The increasing incidence of stage IV cervical cancer in the USA: what factors are related?

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ABSTRACT

Objective Cervical cancer (International Federation of Gynecology and Obstetrics (FIGO)) stage IVA-B (distant stage) is a rare diagnosis with an approximate 5 year survival rate of 17% and with limited treatment options. The objective of this study was to determine the trends in distant stage cervical cancer in the USA and identify possible factors related to these trends.

Methods Data were obtained from the United States Cancer Statistics program from 2001 to 2018. Rates of cervical cancer screening and vaccination were evaluated using the Behavioral Risk Factor Surveillance System and TeenVaxView. SEER*Stat 8.3.8.9.2 and Joinpoint regression program 4.9.0.0 were used to calculate incidence trends.

Results Over the last 18 years, 29 715 women were diagnosed with distant stage cervical carcinoma. Black women have disproportionately higher rates at 1.55/100 000 versus 0.92/100 000 in White women (p<0.001). When examining the trends over time, there has been an annual increase in distant stage cervical cancer at a rate of 1.3% per year (p<0.001). The largest increase is seen in cervical adenocarcinoma with an average annual percent change of 2.9% (p<0.001). When performing an intersection analysis of race, region and age, White women in the South aged 40–44 have the highest rise in distant cervical cancer at a rate of 4.5% annually (p<0.001). Using the Behavioral Risk Factor Surveillance System and TeenVax data, compared with Black women, we found that White women have a nearly two-fold higher rate of missed or lack of guideline screening, 26.6% vs 13.8%. White teenagers (13–17 years) have the lowest human papillomavirus vaccination rate at 66.1% compared with others at 75.3%.

Conclusions Black women have a higher incidence of distant stage disease compared with White women. However, White women have a greater annual increase, particularly in adenocarcinomas. Compared with Black women, White women also have lower rates of guideline screening and vaccination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have demonstrated overall decreasing rates of cervical cancer in the USA. Prior studies have found that distant stage cervical cancer is rising, but did not examine the trends by region, race/ethnicity, and age.

WHAT THIS STUDY ADDS

⇒ This study found that while rates of early stage cervical cancer are decreasing, rates of distant stage cervical cancer are either stable or increasing. Histologically, the rates of increase are seen in both squamous cell carcinoma and adenocarcinoma. The largest rate of increase is seen in White women and younger women. This study also finds that White women have the highest rates of non-guideline screening and the lowest rates of human papillomavirus vaccination.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides an update to trends of distant stage cervical cancer in the USA. It identifies a continued problem with increasing rates of distant stage cervical cancer, a diagnosis with a poor 5 year survival rate, and typically no cure. It also emphasizes the continued importance of vaccination, especially in young girls.

INTRODUCTION

In high income countries, cervical cancer is the sixth most common cause of female malignancy and the ninth most common cause of female cancer mortality.[1] In general, cervical cancer affects women at a median age of 50 years; however, 50% of cases are diagnosed in women under 35 years old in the USA, a significant malignant burden on reproductive age women.[2] There are effective prevention strategies for cervical cancer including screening and vaccination. The human papillomavirus (HPV) vaccine has been approved by the US Food and Drug Administration since 2006, providing protection against 90% of HPV strains that can lead to cervical cancer.[3] The vaccine has been directly shown to decrease the incidence of cervical cancer in countries such as Sweden, using large population databases.[4]

While most cases of cervical cancer in developed countries are diagnosed early, 16% are diagnosed at a distant stage of disease, defined as International Federation of Gynecology and Obstetrics (FIGO) stage IVA-B. Five-year survival rates are very different; 17% for distant stage compared with 92% for localized cervical cancer.[5] Known disparities in cervical cancer exist in the USA; non-Hispanic Black (Black) women are more likely to be diagnosed with distant stage cervical cancer and more likely to

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have higher mortality compared with non-Hispanic White (White) women.[6 7]

Prior studies examining trends in distant cervical cancer were limited by less comprehensive datasets and did not include data on screening and prevention.[8] Additionally, most studies examined trends in cervical cancer as a whole or in the context of HPV-associated cancers and did not specifically look at details in trends of different stages of disease.[9 10] Given these limitations, our primary objective was to determine the trends of distant stage cervical cancer rates over the last 18 years using the United States Cancer Statistics data. As a secondary objective, we used national survey data to explore concurrent temporal trends in screening and vaccination.

