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Population-Based Trends in High-Grade Cervical Lesions in the Early Human Papillomavirus Vaccine Era in the United States

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BACKGROUND: Cervical intraepithelial neoplasia grade 2, 3, and adenocarcinoma in situ (CIN2+) lesions can be monitored as early indicators of human papillomavirus (HPV) vaccine impact. Changes to screening utilization will affect observed reductions in CIN2+ rates and complicate the interpretation of vaccine impact. **METHODS:** From 2008 to 2012, 9119 cases of CIN2+ among 18- to 39-year-old residents of catchment areas in California, Connecticut, New York, and Oregon were reported to the HPV-IMPACT Project, a sentinel system for monitoring the population impact of HPV vaccine. Age-stratified CIN2+ incidence rates were calculated for each catchment. Annual cervical screening was estimated for California, New York, and Oregon catchments with administrative and survey data. The Cochran-Armitage test was used to examine trends. **RESULTS:** From 2008 to 2012, the incidence of CIN2+ significantly decreased among 18- to 20-year-olds (California, from 94 to 5 per 100,000 women; Connecticut, from 450 to 57 per 100,000 women; New York, from 299 to 43 per 100,000 women; and Oregon, from 202 to 37 per 100,000 women; $P_{trend} < .0001$) and among 21- to 29-year-olds in Connecticut (from 762 to 589 per 100,000 women) and New York (from 770 to 465 per 100,000 women; $P_{trend} < .001$); rates did not differ among 30- to 39-year-olds. During the same period, screening rates also declined, with the largest decreases among 18- to 20-year-olds (from 67% in Oregon to 88% in California) and with smaller declines among 21- to 29-year-olds (13%-27%) and 30- to 39-year-olds (3%-21%). **CONCLUSIONS:** The declines in CIN2+ detection in young women were likely due to reduced screening but could also reflect the impact of vaccination. These data illustrate challenges in interpreting CIN2+ ecologic trends in the new era of cervical cancer prevention and emphasize the importance of information such as HPV types detected in lesions to assess the impact of HPV vaccine on cervical precancers. ***Cancer*** **2015;121:2775-81.** © *2015 American Cancer Society.*

KEYWORDS: cervical cancer screening, cervical intraepithelial neoplasia (CIN), cervical precancers, high-grade cervical lesions, human papillomavirus (HPV), human papillomavirus vaccine effectiveness, human papillomavirus vaccines.

INTRODUCTION

Persistent infection with oncogenic types of human papillomavirus (HPV) can cause high-grade cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (CIN2+); these asymptomatic lesions can, over decades, progress to invasive cervical cancer if they are left untreated.[1,2] Two vaccines against HPV 16 and HPV 18, types that are responsible for 70% of cervical cancers and >50% of CIN2+ lesions, are available in the United States, one since 2006.[3] In clinical trials,

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See editorial on pages 2674-7, this issue.

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both vaccines demonstrated high prophylactic efficacy against CIN2+ lesions, and this was the main endpoint used for vaccine licensure.[4,5]

In countries with widespread cervical cancer screening programs, CIN2+ lesions can be monitored as early indicators of the population impact of HPV vaccination. Less than a decade since the introduction of HPV vaccination, reductions in CIN2+ have been observed in countries such as Australia and Denmark where vaccination programs have included catch-up vaccine for older women and have achieved high vaccination coverage shortly after implementation.[6-8] Because CIN2+ is detectable only through routine cervical cancer screening, changes to screening utilization will contribute to observed reductions in CIN2+ rates and complicate the interpretation of vaccine impact. To account for this, studies in Denmark and Australia have examined CIN2+ rates in vaccinated and unvaccinated individuals by linking disease, screening, and immunization data across regional or national population-based registries.[6-8]

Demonstrating vaccine impact on CIN2+ is more challenging in the United States because of incomplete reporting of adolescent vaccination to state-based immunization registries, a lack of national screening registries, and, importantly, evolving cervical cancer screening practices. Over the past decade, the recommended age for initiating cervical cancer screening has been raised to 21 years, and screening intervals have been increased, particularly if HPV-based cotesting is used.[9] The objectives of this ecologic study were to 1) describe trends in CIN2+ diagnosis rates in different geographic areas in the United States with population-based data from the first 5 years of the HPV-IMPACT Project[10] and 2) examine cervical cancer screening rates in the women residing in the HPV-IMPACT catchment areas.

