Assessing Impact of HPV Vaccination on Cervical Cancer Incidence among Women Aged 15–29 Years in the United States, 1999–2017: An Ecologic Study

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ABSTRACT

Background: To date, the impact of the human papillomavirus (HPV) vaccine on invasive cervical cancers in the United States has not been documented due, in part, to the time needed for cancer to develop and to recent changes to cervical cancer screening guidelines and recommendations, which complicate data interpretation.

Methods: We examined incidence rates of cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) among women aged 15–29 years diagnosed during 1999–2017 using population-based cancer registry data covering 97.8% of the U.S. population. Trends were stratified by age and histology. The annual percent change in cervical cancer incidence per year was calculated using joinpoint regression.

Results: During 1999–2017, SCC rates decreased 12.7% per year among women aged 15–20 years, 5.5% among women aged 21–24 years, and 2.3% among women aged 25–29 years. The declines in SCC rates were largest among women aged 15–20 years during 2010–2017, with a decrease of 22.5% per year. Overall, AC rates decreased 4.1% per year among women aged 15–20 years, 3.6% per year among women aged 21–24 years, and 1.6% per year among women aged 25–29 years. AC rates declined the most among women aged 15–20 years during 2006–2017, decreasing 9.4% per year.

Conclusions: Since HPV vaccine introduction, both SCC and AC incidence rates declined among women aged 15–20 years, a group not typically screened for cervical cancer, which may suggest HPV vaccine impact.

Impact: Timely vaccination and improved screening and follow-up among recommended age groups could result in further reductions in invasive cervical cancer.

Introduction

In the United States, cervical cancer incidence rates have declined since the introduction of cervical cancer screening with the Papanicolaou (Pap) test in the 1950s. This reduction has mainly been observed among squamous cell carcinomas (SCC), which account for 75% of cervical cancers. Similar declines in the incidence of adenocarcinomas (AC) have not been observed because of the lower detection of glandular cancers with the Pap test, and the relatively short time since HPV vaccine introduction. Despite the decline in incidence, cervical cancer continues to be a burden in the United States. In 2017, 12,831 new cases of invasive cervical cancer were reported (8 per 100,000 women); approximately 5% of these occurred among women younger than age 30 (1).

Routine vaccination with the HPV vaccine for females aged 11–12 years was recommended in 2006. Most vaccinations given through 2014 were the quadrivalent vaccine, which targets oncogenic HPV types 6, 11, 16, and 18 (2). The 9-valent HPV vaccine became available in 2015 which targets the same types as the quadrivalent vaccine, plus five additional oncogenic types (31, 33, 45, 52, and 58) and in 2016 became the only vaccine distributed in the United States (3). Current recommendations for routine HPV vaccination include all persons aged 11–12 years, and catch-up vaccination for those who have not been adequately vaccinated through age 26 (4). Although the HPV vaccine is approved for use in adults up to age 45, vaccination is not routinely recommended for persons older than age 26; instead, shared clinical decision-making is recommended for persons in this age group to determine if vaccination is likely to be beneficial (4). HPV vaccination coverage in the United States has gradually increased since its introduction; coverage of ≥1 dose of HPV vaccine among female adolescents aged 13 to 17 years increased from 37% in 2008 to 73% in 2019 (5, 6).

Despite suboptimal coverage when the vaccine was first introduced, significant reductions in HPV infection (7), anogenital warts (8), cervical precancers (9, 10), and vaccine-type HPV prevalence among cervical precancers (11) has been observed in the United States. Modeling studies in high-income countries indicate that observing the full impact of HPV vaccination on invasive cervical cancer incidence may take decades, but the earliest impact would be seen in the youngest age groups of women (12), with substantial herd effects even with less optimal HPV vaccine coverage (13). Rapidly aggressive cancers associated with HPV types 16 and 18 that are found more frequently in younger women are also more likely to be affected earlier by the HPV vaccine. Since it has been over a decade since initial implementation of the HPV vaccine in the United States, we can now begin to examine the possible early impact of vaccination on cervical cancer incidence in young U.S. women.