METHODS

De-identified cancer incidence data were reported to the Centers for Disease Control National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. These data are combined to become United States Cancer Statistics. We calculated the incidences and trends of cervical cancer using this public use database including cancer incidence and population data for all 50 states, the District of Columbia, and Puerto Rico. These data provide information on more than 31 million cancer cases, representing 99% of the US population.[11] The 2021 data submission (2001–2018) was used for analysis.[12]

The Behavioral Risk Factor Surveillance System is a national system of health-related telephone surveys, completing more than 400 000 adult interviews each year, making it the largest continuously conducted health survey system in the world.[13] Survey data from 2001 to 2018 were used in this data analysis. These data were used to calculate the percentages and trends of cervical cytology screening (age older than 18). We looked at trends in non-guideline screening, which we defined as last Pap test more than 5 years ago. We chose these criteria as the Behavioral Risk Factor Surveillance System does not report on whether a patient received cervical cytology alone or cervical cytology and HPV testing. The 5 years account for both screening modalities. This follows the United States Preventative Task Force screening guidelines for patients.[14]

Teen HPV vaccination data are collected through the National Immunization Survey-Teen or TeenVaxView. This is a random-digit-dialed survey of parents or guardians of teens 13–17 years old surveying approximately 20 000 adolescents. The telephone survey is followed by a questionnaire mailed to vaccination providers to obtain the teen's vaccination history.[15] TeenVaxView data in 50 states and the District of Columbia from 2008 to 2016 was used in this data analysis. These data were used to calculate the percentage and trends of HPV vaccination (13–17 years old).

Histological subtypes of cervical cancer were divided into carcinoma (including squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and other carcinoma) according to Surveillance, Epidemiology, and End Results Cancer Statistics Review 1975–2018 by the International Classification of Diseases for Oncology, the third edition codes[16] (Online supplemental tables S1 and S2). Race/ethnicity were classified as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, non-Hispanic Asian or Pacific Islander (Asian), and other/unknown.[17] According to the US Census Bureau, the regions of the USA were divided into the Northeast, South, Midwest, and West. Stages of cancer were categorized as local, regional, distant, and unknown.[18] Distant stage of disease was defined as extension to bladder and/or rectum, FIGO class IVA or spread to distant organs, and FIGO class IVB. The 'distant' disease variable was used to identify these cases. These datasets were divided into age groups at 5 year intervals except for the Behavioral Risk Factor Surveillance System 18–24 year age group and the TeenVaxView 13–17 year age group.

Surveillance, Epidemiology, and End Results *Stat software (version 8.3.9.2, released August 10, 2021) was used to abstract the relative data of the United States Cancer Statistics by cancer type, histologic type, race/ethnicity, region, stage, and age group. Statistical Package for Social Sciences (SPSS) (version 27) was used to abstract the relative data for race/ethnicity, age group, cytologic smear, and HPV vaccination. Joinpoint Regression Program 4.9.0.0 was used to calculate incidences and trends. The Grid Search method was selected and the maximum number of joinpoints was set at three.[19] This is reported in tables as 'Trend 1' and Trend 2' with the overall average annual percent change reported in the last column in the online supplemental tables. Age-adjusted incidence rates were calculated per 100 000 women and standardized to the 2000 US population. Age-specific incidence rates were crude rates by age group. Trends were described using annual percent change with 95% confidence intervals (95% CI) in each segment and average annual percent change with 95% CI in the whole interval. If there were not enough data for the program to identify trends, data were not reported. All three discrete datasets were analyzed separately; no geographical or other linking was performed. Because all the data used in this study were derived from de-identified files, no institutional review board approval was required for this study. This study followed Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[20]

RESULTS

Case Numbers

Of 29 715 patients diagnosed with distant stage cervical cancer from 2001 to 2018 in the USA, 18 712 (63.0%) were White, 5433 (18.3%) were Black, 4010 (13.5%) were Hispanic, 1219 (4.1%) were Asian, and 341 (1.1%) were other or unknown. Of these, 11 863 (39.9%) were diagnosed in the South, 6326 (21.3%) in the West, 6166 (20.8%) in the Midwest, and 5360 (18.0%) in the Northeast.

Incidence

In 2018, the age-adjusted incidence of distant stage cervical cancer was 0.99/100 000 compared with 0.78/100 000 in 2001. Based on cell types, squamous cell carcinoma was 0.61, adenocarcinoma 0.20, and adenosquamous carcinoma 0.02 per 100 000. Based on race/ethnicity, Black and Hispanic patients have a higher incidence at, respectively, 1.55/100 000 and 1.01/100 000, compared with White patients at 0.92/100 000. Asian patients have the lowest incidence at 0.67/100 000 (all $p<0.001$). Based on region, the South has the greatest incidence at 1.17/100 000, followed by the Midwest at 0.93/100 000, the Northeast at 0.87/100 000, and the West at 0.82/100 000 (all $p<0.05$). In 2018, the crude incidence of

Table 1 Age adjusted incidence and trends of distant stage cervical cancer, squamous cell carcinoma (SCC), and adenocarcinoma from 2001 to 2018 using USCS database