MATERIALS AND METHODS

System Description

HPV-IMPACT was established in 2008 to monitor the impact of HPV vaccination on CIN2+ through population-based laboratory surveillance. The project is an ongoing collaboration between the Centers for Disease Control and Prevention and 5 sites in the Emerging Infections Program Network. Catchment areas include 8 contiguous cities in northwest Alameda County, Calif.; New Haven County, Conn.; Monroe County, NY; Davidson County, Tenn.; and a contiguous region of Washington and Multnomah Counties, Ore. (which includes the city of Portland). The total population of women who were 18 years old or older ranged from 230,000 to 330,000 at each participating site according to the 2010 US Census data. This project was reviewed by the US Centers for Disease Control, the Oregon Health Authority Public Health Division, and the institutional review boards of Yale University, University of California Berkeley, University of California San Francisco, Vanderbilt University, Alameda County Medical Center, Kaiser Permanente, Unity Health System, and Rochester General Hospital, and it was determined to be exempt from institutional review board approval because the activity constituted routine disease surveillance for disease control program and policy purposes. The project was approved by the State of California Committee for the Protection of Human Subjects. Informed consent was not required from any reviewing/approving institution. All patient records and information were anonymized and deidentified before analysis.

CIN2+ Case Ascertainment

Local and commercial laboratories serving the catchment areas reported cases of histologically confirmed CIN2+ diagnosed in adult ($\geq$18 years) female residents of the areas. Cases were identified through electronic health record searches or manual chart reviews. Classification systems and nomenclature for high-grade cervical lesions that were in use during the monitoring time period were included in the search criteria to identify cases. Because CIN2+ is not a nationally notifiable condition, a variety of methods were undertaken to enhance the completeness of the reporting; these included the establishment of mandated reporting in Connecticut (since 2008) and Oregon (since 2012). Laboratories that did not report before the mandate in Oregon agreed to provide retrospective data from 2008. At the time of this study, legal and logistical challenges prevented the institution of mandates in New York and California, but reporting was ensured through the building of strong relationships with the laboratories and through the engagement of community support. In addition, laboratory audits were performed at all sites to evaluate reporting completeness. The number of reporting laboratories ranged from 4 in New York to 29 in Connecticut; however, more than 80% of the cases were reported by 3 to 5 laboratories in each area. Reports were deduplicated within and between reporting laboratories.

Reported diagnoses were grouped by histologic grade into CIN2, CIN2/3 (grade not discriminated), CIN3, and adenocarcinoma in situ with or without CIN. CIN2+ diagnoses reported for the same individual within 6 months of the initial diagnosis date were considered to be related to

the same CIN2+ lesion, and the case was classified according to the highest grade diagnosis within the 6-month period. For women diagnosed with CIN2+ between the ages of 18 and 39 years, attempts were made to collect the date of birth, race/ethnicity, health insurance status, and clinical and HPV vaccination history. Sources of data differed according to the type of information collected and availability, and they included outpatient provider medical records, administrative and claims databases, immunization registries, and patient interviews.

Study Population

The analysis was restricted to participants aged 18 to 39 years who were diagnosed with CIN2+ between January 2008 and December 2012 in 4 of 5 catchment areas with complete reporting for all years: California, Connecticut, New York, and Oregon. Tennessee was excluded from this analysis because of incomplete reporting for some years. Ages were categorized into 3 age groups: 18 to 20, 21 to 29, and 30 to 39 years. Self-reported race/ethnicity was used to classify women into non-Hispanic white, non-Hispanic black, Hispanic, and Asian groups; all other reported races were combined into an other category, and this field was indicated as missing for those without race/ethnicity information. The vaccination status among those who were age-eligible for vaccination (ie, aged 11-26 years at some point during the study period) was classified as vaccinated (receipt of at least 1 dose), not vaccinated, or unknown.