Assessing the impact of HPV vaccination on cervical cancer incidence rates is complicated by changes in screening and follow-up care over time (**Fig. 1**). Prior to 2009, women were advised to start screening at age of sexual initiation or at age 21 years, whichever came first. In 2009, the American College of Obstetricians and Gynecologists

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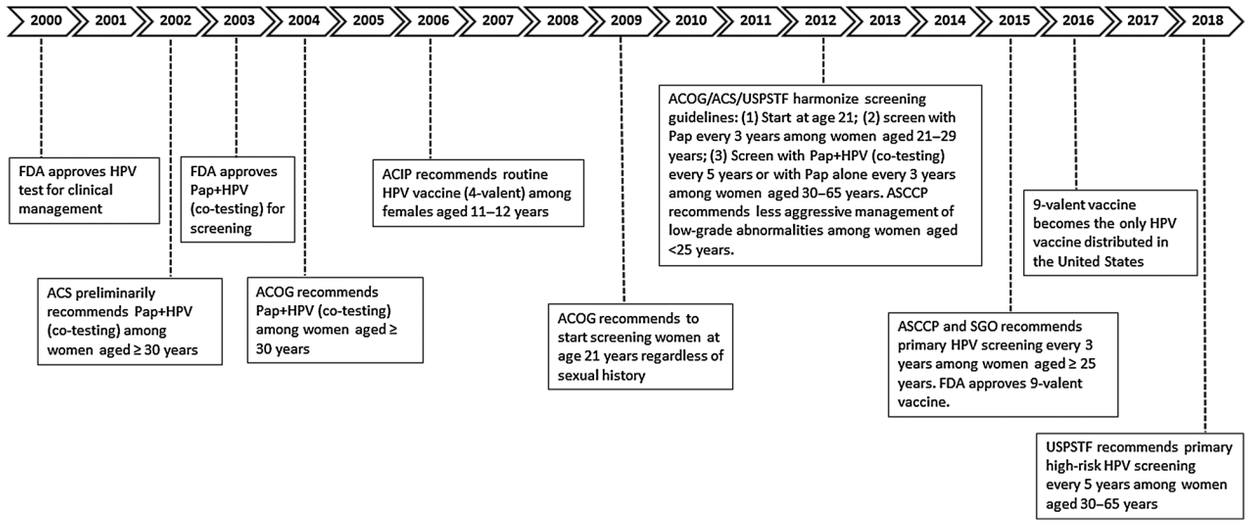

Figure 1.

Timeline of relevant recommendations and guidelines in the United States for cervical cancer testing, HPV vaccination, screening, and management. This timeline depicts relevant events in the type of testing (Pap, HPV, and HPV+Pap [co-testing]), HPV vaccination, age and frequency of testing, and management of cervical cancers and precancers. ACIP, Advisory Committee for Immunization Practices; ACOG, American College of Obstetrics and Gynecology; ACS, American Cancer Society; FDA, Food and Drug Administration; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.

(ACOG) recommended to starting screening at age 21 years regardless of sexual initiation (14); in 2012, the American Cancer Society (ACS) and United States Preventive Services Tasks Force made similar recommendations. In 2012, all three organizations recommended Pap screening intervals be extended to 3 years among women aged 21–65 years and to stop annual testing. Additionally in 2012, U.S. consensus management guidelines recommended less aggressive management and more observation of women aged under 25 years with low-grade abnormalities (15).

In this study, we examined population-based national cancer registry data in the United States to describe trends in cervical cancer incidence among women aged 15–29 years by age group, histology, and cancer stage. We also estimated cervical cancer incidence rates based on trends during the pre-HPV vaccine period and compared these with observed rates to provide further insight on the potential impact of the HPV vaccine.

Materials and Methods

Study population and design

We analyzed cancer incidence data from the United States Cancer Statistics (USCS) database, which combines data from population-based cancer registry data from the Centers for Disease Control and Prevention's (CDC's) National Program of Cancer Registries data set and the NCI's Surveillance, Epidemiology, and End Results Program data set (16). Cancer registries demonstrate that data were of high quality by meeting U.S. Cancer Statistics publication criteria (16); during 1999–2017, data from 48 cancer registries met these criteria, covering 97.8% of the U.S. population. Invasive cervical cancers among women aged 15–29 years were identified using the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) site codes C53.0–C53.9 (17) diagnosed during 1999–2017, excluding histology codes 9050–9055, 9140, and 9590–9992. We examined microscopically confirmed cases separately for SCC (8050–8084 and 8120–8131) and adenocarcinoma (AC; 8140–8575, adenosquamous included).

Statistical analysis

We calculated age-adjusted incidence rates for women aged 15–29 years per 100,000 women standardized to the 2000 U.S. population. Data were suppressed for groups with fewer than 6 cases. Analyses were stratified into three age groups based on cutoffs used for current cervical cancer screening guidelines and recommendations: 15–20, 21–24, and 25–29 years. Because of sparse data in the women aged 15–20 years, particularly at the end of the study period, years of diagnosis were aggregated into 2-year intervals from 1999 to 2014 and one 3-year interval from 2015 to 2017. Rates were calculated using SEER*Stat software version 8.3.6 (18).