	AAI	AAPC		AAI	AAPC		AAI	AAPC
	2001 to 2018	2001–2018 (95% CI)		2001 to 2018	2001–2018 (95% CI)		2001 to 2018	2001–2018 (95% CI)
Advanced stage cervical cancer	0.81 to 0.99	1.30* (0.77 to 1.84)	Advanced stage SCC	0.52 to 0.62	0.77* (0.11 to 1.42)	Advanced stage adenocarcinoma	0.15 to 0.20	2.95* (2.30 to 3.60)
Age group (years)								
30–34	0.37 to 0.67	3.32* (2.01 to 4.64)	30–34	0.26 to 0.43	2.81* (1.14 to 4.50)	30–34	–	–
35–39	0.8 to 1.05	1.99* (0.91 to 3.08)	35–39	0.61 to 0.65	1.33* (0.08 to 2.60)	35–39	–	–
40–44	1.17 to 1.33	1.12 (–0.57 to 2.83)	40–44	0.82 to 0.89	1.28 (–0.05 to 2.63)	40–44	–	–
45–49	1.23 to 1.93	2.17* 1.27 to 3.08)	45–49	0.87 to 1.26	1.42* (0.03 to 2.57)	45–49	–	–
50–54	1.68 to 2.2	2.17* (1.4 to 2.94)	50–54	1.22 to 1.50	2.04* (0.59 to 3.51)	50–54	0.24 to 0.38	3.00* (1.66 to 4.35)
55–59	1.71 to 2.3	1.29* (0.21 to 2.37)	55–59	1.11 to 1.59	1.55* (1.21 to 3.92)	55–59	0.24 to 0.37	3.75* (1.95 to 5.58)
60–64	1.99 to 2.18	1.13 (–0.05 to 2.33)	60–64	1.32 to 1.23	0.28 (–0.67 to 1.23)	60–64	0.38 to 0.62	3.27* (1.58 to 4.99)
65–69	2.4 to 2.27	0.51 (–0.22 to 1.23)	65–69	1.24 to 1.13	0.02 (–1.09 to 1.14)	65–69	0.51 to 0.67	2.00* (0.72 to 3.30)
70–74	1.96 to 2.26	1.34 (–1.22 to 3.97)	70–74	1.13 to 1.21	2.19 (–0.35 to 4.79)	70–74	0.51 to 0.55	2.24* (0.38 to 2.75)
75–79	1.68 to 2.03	1.77* (0.59 to 2.95)	75–79	0.83 to 1.28	1.54 (–0.42 to 3.53)	75–79	–	–
80+	2.04 to 1.88	–0.08 (–1.15 to 1.01)	80+	1.1 to 0.94	0.58 (-0.7 to 1.88)	80+	–	–
Race/ethnicity								
NHW	0.68 to 0.92	1.69* (0.91 to 2.47)	NHW	0.51 to 0.51	1.12* (0.06 to 2.19)	NHW	0.13 to 0.18	3.35* (2.54 to 4.16)
NHB	1.4 to 1.55	0.67 (0.03 to 1.32)	NHB	0.53 to 0.6	0.98 (–0.4 to 2.39)	NHB	0.21 to 0.29	1.71* (0.45 to 3)
Hispanic	1.22 to 1.01	–0.08 (–2.25 to 2.13)	Hispanic	0.52 to 0.73	1.3 (–0.09 to 2.71)	Hispanic	0.22 to 0.23	0.02 (–4.54 to 4.79)
NHAPI	0.93 to 0.67	0.14 (–1.27 to 1.56)	NHAPI	0.54 to 0.51	0.33 (–0.38 to 1.04)	NHAPI	–	–
Region								
Northeast	0.82 to 0.87	1.38* (0.59 to 2.18)	Northeast	0.44 to 0.57	1.37* (0.54 to 2.2)	Northeast	0.16 to 0.18	2.46* (1.34 to 3.6)
Midwest	0.79 to 0.93	1.15 (–0.07 to 2.39)	Midwest	0.95 to 0.99	0.08 (–0.69 to 0.85)	Midwest	0.14 to 0.18	3.14* (1.85 to 4.44)
South	0.8 to 1.17	2.12* (1.25 to 2.99)	South	0.86 to 0.59	-0.57 (–1.68 to 0.55)	South	0.14 to 0.24	3.84* (2.92 to 4.76)
West	0.84 to 0.82	0.65 (–0.02 to 1.31)	West	0.52 to 0.43	0.49 (–1.35 to 2.36)	West	0.15 to 0.18	1.66* (0.64 to 2.69)

Blank spaces indicate no data available.
AAPC is a summary measure of the trend over a pre-specified fixed interval.
*Percentages may not total 100 because of rounding.
AAI, age-adjusted incidence; AAPC, average annual percent change; NHAPI, non-Hispanic Asian or Pacific Islander; NHB, non-Hispanic Black; NHW, non-Hispanic White; USCS, United States Cancer Statistics.

