoing screening include

discomfort, pain, embarrassment, and the intrusiveness of speculum-based exams (25,26). Another reason can be lack of follow-up after an abnormal screen. As many as 50% of women with abnormal results do not receive follow-up care (27,28). Comorbidities can also contribute to late-stage cancer diagnoses. Comorbidities increase with age and can result in a delayed diagnosis because of distraction from other health issues (29,30). Worse survival with older age can result from more late-stage diagnoses but can also result from less aggressive treatments in women 65. Eggemann et al. reported that patients 61 were less likely to undergo surgery and radiochemotherapy compared to patients <61 (31). Diver et al. likewise found that women 65 were less likely to receive surgery (7).

Another issue that could contribute to late-stage diagnosis is the use of supracervical hysterectomy. This procedure leaves the cervix intact and accounted for approximately 7.1% of laparoscopic hysterectomies in 2016 in the US (32). Unfortunately, some women do not realize the need to continue screening; Mattingly et al. found that only 67% of women who had undergone minimally invasive hysterectomy correctly identified whether their cervix had been removed and if they needed screening (33). McHale et al. found that 5.3% of women undergoing a secondary resection of a retained cervix after supracervical hysterectomy had cervical cancer (34).

Despite adequate prior screening, some women 65 are still diagnosed with cervical cancer (35,36). Pap testing can be difficult post-menopause when cytology tests may become less sensitive due to retraction of the squamocolumnar junction and vulvovaginal and cervical epithelium atrophy (26,37). Additionally, Pap testing is more effective at detecting squamous cell carcinoma and its precursors than adenocarcinoma which has been increasing in incidence (35,38,39). However, our study found that women with non-adenocarcinoma histologies were more likely to be diagnosed late-stage.

HPV testing provides increased sensitivity for cervical cancer precursors compared to Pap smear testing (11,40,41), but there is evidence that many women approaching age65 have not received HPV testing (42) and acceptance of it has been found to be low (43). Less intrusive options for HPV testing are becoming available including self-testing through vaginal swabs and urine collection and have been successfully used in other countries (44–47). Self-testing has been shown to be accurate and a good alternative to speculum-based exams that can be a reason to delay or altogether avoid testing as noted (25,48).

Year of diagnosis was not associated with stage at diagnosis, indicating that the proportion of late-stage cervical cancer diagnosis has not changed over time among women 65 in California. This differs from a previous US study that found that the proportion of regional and distant cervical cancer has in fact increased from 2001–2009 in most states, which might have been driven by the removal of pre-malignant lesions and the resulting increase in the proportion of invasive cervical cancer in unscreened women and those who did not receive adequate follow-up (49). However, our data are more recent and restricted to women 65, for many of whom advances in screening technologies and changes in guidelines were not applicable. This highlights the importance of ensuring women 65 have met the screening criteria prior to exiting as well as strategies aimed at enhancing follow-up after abnormal screening tests.

Prior studies of younger women have found increased late-stage cervical cancer diagnoses among women of Hispanic ethnicity, African American/Black race, and lower SES (49–51). Our study did not observe these associations and instead found that older Hispanic women were less likely than non-Hispanic White women to be diagnosed late-stage. Consistent with prior studies (8), our sensitivity analyses suggest that unmarried women 65 were diagnosed more often with late-stage cervical cancer. Increased late-stage diagnosis in unmarried patients could be related in part to differences in exposure to sexually transmitted infections between unmarried women and married women, as HPV is the causative agent in approximately 91% of cervical cancer cases (52). While the percent of HPV cases attributable to reactivation remains constant with age (18%−36%), the remaining HPV infections are caused by sexual exposure (53). The risk of acquiring HPV increases for women with new, casual, or concurrent sexual partners (53). Additionally, unmarried patients may be diagnosed late-stage more often due to economic disadvantage and less social, emotional, and practical support compared to married patients (54).

Our study had some limitations. We were unable to determine adherence to screening guidelines of our cohort or capture any HPV information, such as new or recurring infection. Additionally, we excluded 10.3% of women 65 (n=249) with unknown stage from our main analysis. However, when we included these women in our sensitivity analysis, our logistic regression results were similar. Despite these limitations, we utilized high-quality, large, population-based registry data to evaluate the stage at diagnosis and associated relative survival of women 65 diagnosed with cervical cancer.