Cervical Cancer Screening Estimation

Aggregate or individual-level data were used to estimate cervical cancer screening rates among female residents aged 18 to 39 years for 3 project sites: California, New York, and Oregon. Screening estimates for the catchment population were not available for Connecticut. In California and Oregon, a variety of data sources, including national and state-based surveys and administrative data, were used to calculate a weighted estimate of screening by age group. Women in the catchment area were divided into 2 groups based on insurance status (insured or uninsured), and annual screening rates were obtained for each group with data from the American Community Survey and the Behavioral Risk Factor Surveillance Survey to estimate the relative proportions and the differences in screening rates between the groups. The insured and uninsured groups were then combined to estimate overall annual screening rates by age group (18-20, 21-29, and 30-39 years), which were adjusted for insurance status.

New York obtained deidentified cervical cancer screening reports from each of 3 local cytopathology laboratories serving Monroe County, NY. Each report was deduplicated within the laboratory and included the patient's age and the results of the first screen in a given calendar year. Reports across the 3 laboratories were combined and categorized into specified age groups. Screening rates were estimated with 2010 US Census data.

CIN2+ Incidence Estimation

CIN2+ incidence was determined using the date of the first diagnosis reported within a 6-month period. Any subsequent reports from the same person during the 6 months succeeding the incident were excluded. Annual CIN2+ incidence rates were calculated with 2010 US Census data. Age-adjusted and age-specific CIN2+ incidences were estimated for each catchment area. Incidence rates are reported per 100,000 female population.

Percent changes and 95% confidence intervals were calculated for the initial and final years. The Cochrane-Armitage test for linear trends was used to examine the statistical significance of CIN2+ incidence trends. Two-sided statistical tests were considered significant at the α level of .05.

RESULTS

CIN2+ Diagnosis by Population Characteristics

From 2008 to 2012, a total of 11,394 CIN2+ diagnoses among adult women aged 18 years and older were reported to 4 HPV-IMPACT catchment areas; 9119 (80.0%) were aged 18 to 39 years and are included in this report. CIN2 was the most common histologic diagnosis reported overall (50.8%) and in all catchment areas; the incidence ranged from 41.1% in California to 57.9% in Connecticut (Table 1). CIN3 constituted 30.9% of diagnoses overall and was highest in California (36.2%). Adenocarcinoma in situ, with or without CIN, accounted for only 2.3% of diagnoses. The majority of CIN2+ diagnoses (59.2%) occurred in women aged 21 to 29 years; 18- to 20-year-olds represented only 4.6% of all reported cases. Among the 81.9% with known race/ethnicity, 61.1% were non-Hispanic white, 14.7% were non-Hispanic black, 15.9% were Hispanic, and 4.8% were Asian. Private insurance was most commonly reported overall (66.2%), and only 3.5% reported no insurance. The HPV vaccination status was available for 2991 of 6299 women with CIN2+ (47.5%) who were age-eligible for vaccination during the analysis time period. The proportion of those for whom the vaccination history was ascertained ranged by site from 23.2% in California to 62.8% in New York.

TABLE 1. Selected Characteristics Among Women Aged 18 to 39 Years Who Were Diagnosed With CIN2+ (HPV-IMPACT, 2008-2012)