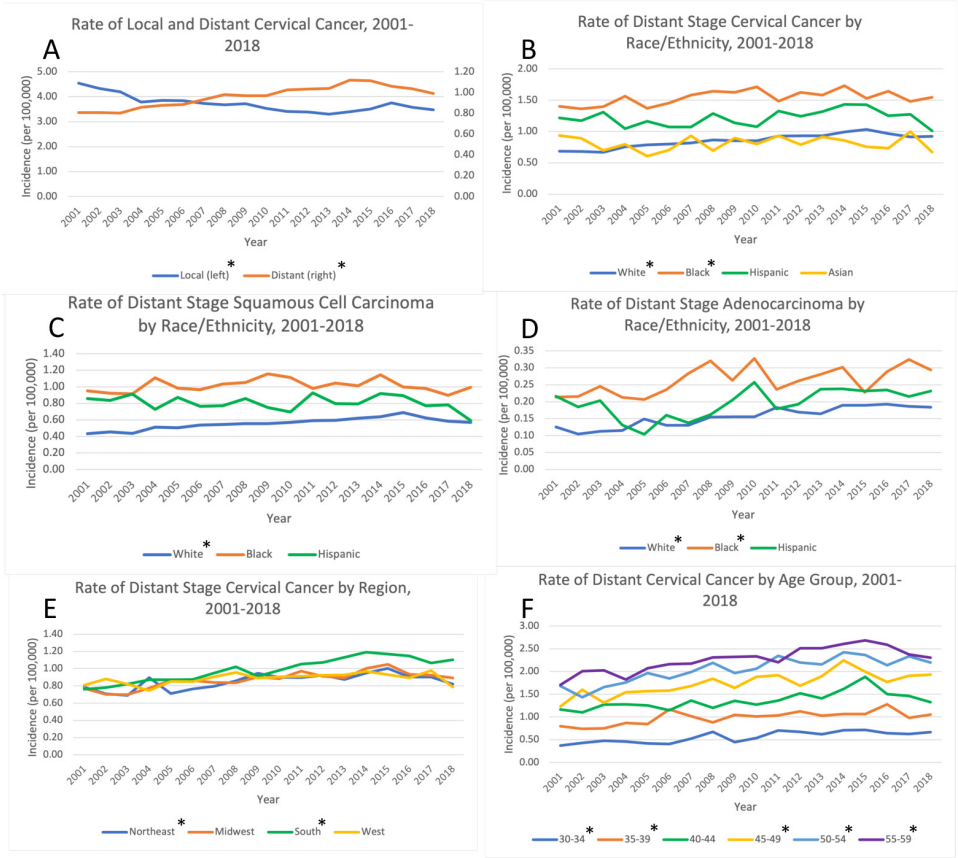

Figure 1 Trends in cervical cancer from 2001 to 2018 from the United States Cancer Statistics data. All legends with an * indicate p<0.05. All incidence rates are cases per 100 000. (A) Trends in incidence of early stage cervical cancer compared with distant stage cervical cancer. (B) Trends in distant stage cervical cancer by race and ethnicity. (C) Trends in distant stage squamous cell cervical cancer by race and ethnicity. (D) Trends in distant stage adenocarcinoma of the cervix by race and ethnicity. (E) Trends in distant stage cervical cancer by region in the USA. (F) Trends in distant stage cervical cancer by age groups.

distant stage cancer was the 55–59 age group at 2.30/100 000, the highest of all age groups. The intersectionality of Black women, age group 55–59, and residing in the South had the highest incidence at 2.61/100 000. This incidence was nearly two times higher than White women of the same age group in the South at only 1.39/100 000 (Table 1).

Trends

When examining trends in distant stage cervical cancer over time, there has been an annual increase at a rate of 1.3% per year (p<0.001); however, those with local stage cancers have decreased at 1.59% annually (p<0.001) (Table 1, Online supplemental table S3) (Figure 1A). The rates of distant cancer are increasing in White women at a rate of 1.69% per year (p<0.001) versus 0.67% annually in Black women (p=0.042) (Figure 1B). The largest increase was observed in adenocarcinoma with an average annual percent increase of 2.95% (p<0.001) (Table 1, Online supplemental table S4). Squamous cell carcinoma is increasing annually at 0.77% (p=0.021) (Table 1, Online supplemental table S5). Of those with adenocarcinomas, White women have a higher increase compared with Black women with corresponding annual increases of 3.40% and 1.71%, respectively (p<0.001 and p=0.011) (Figure 1C). However, squamous cell carcinoma is only increasing in White women at a rate of 1.4% per year (p=0.001) (Figure 1D). Based on region, the South has the largest increase with an annual increase of 2.1% (p<0.001), followed by the Northeast of 1.4% (p<0.001) (Figure 1E). The intersection of White women in the South aged 40–44 have the highest rise in distant cervical cancer at an increase of 4.5% annually (p<0.001).