To describe trends in cervical cancer incidence rates, we used joinpoint regression, which fits a series of joined straight lines on a logarithmic scale to the trends in the age-adjusted rates (19). Year of diagnosis was included as a continuous independent variable using the midpoint of each interval. The number of observations allowed us to fit a maximum of 1 joinpoint (2 trend segments) for women aged 15–20 years and a maximum of 2 joinpoints (3 trend segments) for women aged 21–24 and 25–29 years. Statistics derived from these models included the annual percent change (APC) between two time points and the average annual percent change (AAPC), which is a weighted average of the APCs over the entire time period under study. We used Bayesian information criteria (BIC) for model selection and the empirical quantile method (method 2) to calculate confidence intervals for APCs and AAPCs (20). Rates were considered to increase if the APC or AAPC was greater than zero and to decrease if the APC/AAPC was less than zero ($P < 0.05$). Otherwise, rates were considered stable.

To descriptively visualize impact, we calculated predicted rates of cervical cancer incidence if trends during the prevaccine period continued. First, we used weighted least squares (WLS) regression models to calculate the slope of the linear trend of the incidence rate for each age and histology group during 1999–2008. This time period was used to calculate predicted trends based on studies that show HPV impact in cervical precancers in 3 to 4 years after vaccination. We then calculated the predicted values from the WLS regression models for

Table 1. Cervical cancer incidence rates[a] among women aged 15–29 years by histology[b] and year of diagnosis, United States[c], 1999–2017.

	Age 15–20 years								Age 21–24 years								Age 25–29 years							
	Total		SCC			AC			Total		SCC			AC			Total		SCC			AC		
Year[d]	*n*	Rate	*n*	(%)	Rate	*n*	(%)	Rate	*n*	Rate	*n*	(%)	Rate	*n*	(%)	Rate	*n*	Rate	*n*	(%)	Rate	*n*	(%)	Rate
1999–2017	485	0.21	193	39.8	0.08	122	25.2	0.05	2,208	1.41	1,491	67.5	0.95	417	18.9	0.27	10,538	5.65	7,246	68.8	3.89	2,518	23.9	1.35
1999	79	0.35	43	54.4	0.19	14	17.7	0.06	151	2.13	100	66.2	1.41	31	20.5	0.44	685	7.21	494	72.1	5.21	142	20.7	1.49
2000									136	1.89	89	65.4	1.23	23	16.9	0.32	676	7.27	474	70.1	5.10	153	22.6	1.64
2001	61	0.26	24	39.3	0.10	14	23.0	0.06	120	1.61	86	71.7	1.15	17	14.2	0.23	618	6.85	430	69.6	4.77	147	23.8	1.62
2002									147	1.91	112	76.2	1.45	23	15.6	0.30	580	6.52	397	68.4	4.45	128	22.1	1.44
2003	53	0.23	21	39.6	0.09	14	26.4	0.06	134	1.68	88	65.7	1.10	27	20.1	0.34	550	6.12	395	71.8	4.39	115	20.9	1.29
2004									131	1.63	87	66.4	1.08	27	20.6	0.33	509	5.62	354	69.5	3.91	122	24.0	1.35
2005	72	0.30	31	43.1	0.13	20	27.8	0.08	132	1.62	87	65.9	1.07	29	22.0	0.35	507	5.56	334	65.9	3.69	132	26.0	1.44
2006									125	1.55	90	72.0	1.12	21	16.8	0.26	543	5.73	355	65.4	3.75	146	26.9	1.55
2007	59	0.24	22	37.3	0.09	17	28.8	0.07	119	1.47	74	62.2	0.91	26	21.8	0.32	524	5.39	366	69.8	3.77	118	22.5	1.23
2008									109	1.34	74	67.9	0.91	21	19.3	0.26	551	5.53	367	66.6	3.68	135	24.5	1.38
2009	54	0.21	24	44.4	0.09	12	22.2	0.05	135	1.64	80	59.3	0.97	24	17.8	0.29	574	5.71	382	66.6	3.80	153	26.7	1.52
2010									113	1.36	82	72.6	0.98	18	15.9	0.22	514	5.10	351	68.3	3.47	134	26.1	1.35
2011	48	0.19	15	31.3	0.06	13	27.1	0.05	116	1.37	79	68.1	0.94	20	17.2	0.24	499	4.89	324	64.9	3.18	139	27.9	1.37
2012									121	1.39	85	70.2	0.98	22	18.2	0.25	462	4.52	322	69.7	3.17	111	24.0	1.07
2013	27	0.11	7	25.9	0.03	9	33.3	0.04	93	1.04	63	67.7	0.70	21	22.6	0.24	553	5.38	349	63.1	3.40	154	27.8	1.51
2014									97	1.07	67	69.1	0.73	20	20.6	0.22	562	5.40	407	72.4	3.92	119	21.2	1.14
2015	32	0.09	6	18.8	0.02	9	28.1	0.02	77	0.84	54	70.1	0.59	13	16.9	0.14	556	5.30	378	68.0	3.61	134	24.1	1.28
2016									83	0.93	55	66.3	0.61	15	18.1	0.17	583	5.45	420	72.0	3.94	134	23.0	1.24
2017									69	0.79	39	56.5	0.45	19	27.5	0.22	492	4.50	347	70.5	3.16	102	20.7	0.95