In California, nearly one fifth of cervical cancers were diagnosed in women 65 and the majority were late-stage. Late-stage cervical cancer diagnoses increased with age and were associated with low 5-year relative survival of 36.8% to 23.2%. Our findings highlight the need to better understand how the current screening paradigm might be failing women 65. Future work should focus on determining past screening history of older women, determining lapses in follow-up care, and non-invasive testing approaches for women nearing age 65 or those who might need catch up screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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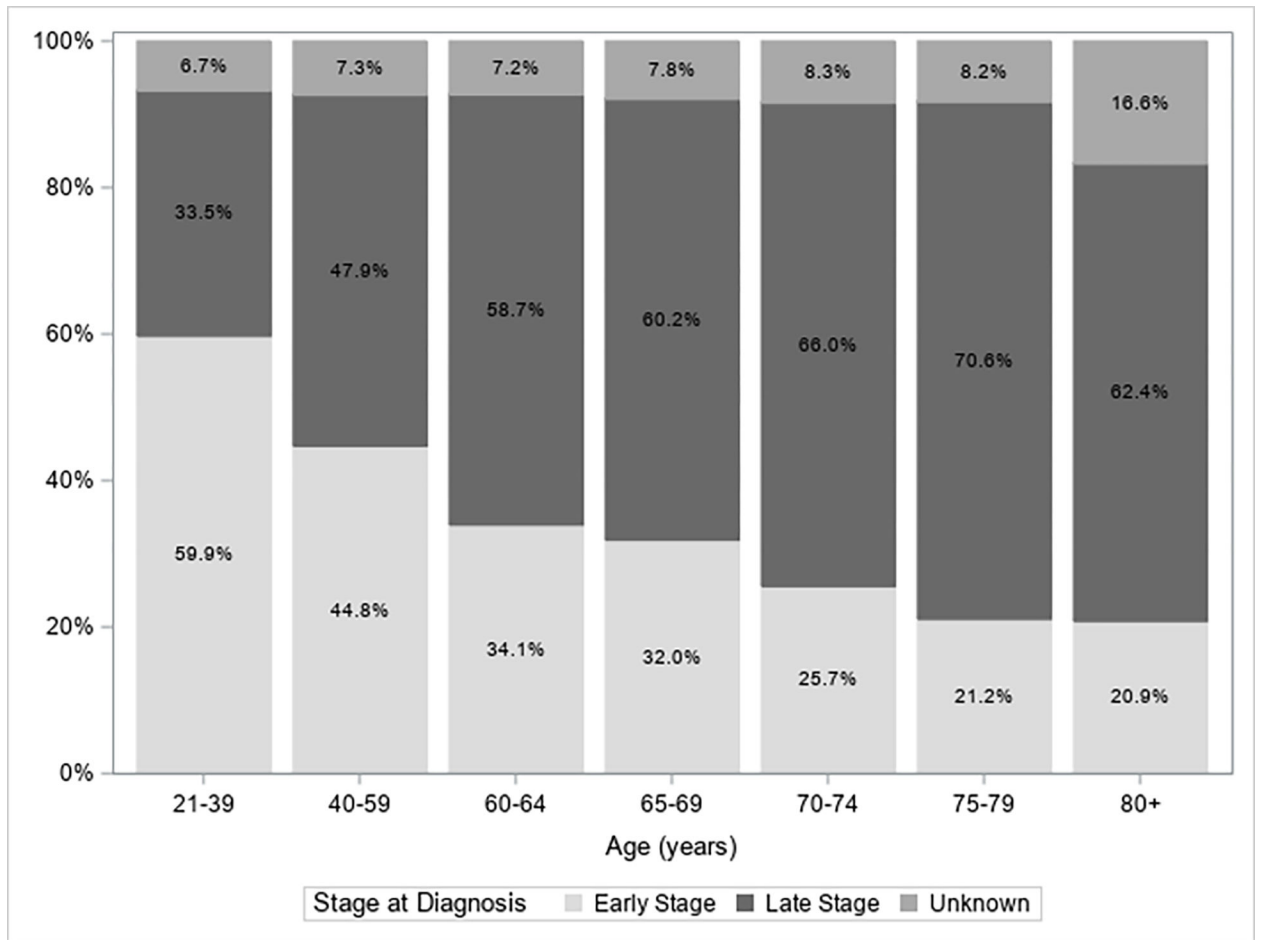
Figure 1.
Stage at Cervical Cancer Diagnosis by Age Group, 2009–2018 (N=13,485)
Bar chart showing the percentage of women diagnosed early, late, or unknown stage by seven age groupings.
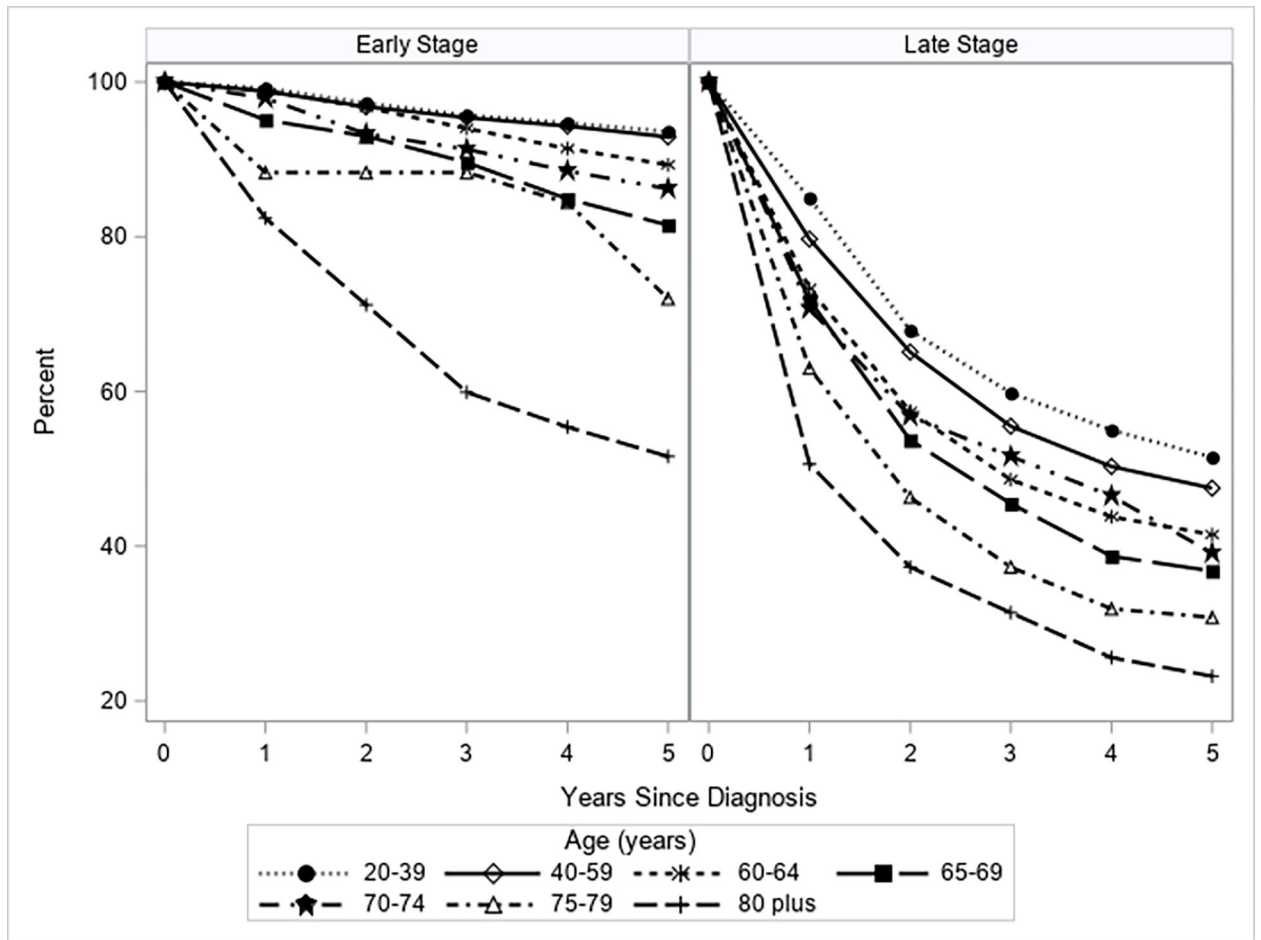
Figure 2.
Relative Survival for Cervical Cancer Patients by Stage at Diagnosis and Age Group, 2009–2018