Screening and Vaccination

Using the Behavioral Risk Factor Surveillance System data, we found that there is an increasing trend in non-guideline screening in all race/ethnicity groups. More specifically, White patients have the higher rates of non-guideline screening at 26.6% compared with Black patients at 13.8% (p<0.001) (Table 2) (Figure 2B). Women aged 60–64 are most likely to report non-guideline screening at a rate of 22.8%, while women aged 25–29 have the lowest rate at 2.6%. To evaluate the association with vaccination, we employed the TeenVaxView and showed that White teenagers aged 13–17 have the lowest vaccination rate at 66.1% compared with Hispanics at 75.3% (p<0.001). Black teenagers have a rate of 74.6%, and Asians have a rate of 68.1%. Vaccination rates in all race/ethnicity groups are increasing with the highest increase in Black teenagers at 6.9% annually (p<0.001) (Table 3) (Figure 2A).

Table 2 Age adjusted incidence and trends of non-guideline cervical cancer screening using BRFSS and database

	AAI	AAPC
	2001 to 2016 (%)	2001–2018 (95% CI)
Non-guideline Pap screening	8.51 to 24.20	7.0* (6.3 to 7.6)
Age group (years)		
25–29	0.97 to 2.56	6.8* (3.6 to 10.0)
30–34	2.19 to 4.64	4.1* (2.9 to 5.3)
35–39	4.48 to 6.51	3.1* (1.9 to 4.4)
40–44	5.13 to 8.95	2.6* (0.9 to 4.4)
45–49	7.48 to 11.98	3.6* (2.5 to 4.6)
50–54	8.65 to 15.95	4.3* (3.7 to 4.9)
55–59	9.82 to 20.01	4.6* (3.7 to 5.5)
60–64	13.20 to 22.81	3.7* (3.1 to 4.4)
65–69	14.49 to 28.51	4.7* (3.9 to 5.6)
70–74	19.64 to 38.71	4.7* (3.9 to 5.6)
75–79	20.39 to 47.05	5.2* (4.4 to 6.0)
80+	28.21 to 56.26	4.8* (4.0 to 5.5)
Race/ethnicity		
NHW	9.56 to 26.65	7.1* (6.5 to 7.7)
NHB	4.09 to 13.79	8.2* (6.3 to 10.1)
Hispanic	4.63 to 11.42	5.8* (4.0 to 7.6)
NHAP		

Blank spaces indicate no data available.
AAPC is a summary measure of the trend over a pre-specified fixed interval. It was computed as a weighted average of the APC from the joinpoint model, with the weights equal to the length of the APC interval.
*Percentages may not total 100 because of rounding.
AAI, age-adjusted incidence; AAPC, average annual percent change; APC, annual percent change; BRFSS, Behavioral Risk Factor Surveillance System; NHAPI, non-Hispanic Asian or Pacific Islander; NHB, non-Hispanic Black; NHW, non-Hispanic White.

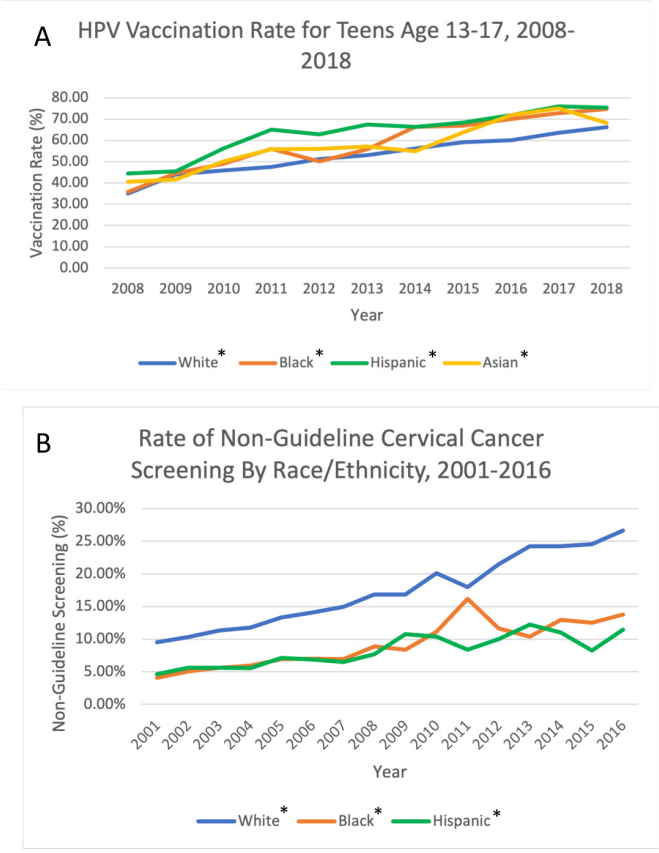

Figure 2 Trends in cervical cancer screening and vaccination. All legends with an * indicate p<0.05. (A) HPV vaccination rates in teens aged 13–17 from 2008 to 2018. Data from TeenVaxView database. (B) Trends in non-guideline cervical cancer screening rates in the USA from 2001 to 2016. Defined as last Pap smear >5 years ago. Data from Behavioral Risk Factor Surveillance System database. Rates are divided by race and ethnicity. HPV, human papillomavirus.