Note: Data sources are the Centers for Disease Control and Prevention's National Program of Cancer Registries and the NCI's Surveillance, Epidemiology, and End Results Program.

Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma.

[a]Per 100,000 women, age adjusted to the U.S. standard population.

[b]Cervical cancers (*International Classification of Diseases for Oncology, Third Edition [ICD-O-3]* site codes C53.0–C53.9) are limited to microscopically confirmed cases and exclude ICD-O-3 histology codes 9050–9055, 9140, and 9590–9992; SCC includes ICD-O-3 codes 8050–8084, 8120–8131; AC includes ICD-O-3 codes 8140–8575.

[c]Cancer incidence compiled from cancer registries that meet the data quality criteria for all invasive cancer sites combined for each year during the period 1999–2017 (covering 97.8% of the U.S. population).

[d]Year of diagnosis in women aged 15–20 years is grouped into 2-year intervals during the years 1999–2014, and one 3-year interval (2015–2017) due to sparse data.

Table 2. Cervical cancer[a] incidence rate trends among women aged 15–29 years, United States 1999–2017[b].

Age (years)	Histology[a]	Trends 1999–2017 Trend 1 Years	Trend 1 APC (95% CI)	Trend 2 Years	Trend 2 APC (95% CI)	Trend 3 Years	Trend 3 APC (95% CI)	AAPC (95% CI) 1999–2017
15–20[c]	Total	1999–2012	−4.2 (−8.5 to 8.2)	2012–2017	−17.4[d] (−30.6 to −5.8)	—	—	−8.0[d] (−12.0 to −4.7)
	SCC	1999–2010	−5.6 (−10.3 to 6.3)	2010–2017	−22.5[d] (−45.2 to −13.2)	—	—	−12.7[d] (−19.5 to −8.8)
	AC	1999–2006	6.0 (−1.1 to 25.2)	2006–2017	−9.4[d] (−19.7 to −6.7)	—	—	−4.1[d] (−7.8 to −0.9)
21–24	Total	1999–2012	−3.1 (−4.2 to 1.4)	2012–2017	−9.9[d] (−25.4 to −5.2)	—	—	−5.0[d] (−6.9 to −3.7)
	SCC	1999–2012	−3.1 (−4.3 to 1.6)	2012–2017	−11.2[d] (−29.2 to −5.7)	—	—	−5.5[d] (−7.7 to −3.9)
	AC	1999–2017	−3.6[d] (−5.9 to −1.5)	—	—	—	—	−3.6[d] (−5.9 to −1.5)
25–29	Total	1999–2012	−3.0 (−6.6 to 4.1)	2012–2015	5.7 (−7.8 to 9.4)	2015–2017	−9.1 (−18.0 to 2.2)	−2.3[d] (−3.4 to −1.0)
	SCC	1999–2012	−3.6 (−7.2 to 4.8)	2012–2015	7.9 (−9.5 to 12.3)	2015–2017	−8.4 (−18.5 to 4.3)	−2.3[d] (−3.4 to −1.0)
	AC	1999–2017	−1.6[d] (−2.8 to −0.4)	—	—	—	—	−1.6[d] (−2.8 to −0.4)

Note: Data sources are the Centers for Disease Control and Prevention's National Program of Cancer Registries and the NCI's Surveillance, Epidemiology, and End Results Program.

Abbreviations: AAPC, average annual percent change; AC, adenocarcinoma; APC, annual percent change; SCC, squamous cell carcinoma.