Series plot showing relative survival rates over five years by seven age groupings. Left panel shows relative survival rates for women diagnosed early stage and right panel shows relative survival rates for women diagnosed late stage.

Table 1.

Characteristics of Cervical Cancer Patients Diagnosed 2009-2018 in California by Age Group and Stage (N=12,442)

| | 21–64 N=10,271 (82.6%) | | | 65+ N=2,171 (17.4%) | | |
| | Stage I | Stage II-IV | | Stage I | Stage II-IV | |
Characteristics	N (%)	N (%)	P*	N (%)	N (%)	P*
Age Group			<.0001			
21–39	2162 (40.2)	1204 (24.6)				
40–59	2809 (52.2)	2995 (61.2)				
60–64	406 (7.6)	695 (14.2)				<.0001
65–69				261 (41.6)	490 (31.7)	
70–74				151 (24.1)	386 (25.0)	
75–79				88 (14.0)	293 (19.0)	
80+				127 (20.3)	375 (24.3)	
Year of Diagnosis			0.0406			0.9414
2009–2012	2207 (41.0)	1926 (39.4)		241 (38.4)	581 (37.7)	
2013–2015	1529(28.4)	1501 (30.7)		187 (29.8)	468 (30.3)	
2016–2018	1641 (30.5)	1467 (30.0)		199 (31.7)	494 (32.0)	
Marital Status			<.0001			0.0004
Married	2592 (48.2)	1952 (39.9)		235 (37.5)	475 (30.8)	
Not Married	2482 (46.2)	2776 (56.7)		349 (55.7)	995 (64.5)	
Unknown	303 (5.6)	166 (3.4)		43 (6.9)	73 (4.7)	
Health Insurance			<.0001			0.0806
Private/military	3330 (61.9)	2107 (43.1)		251 (40.0)	579 (37.5)	
Public/Medicaid	1780 (33.1)	2535 (51.8)		353 (56.3)	914 (59.2)	
Uninsured	143 (2.7)	142 (2.9)		4 (0.6)	22 (1.4)	
Unknown	124 (2.3)	110 (2.2)		19 (3.0)	28 (1.8)	
Socioeconomic Status			<.0001			0.2017
Lowest	2018 (37.5)	2276 (46.5)		224 (35.7)	613 (39.7)	
Medium	1900 (35.3)	1677 (34.3)		225 (35.9)	531 (34.4)	
Highest	1459 (27.1)	941 (19.2)		178 (28.4)	399 (25.9)	
Race/ Ethnicity			<.0001			0.0532
Non-Hispanic white	2104 (39.1)	1741 (35.6)		246 (39.2)	627 (40.6)	
Non-Hispanic black	269 (5.0)	353 (7.2)		39 (6.2)	107 (6.9)	
Hispanic	2142 (39.8)	2001 (40.9)		211 (33.7)	478 (31.0)	
Asian/Pacific Islander	747 (13.9)	738 (15.1)		119 (19.0)	321 (20.8)	
Other/ Unknown	115 (2.1)	61 (1.2)		12 (1.9)	10 (0.6)	
Rural/ Urban			0.0667			0.5607

	21–64 N=10,271 (82.6%)			65+ N=2,171 (17.4%)		
	Stage I	Stage II-IV		Stage I	Stage II-IV	
Characteristics	N (%)	N (%)	P*	N (%)	N (%)	P*
Rural	661 (12.3)	661 (13.5)		80 (12.8)	183 (11.9)	
Urban	4716 (87.7)	4233 (86.5)		547 (87.2)	1360 (88.1)	
Comorbidities			<.0001			0.0003
0	3365 (62.6)	2622 (53.6)		281 (44.8)	595 (38.6)	
1	592 (11.0)	685 (14.0)		133 (21.2)	283 (18.3)	
>1	189 (3.5)	530 (10.8)		102 (16.3)	369 (23.9)	
Missing	1231 (22.9)	1057 (21.6)		111 (17.7)	296 (19.2)	
Histology			<.0001			<.0001
Adenocarcinoma	2060 (38.3)	968 (19.8)		170 (27.1)	298 (19.3)	
Squamous Cell Carcinoma	2966 (55.2)	3401 (69.5)		420 (67.0)	1070 (69.3)	
Other	351 (6.5)	525 (10.7)		37 (5.9)	175 (11.3)	

*
Chi-square p-value

Table 2.

Association between sociodemographic and clinical characteristics with late-stage (II-IV) cervical cancer diagnosis for patients   65 years, 2009–2018 (N=2,171)

Characteristics	OR Estimate (95% CI)
Age	
Each year increase	1.02 (1.01, 1.04)
Year of Diagnosis	
2009–2012	Reference
2013–2015	1.04 (0.83, 1.32)
2016–2018	1.04 (0.83, 1.32)
Marital Status	
Married	Reference
Not Married	1.22 (0.93, 1.60)
Unknown	0.80 (0.52, 1.24)
Health Insurance	
Private/military	Reference
Public/Medicaid	1.09 (0.89, 1.34)
Uninsured	2.19 (0.73, 6.54)
Unknown	0.76 (0.40, 1.45)
Neighborhood Socioeconomic Status (Tertile)	
Highest	Reference
Lowest	1.27 (0.98, 1.64)
Medium	1.08 (0.85, 1.38)
Race/Ethnicity	
Non-Hispanic White	Reference
Non-Hispanic Black	0.86 (0.57, 1.30)
Hispanic	0.76 (0.60, 0.97)
Asian/Pacific Islander	1.04 (0.79, 1.36)
Other/Unknown	0.35 (0.14, 0.86)
Rural residence	
Urban	Reference
Rural	0.97 (0.72, 1.30)
Comorbidity Score	
0	Reference
1	0.99 (0.77, 1.28)
>1	1.59 (1.21, 2.08)
Unknown	1.22 (0.93, 1.60)
Histology	

Characteristics	OR Estimate (95% CI)
Adenocarcinoma	Reference
Squamous Cell Carcinoma	1.38 (1.10, 1.74)
Other	2.52 (1.68, 3.79)

Abbreviations: OR, odds ratio; CI, confidence interval