DISCUSSION

Summary of Main Results

This study reaffirms continued well known racial disparities in distant stage cervical cancer. While rates of early-stage cervical cancer have fallen, distant stage cancer is on the rise in White and Black women, a finding most pronounced in adenocarcinoma subtypes. Even with screening and vaccination, there is not one racial/ethnic group, region in the USA, or age group where distant stage cervical cancer has been decreasing over the last 18 years. This study also found that White patients have the lowest rate of childhood HPV vaccination and are the most likely to have non-guideline Pap smear cervical cancer screening which could be contributing to this finding.

Results in the Context of the Published Literature

Known disparities exist in access to screening programs and healthcare in the USA; this is associated with our finding that Black and Hispanic women have higher rates of distant stage cervical cancer diagnosis compared with White women, similar to prior studies.[21] While some studies have found that Hispanic women have the highest rates of cervical cancer, we found that Black women have the highest rate, followed by Hispanic women, as these other studies used Surveillance Epidemiology and End Results data.[22] Studies have found Black women to have higher rates of mortality from cervical cancer due to lack of access to insurance and appropriate treatment, an effect which can be mediated by insurance coverage.[23] Additionally, Black and Hispanic women are less likely to receive guideline-based care than White women with cervical cancer, such as not receiving chemotherapy or brachytherapy with their external beam radiation.[24] These findings, along with the persistent disparities noted in our study, highlight the importance to continue to improve access to minority populations.

While known disparities in incidence of distant cervical cancer are well known, fewer studies have examined trends in this disease. Distant stage adenocarcinoma is increasing at a rate three times that of squamous cell carcinoma. Distant stage adenocarcinoma has been increasing in White women at a rate double that of Black women, especially in younger women. Previous studies

Table 3 Age adjusted incidence and trends of HPV vaccination. TeenVaxView database

	AAI	Trend 1		Trend 2		AAPC
	2008 to 2018 (%)	Years	APC (95% CI)	Year	APC (95% CI)	2001–2018 (95% CI)
HPV vaccination rate age 13–17 years	37.20 to 69.90	2008–2011	15.2* (10.7 to 20.0)	2010–2018	4.5* (4.1 to 5.0)	6.6* (5.8 to 7.3)
Race/ethnicity						
NHW	35.00 to 66.10	2008–2010	13.6* (8.3 to 19.1)	2010–2018	4.5* (4.0 to 5.0)	6.3* (5.4 to 7.1)
NHB	35.70 to 74.60	2008–2018	6.9* (5.2 to 8.7)			6.9* (5.2 to 8.7)
Hispanic	44.40 to 75.30	2008–2011	13.6* (6.5 to 21.2)	2011–2018	2.7* (1.0 to 4.5)	5.9* (4.0 to 7.8)
NHAPI	40.60 to 68.20	2008–2018	5.9* (4.2 to 7.6)			5.9* (4.2 to 7.6)

Blank spaces indicate no data available.
Trends based on incidence were analyzed using the Joinpoint Regression Program, version 4.8.0.1, allowing up to three joinpoints. AAPC is a summary measure of the trend over a pre-specified fixed interval. It was computed as a weighted average of the APC from the joinpoint model, with the weights equal to the length of the APC interval.
*Percentages may not total 100 because of rounding.
AAI, age-adjusted incidence; AAPC, average annual percent change; APC, annual percent change; BRFSS, Behavioral Risk Factor Surveillance System; HPV, human papillomavirus; NHAPI, non-Hispanic Asian or Pacific Islander; NHB, non-Hispanic Black; NHW, non-Hispanic White.

looking at recent trends in cervical cancer have not focused only on distant disease. Additionally, several studies only found an increase in the rate of distant cervical carcinoma in Hispanic women and a decrease in distant stage adenocarcinoma in Asian women. This may be due to changes in incidence from 2015 to 2018 that may affect trends as this prior study only reports data from United States Cancer Statistics up to 2015.[9] Additionally, some studies have used smaller cancer registries rather than comprehensive population-based incidence data.[8 25]

Adenocarcinoma is less likely to be detected on routine cytology compared with squamous cell carcinoma.[26] Studies have shown that patients diagnosed with adenocarcinoma were more likely to have preceding false negative Pap smears compared with those diagnosed with squamous cell carcinoma of the cervix.[27] Cervical adenocarcinoma is associated with HPV 16 and 18, with a larger proportion of women with adenocarcinoma testing positive for HPV 18.[28] Recent changes in cervical dysplasia treatment guidelines now recommend cervical excision for patients with HPV 16 and high grade squamous intraepithelial lesion (HSIL). Patients with HPV 18 and HSIL instead are recommended to undergo colposcopy.[29] Additional research is needed to identify more ways to find women at higher risk of cervical adenocarcinoma.

Adenocarcinoma risk is increased in nulliparous women as well as women who are obese.[30 31] Increasing rates of obesity and age at first birth could be contributing to the increases seen in this histology type in the USA. This, along with studies that highlight the different rates in adenocarcinoma around the world (23.7% in North America compared with 4.3% in Africa) may indicate that there are differing biologic pathways responsible for the development of this histology of cervical cancer.[32] Additionally, societal and geographic factors may also play a role in this difference. More research is needed to understand the biologic underpinnings for the differences noted in squamous cell carcinoma and adenocarcinoma.