[a]Cervical cancers (*International Classification of Diseases for Oncology, Third Edition [ICD-O-3]* site codes C53.0–C53.9) are limited to carcinomas (ICD-O-3 histology codes 8010–8671, 8940–8941); SCC includes ICD-O-3 codes 8050–8084, 8120–8131; AC includes ICD-O-3 codes 8140–8575. Rates were calculated as number of cases per 100,000 women and age adjusted to the 2000 U.S. standard population.

[b]Cancer incidence compiled from cancer registries that meet the data quality criteria for all invasive cancer sites combined for each year during the period 1999–2017 (covering 97.8% of the U.S. population).

[c]Year of diagnosis in women aged 15–20 years is grouped into 2-year intervals during the years 1999–2014, and one 3-year interval (2015–2017) due to sparse data.

[d]Significant at $P < 0.05$. Rates were considered to increase if the APC or AAPC was greater than zero and to decrease if the APC/AAPC was less than zero; otherwise, rates were considered stable.

each year during 2009–2017 and transformed those predicted values back to incidence rates for 2009–2017. All predicted trends were calculated using SAS 9.4 (SAS Institute).

To examine whether cervical cancer screening guideline changes may have resulted in increased diagnosis of late-stage cancers over time, we categorized cancer stage at diagnosis into early (localized), late (regional and distant), or unstaged using SEER Summary Stage guidelines (21–23). Data were grouped into 2-year or 3-year intervals and we calculated rate ratios (RR) and 95% confidence intervals to compare incidence rates in each age group using 1999–2000 as the referent time period. Confidence intervals were calculated using the Tiwari method (24).

Results

During 1999 to 2017, a total of 13,231 invasive cervical cancer cases (an average of approximately 700 each year) among women aged 15–29 years were reported (**Table 1**). Of these, 67.5% ($n = 8{,}930$) were SCCs and 23.1% ($n = 3{,}057$) were ACs. The total number of cervical cancer cases in all age groups decreased from the beginning of the study period to the most recent time period. In women aged 15–20 years, the total number of cervical cancer cases decreased from 79 (1999–2000) to 32 (2015–2017); among women aged 21–24 years, the number of cases decreased from 151 (1999) to 69 (2017), and in women aged 25–29 years, the number of cases decreased from 685 (1999) to 492 (2017). Among women aged 15–20, the total proportion of SCC decreased from 1999–2000 to 2015–2017 (54.4%–18.8%), whereas the proportion of AC increased (17.7%–28.1%). Among women aged 21–24 years, the proportion of SCC decreased during 1999 to 2017 from 66.2% to 56.5%, and the proportion of AC increased from 20.5% to 27.5%. There was very little change in the proportion of SCC and AC in women aged 25–29 during 1999–2017 (72.1%–70.5% among SCC, and no change in AC).

Squamous cell carcinoma

SCC incidence rates decreased during 1999 to 2017 in all age groups (**Table 2**). Among women aged 15–20 years, SCC rates decreased 12.7% per year on average, with the largest decline occurring during 2010 to 2017, with a decrease of 22.5% per year. Among women aged 21–24 years, SCC rates during 1999 to 2017 declined on average 5.5% per year, with the largest decline occurring during 2012 to 2017 at 11.2% per year. Among women aged 25–29 years, SCC decreased on average 2.3% per year during 1999 to 2017, with a nonsignificant increase of 7.9% per year during 2012–2014 followed by a nonsignificant decrease of 8.4% during 2015 to 2017.

Descriptively comparing observed and predicted incidence rates of SCC, we found that the observed rates declined faster than predicted rates during 2011–2017 among women aged 15–20 years (**Fig. 2A**). In women aged 21–24 years and 25–29 years, trends in observed and predicted rates were similar (**Fig. 2B** and **C**, respectively).

Adenocarcinoma

On average, trends in AC incidence rates decreased during 1999 to 2017 in all age groups. Among women aged 15–20 years, rates decreased 4.1% per year on average, with the largest decline during 2006–2017 of 9.4% per year. Among women aged 21–24 years, rates decreased on average 3.6% per year; in women aged 25–29, rates decreased 1.6% per year. Descriptively comparing observed and predicted incidence rates of AC, observed rates decreased during 2006 to 2017 (**Fig. 2A**). This was in contrast to predicted rates, which increased during 1999 to 2017. No differences in the observed or predicted rates of AC were observed in women aged 21–24 or 25–29 years (**Fig. 2B** and **C**, respectively).

Cancer stage

Compared with the referent period, the rate of early-stage cancer decreased in all age groups over time, where rates of late-stage cancers did not change over time (Supplementary Table). Unstaged cancers appeared to decrease in all age groups, but not all RR were significant.

Discussion

In this analysis of population-based cancer registry data in the United States, we found that during 1999–2017, cervical SCC declined

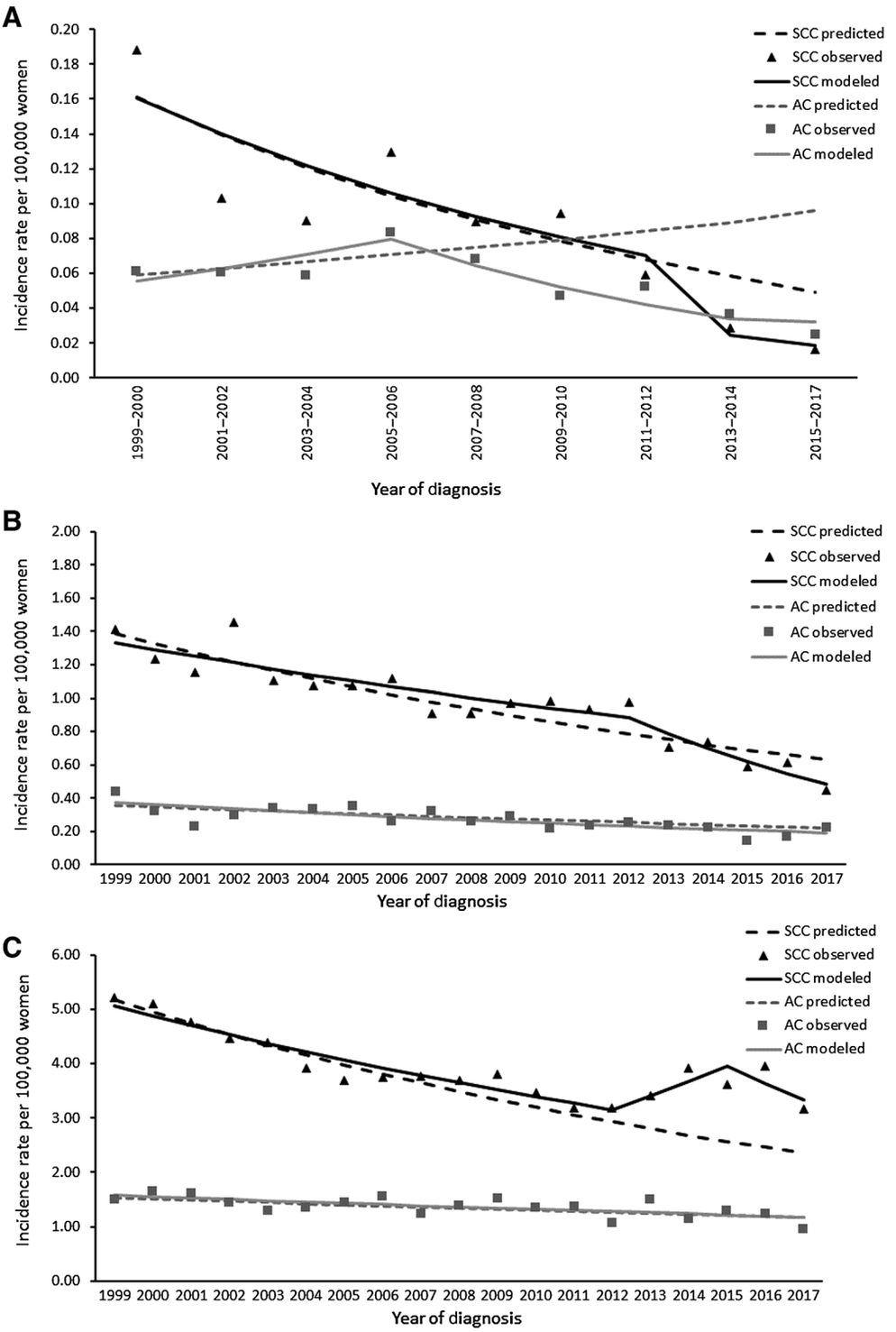

Figure 2.