Our findings show that White women are more likely to self-report no cervical cancer screening in >5 years than other racial/ethnic groups. Additionally, White teens have the lowest rate of HPV vaccination. Over 90% of cervical cancer is caused by HPV; the lower rate of vaccination in White women coupled with non-guideline screening in this population could explain the trend toward the higher rate of increase in distant disease in White women. This challenges the idea that Black and Hispanic women have higher rates of distant stage diagnosis due to lower access to screening.[33] This finding demonstrates the public health imperative to vaccinate more young girls and women. A study looking at the same database found that White parents were more likely to cite safety concerns, an inappropriate age, or that their child was not sexually active as reasons for not vaccinating their child against HPV.[34] While the Behavioral Risk Factor Surveillance System data do not specify the type of cervical cancer screening the patient received, such as cytology alone or cytology with HPV screening, by using a cut-off of 5 years since the last Pap this encompasses both screening modalities. These findings come from different datasets, but they suggest that lower rates of screening and vaccination could be contributing to the disproportionately higher rates of increase in distant stage cervical cancer in White women.

Strengths and Limitations

This study has several strengths. The cancer incidence data are reliable as the United States Cancer Statistics database is comprehensive, representing 99% of the US population. Other studies have included all stages of cervical cancer, not just focusing on distant stage disease and stratifying by race, ethnicity, region, age group, and histology type to really understand the trends. To our knowledge this is one of the only studies that incorporates data from a national cancer registry database with national surveys on screening and vaccination to evaluate distant stage cervical cancer incidence and trends.

In addition to the retrospective nature of this report, our results may be confounded by reporting information bias, missing data, and lack of central pathology review. A national registry of screening

and vaccination does not exist in the USA; we were only able to obtain data from national surveys to evaluate cancer screening and vaccination trends. Thus, the use of multiple datasets composed of different patient populations limits the ability to correlate data between databases and much of this work is hypothesis generating. These datasets had different time endpoints, which can also bias the results. Datasets relying on self-report may be inaccurate due to recall bias. Additionally, with a large number of cases, significance may not always indicate causation. Different access to insurance and Medicare across different regions of the USA may have contributed to some of the trends seen. This study did not correct for hysterectomy. Prior studies that corrected for hysterectomies showed more pronounced racial disparities given that Black women are more likely to undergo hysterectomy.[35] However, a prior study using the same database correcting for hysterectomy found no significant changes in trends.[36]

Implications for Practice and Future Research

This study demonstrates that in spite of cervical cancer screening and HPV vaccination uptake in the USA, there still exist significant racial and ethnic disparities in distant stage cervical cancer. While this is well known in the literature, this study also found that there is an increase in the rate of distant stage cervical cancer, largely due to the increase in rate of distant stage adenocarcinoma in younger White women. These findings highlight the importance of proper cervical cancer screening and HPV vaccination as well as additional research to explore why rates of adenocarcinoma are increasing.

CONCLUSIONS

In conclusion, rising rates of distant stage cervical cancer in the USA warrants further research and investigation into causes and drivers to address this growing problem. Continued disparities in distant stage disease need to be addressed. Differences in HPV vaccination uptake could be contributing to some of these trends.

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Correction notice This article has been corrected since it was first published due to errors in tables 1, S3, S4, and S5. Please see the correction notice for further details.

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Correction: *The increasing incidence of stage IV cervical cancer in the USA: what factors are related?*

Francoeur AA, Liao C, Casear MA, *et al*. The increasing incidence of stage IV cervical cancer in the USA: what factors are related? *Int J Gynecol Cancer* 2022;32:1115–1122.

The third author's last name was spelt incorrectly, the correct spelling is Michelle Ann Caesar.

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Correction: *The increasing incidence of stage IV cervical cancer in the USA: what factors are related?*

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We have realized an unintentional error in our table for our submission to the *International Journal of Gynecologic Cancer*. The old table data for Tables 1, S3, S4, and S5 were mistakenly imported into the manuscript during the revision phase of the corrections. It does not change the focus of the paper or the results in the text. All other parts of the paper including the abstract, text, and figures are correct and based off of these tables. Tables 2, 3, S1, and S2 are not affected by this. The supplementary material has been replaced and please find the correct table 1 below.