Cervical cancer observed and predicted incidence trends among women aged 15–29 years by histology, United States, 1999–2017. Women aged 15–20 years (**A**); women aged 21–24 years (**B**); and women aged 25–29 years (**C**). Data Sources: Centers for Disease Control and Prevention's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Incidence data were compiled from cancer registries that met data quality standards from 1999 to 2017, covering 97.8% of the U.S. population. AC refers to adenocarcinomas defined by ICD-O-3 histology codes 8140-8575; SCC refers to squamous cell carcinomas defined by ICD-O-3 histology codes 8050-8084 and 8120-8131. Black triangles represent observed incidence rates of SCC per 100,000 women; black solid lines are the SCC modeled trends; black dotted lines are the SCC predicted trends. Gray squares represent observed incidence rates of AC per 100,000 women; gray dotted lines are the AC modeled trends; gray dotted lines are the AC predicted trends. Predicted rates were estimated based on the trends from 1999 to 2008 continuing to 2017. See Materials and Methods section for further information.

in young women aged 15–29 years. We found the largest reduction occurred in women aged 15–20 years during 2010–2017, just 3–4 years after the introduction of the HPV vaccine. In addition, observed incidence rates of SCC and AC in women aged 15–20 years were lower than rates that would be expected if trends in the prevaccine period had continued.

Early evidence of the impact of HPV vaccination on the incidence of cervical precancers has been demonstrated in high-income countries with established HPV vaccination programs, such as Australia (25) and Scotland (26) and in the United States. For example, a statewide registry in New Mexico collecting both cervical precancer and screening data observed significant reductions in cervical intraepithelial neoplasia grade 2 (CIN2) and grade 3 (CIN3) incidence from 2007 to 2014 among women aged 15–19 years and a decrease in CIN2 incidence among women aged 20–24 years even after adjusting for changes in cervical screening across the study period (9). Another U.S. study using population-based surveillance of high-grade cervical lesions in 5 catchment areas in the United States reported significant reductions in CIN2, CIN3, and adenocarcinoma *in situ* ($CIN2^+$) incidence from 2008 to 2015 among women aged 18–24 years (also adjusted for screening) just 4 to 5 years after vaccine implementation (10, 27). Further, a decreasing trend in the proportion of HPV types 16 and 18 in $CIN2^+$ lesions was observed among vaccinated women (11). Taken altogether, these U.S. studies show a population-level impact of HPV vaccination on high-grade cervical precancers, a proximal outcome to invasive cervical cancer.

On the other hand, few studies have examined the efficacy or effectiveness of HPV vaccine on invasive cervical cancer. Recently, results from long-term passive follow-up of two large HPV vaccination trial cohorts (65,656 women years) and unvaccinated control cohorts (124,245 women years) conducted in Finland from 2007 to 2015 showed 100% vaccine efficacy among invasive cervical cancer cases (28). A large study of HPV vaccine effectiveness in Sweden used nationwide population-based registry data to perform a longitudinal cohort study examining cervical cancer incidence rates in over 1.5 million women aged 10 to 30 years during 2006 to 2017 (29). The authors observed a 63% reduction in incidence (adjusted RR: 0.37 (0.21–0.57)) among vaccinated women compared to unvaccinated women, with a greater reduction of 88% among women vaccinated before 17 years of age (adjusted RR: 0.12 (0.00–0.34)). These results highlight the relative importance of HPV16/18 for cervical cancers occurring in younger women and provides further evidence that our findings may be in part a result of HPV vaccine. However, no cases of cervical cancer occurred in women younger than age 18 years in the Swedish study (29). A limiting factor for examining the impact of HPV vaccine on cervical cancer incidence in most countries outside of the U.S. is a small population size in the youngest cohorts of women, where we are most likely to observe the first indications of vaccine-related decline. In addition, a large population size is needed to examine trends in cervical cancer incidence by characteristics such as age or histology. In the United States, one study compared cervical cancers 4-year periods before and after HPV vaccination introduction (2003–2006 and 2010–2014) and noted a 29% reduction in cervical cancer in women aged 15–24 years and a 13% reduction in those aged 25–34 years (30). However, the analysis was limited by not being able to examine AC specifically or to examine age groups that aligned with screening guidelines. In the current study of the U.S. population over 19 years, we were able to examine incidence trends for both SCC and AC among women aged younger than 30 years which allowed us to explore the potential impact of HPV vaccination alongside changes in screening among women aged 15–20 years.