Table 1 Age adjusted incidence and trends of distant stage cervical cancer, Squamous cell carcinoma (SCC), and adenocarcinoma from 2001 to 2018 using USCS database

	AAI	2001–2018		AAI	2001–2018		AAI	2001–2018
	2001 to 2018	AAPC (95% CI)		2001 to 2018	AAPC (95% CI)		2001 to 2018	AAPC (95% CI)
Advanced Stage Cervical Cancer	0.81 to 0.99	1.30* (0.77 to 1.84)	Advanced Stage SCC	0.52 to 0.62	0.77* (0.11 to 1.42)	Advanced Stage Adeno carcinoma	0.15 to 0.20	2.95* (2.30 to 3.60)
Age Group			Age Group			Age Group		
30–34	0.37 to 0.67	3.32* (2.01 to 4.64)	30–34	0.26 to 0.43	2.81* (1.14 to 4.5)	30–34		
35–39	0.8 to 1.05	1.99* (0.91 to 3.08)	35–39	0.61 to 0.65	1.33* (0.08 to 2.6)	35–39		
40–44	1.17 to 1.33	1.12 (–0.57 to 2.83)	40–44	0.82 to 0.89	1.28 (–0.05 to 2.63)	40–44		
45–49	1.23 to 1.93	2.17* (1.27 to 3.08)	45–49	0.87 to 1.26	1.42* (0.3 to 2.57)	45–49		
50–54	1.68 to 2.2	2.17* (1.4 to 2.94)	50–54	1.22 to 1.5	2.04* (0.59 to 3.51)	50–54	0.24 to 0.38	3.00* (1.66 to 4.35)
55–59	1.71 to 2.3	1.29* (0.21 to 2.37)	55–59	1.11 to 1.59	1.55* (0.84 to 2.25)	55–59	0.24 to 0.37	3.75* (1.95 to 5.58)
60–64	1.99 to 2.18	1.13 (–0.05 to 2.33)	60–64	1.32 to 1.23	0.28 (–0.67 to 1.23)	60–64	0.38 to 0.62	3.27* (1.58 to 4.99)
65–69	2.4 to 2.27	0.51 (–0.22 to 1.23)	65–69	1.24 to 1.13	0.02 (–1.09 to 1.14)	65–69	0.51 to 0.67	2.00* (0.72 to 3.3)
70–74	1.96 to 2.26	1.34 (–1.22 to 3.97)	70–74	1.13 to 1.21	2.19 (–0.35 to 4.79)	70–74	0.51 to 0.55	2.24* (0.92 to 3.59)
75–79	1.68 to 2.03	1.77* (0.59 to 2.95)	75–79	0.83 to 1.28	1.54 (–0.42 to 3.53)	75–79		
80+	2.04 to 1.88	–0.08 (–1.15 to 1.01)	80+	1.1 to 0.94	0.58 (–0.7 to 1.88)	80+		
Race/ Ethnicity			Race/ Ethnicity			Race/ Ethnicity		
NHW	0.68 to 0.92	1.69* (0.91 to 2.47)	NHW	0.51 to 0.51	1.12* (0.06 to 2.19)	NHW	0.13 to 0.18	3.35* (2.54 to 4.16)

	AAI	2001–2018		AAI	2001–2018		AAI	2001–2018
	2001 to 2018	AAPC (95% CI)		2001 to 2018	AAPC (95% CI)		2001 to 2018	AAPC (95% CI)
NHB	1.4 to 1.55	0.67* (0.03 to 1.32)	NHB	0.53 to 0.6	0.98 (–0.4 to 2.39)	NHB	0.21 to 0.29	1.71* (0.45 to 3)
Hispanic	1.22 to 1.01	–0.08 (–2.25 to 2.13)	Hispanic	0.52 to 0.73	1.3 (–0.09 to 2.71)	Hispanic	0.22 to 0.23	0.02 (–4.54 to 4.79)
NHAPI	0.93 to 0.67	0.14 (–1.27 to 1.56)	NHAPI	0.54 to 0.51	0.33 (–0.38 to 1.04)	NHAPI		
Region			Region			Region		
Northeast	0.82 to 0.87	1.38* (0.59 to 2.18)	Northeast	0.44 to 0.57	1.37* (0.54 to 2.2)	Northeast	0.16 to 0.18	2.46* (1.34 to 3.6)
Midwest	0.79 to 0.93	1.15 (–0.07 to 2.39)	Midwest	0.95 to 0.99	0.08 (–0.69 to 0.85)	Midwest	0.14 to 0.18	3.14* (1.85 to 4.44)
South	0.8 to 1.17	2.12* (1.25 to 2.99)	South	0.86 to 0.59	–0.57 (–1.68 to 0.55)	South	0.14 to 0.24	3.84* (2.92 to 4.76)
West	0.84 to 0.82	0.65 (–0.02 to 1.31)	West	0.52 to 0.43	0.49 (–1.35 to 2.36)	West	0.15 to 0.18	1.66* (0.64 to 2.69)

Blank spaces indicate no data available.
AAPC is a summary measure of the trend over a pre-specified fixed interval.
*Percentages may not total 100 because of rounding.
AAI, age-adjusted incidence; AAPC, average annual percent change; NHAPI, Non-Hispanic Asians or Pacific Islander; NHB, Non-Hispanic Black; NHW, Non-Hispanic White; USCS, United States Cancer Statistics.

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