Although the natural history of HPV infection and cervical cancer development can take decades, there is evidence that suggests that HPV impact can be observed earlier in younger women. First, rapidly progressing cervical cancers most frequently occur in women younger than age 35 years (31), can occur as early as 3 years from HPV infection (31), and are frequently associated with HPV18 (32). Our finding of decreasing incidence rates of SCC and AC among women aged 15–20 years may be a result HPV impact in the number of rapidly progressing cancers. Also, as HPV16 represents a larger attributable fraction of cervical cancers among younger women (33), and HPV18 is more frequent in ACs (10, 34), this may allow better observation of cancer reduction due to HPV vaccine in this age group (31, 35).

An alternative explanation of declining cervical cancer incidence in women aged 15–20 years is that screening guidelines that recommended delaying screening to age 21 has resulted in less cancers being diagnosed in this age group. However, we might then expect to find increasing incidence rates of cancers, or cancers diagnosed at a later stage among women aged 21–24 years and 25–29 years, which we did not observe. Our model estimated during 2012 to 2017, the annual percent decline in SCC among women 21–24 years was 11.2% per year, and the fluctuations seen in women 25–29 years (first increasing then decreasing) were nonsignificant.

In addition, we found that incidence rates of AC started to decline among women aged 15–20 years around the time HPV vaccine was introduced. ACs are not as easily detected by Pap testing because they are generally located higher in the endocervix (36), which suggests that the decline could be partly a result of HPV vaccination. In contrast, we observed a steady decline in AC incidence rates among women aged 21–24 years and 25–29 years throughout the study period; however, the decline was greater in women aged 21–24 than in the older age group, consistent with another U.S. study that found declines in AIS among women aged 21–24 years after HPV vaccination introduction (10). The observed reduction in ACs among women aged 15–20 years around the time of HPV vaccine introduction lends support that HPV vaccination may also have contributed to the overall reduction in incidence observed in this age group. We did not observe as large of a decline among women aged 21–29 years, possibly explained in part by vaccine uptake being low in the years immediately following implementation and distribution of age at immunization varied over time (6) with most vaccinated women in this study being vaccinated at catch-up ages.

Some limitations to this study warrant consideration. First, cancers are relatively rare in younger women, and as a result there are a relatively small number of cervical cancer cases that occurred among women aged 15–20 years. In order to increase statistical stability in this age group, we aggregated data into multiyear intervals, which hampered our ability to observe more detailed trends. However, given the large population of young women and the comprehensive cancer registry, we still have a relatively large number of cervical cancers in the United States in this age group, where European countries with HPV vaccination programs are much smaller and do not have such a volume of cancers. Our data show an absolute reduction in the number of invasive cervical cancer cases and the rates over time in young women, which reflects progress in light of the World Health Organization's initiative for cervical cancer

elimination (37). Second, this study is ecological, and we were not able to assess vaccination or screening status of invasive cancer cases as linkage to vaccine registries or screening registries is not routine nor robust at a national level in the United States, although it holds promise in select settings for precancers (9, 38). Routine genotyping of all cervical cancers, particularly in younger women, could support these ecologic data in assessing HPV vaccination impact going forward. Third, our estimates of predicted cervical cancer rates are limited because they do not account for population changes in HPV vaccination uptake or cervical cancer screening after 2008.

The major strength of our study is the use of population-based cervical cancer data for nearly the entire U.S. population, allowing us to examine rates and trends by age, especially ages under 20, and histology. These data could be used in the coming years to continue to monitor the impact of HPV vaccination. Comparisons of cervical cancer trends in younger women from countries that have HPV vaccination, cervical cancer screening programs, and high-quality cancer registries could help identify contributing factors to the decreasing incidence rates.

In this population-based study of U.S. cancer registry data from 1999 to 2017, both SCC and AC cervical cancer incidence rates declined, with the largest declines among women aged 15–20 years, an age group most likely to be affected by the introduction of HPV vaccine. Continued monitoring and surveillance can determine the impact of HPV vaccine on invasive cervical cancer incidence. Timely vaccination and improved screening and follow-up among recommended age groups could result in further reductions in invasive cervical cancer.

Authors' Disclosures

No disclosures were reported.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Authors' Contributions

J.M. Mix: Conceptualization, data curation, software, formal analysis, investigation, visualization, methodology, writing–original draft, writing–review and editing. **E.A. Van Dyne:** Conceptualization, data curation, formal analysis, methodology, writing–original draft, writing–review and editing. **M. Saraiya:** Conceptualization, data curation, supervision, validation, visualization, writing–original draft, project administration, writing–review and editing. **B.D. Hallowell:** Conceptualization, data curation, formal analysis, methodology, writing–review and editing. **C.C. Thomas:** Validation, investigation, visualization, writing–review and editing.

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