	Total (n = 9119)		California (n = 1748)		Connecticut (n = 2971)		New York (n = 2301)		Oregon (n = 2099)	
Characteristic	n	%	n	%	n	%	n	%	n	%
Diagnosis										
CIN2	4637	50.8	719	41.1	1720	57.9	1155	50.2	1043	49.7
CIN2/3	1452	15.9	363	20.8	357	12.0	413	17.9	319	15.2
CIN3	2819	30.9	632	36.2	860	28.9	667	29.0	660	31.4
AIS ± CIN	211	2.3	34	1.9	34	1.1	66	2.9	77	3.7
Age										
18-20 y	417	4.6	34	1.9	173	5.8	150	6.5	60	2.9
21-29 y	5400	59.2	937	53.6	1782	60.0	1468	63.8	1213	57.8
30-39 y	3302	36.2	777	44.5	1016	34.2	683	29.7	826	39.4
Race/ethnicity										
Non-Hispanic white	4564	61.1	437	34.2	1419	58.1	1504	69.7	1204	75.7
Non-Hispanic black	1097	14.7	258	20.2	379	15.5	389	18.0	71	4.5
Hispanic	1185	15.9	329	25.8	525	21.5	185	8.6	146	9.2
Asian	356	4.8	193	15.1	49	2.0	43	2.0	71	4.5
Other	267	3.6	60	4.7	71	2.9	37	1.7	99	6.2
Missing	1650	—	471	—	528	—	143	—	508	—
Insurance										
Private	5009	66.2	1039	70.9	1615	59.6	1324	68.1	1031	71.3
Public[a]	2037	26.9	402	27.4	956	35.3	471	24.2	208	14.4
Uninsured[b]	267	3.5	13	0.9	88	3.2	56	2.9	110	7.6
Other	251	3.3	12	0.8	50	1.8	93	4.8	96	6.6
Missing	1555	—	282	—	262	—	357	—	654	—
Vaccination status[c]										
Vaccinated (≥1dose)	1452	23.1	127	11.7	555	26.4	568	33.0	202	14.5
Not vaccinated	1539	24.4	125	11.5	672	32.0	513	29.8	229	16.5
Unknown	3308	52.5	834	76.8	875	41.6	641	37.2	958	69.0
Not age-eligible	2820	—	662	—	869	—	579	—	710	—

Abbreviations: CIN2+, cervical intraepithelial neoplasia grade 2, 3, and adenocarcinoma in situ; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia (numbers following "CIN" indicate the grade).

[a] Includes Medicaid (state assistance), Medicare, Indian Health Services, and Military/Veterans Administration.

[b] Includes documented self-pay or no coverage.

[c] Excludes those who were not eligible for vaccination because of age.

CIN2+ Incidence

Age-adjusted rates of newly diagnosed CIN2+ per 100,000 significantly decreased between 2008 and 2012 in Connecticut (from 543 to 407) and New York (from 505 to 344; $P_{trend} < .0001$). During the same time period, there was a nonsignificant increase in the incidence of CIN2+ in California (from 277 to 293) and Oregon (from 325 to 344).

Reported incidence rates varied across the 4 catchment areas for every year included in the analysis (Fig. 1). For all years, rates were highest in Connecticut, which was followed by New York, Oregon, and California. The age-adjusted incidence was 1.96 times as high in Connecticut versus the rate in California in 2008, but by 2012, the incidence in Connecticut was only 1.39 times that of California.

CIN2+ incidence rates for the 4 catchment areas are presented by age group and year in Table 2. There was a sharp and consistent decrease among 18- to 20-year-old women across all sites between 2008 and 2012; the decrease in incidence ranged from 82% in Oregon to 94% in California ($P_{trend} < .0001$ for all areas). Incidence trends were not consistent across catchment areas in the older age groups in the same 5-year period. In the 21- to 29-year-old group, the CIN2+ incidence significantly decreased by 40% in New York and 23% in Connecticut ($P < .001$) but increased slightly in Oregon (12%; 95% confidence interval, −6% to 34%) and California (13%; 95% confidence interval, −7% to 37%). Among those aged 30 to 39 years, incidence rates did not change significantly in any of the catchment areas.

Trends in CIN2+ Diagnosis and Screening Utilization

Figure 2 displays annual CIN2+ incidence and screening rates by age group in the 3 catchment areas for which screening rates could be estimated. Among 18- to 20-year-olds, both CIN2+ and screening rates decreased substantially in all catchment areas; screening rates decreased

67% in Oregon, 80% in New York, and 88% in California. Although the proportion of women screened in this age group differed across catchment areas in the first year of the study (from 41% in New York to 15% in Oregon), screening rates declined to less than 10% in all areas by 2012, with the steepest decline occurring between 2009 and 2010. Overall CIN2+ rate reductions exceeded estimated declines in screening in this age group by 7% in California, 5% in New York, and 15% in Oregon.

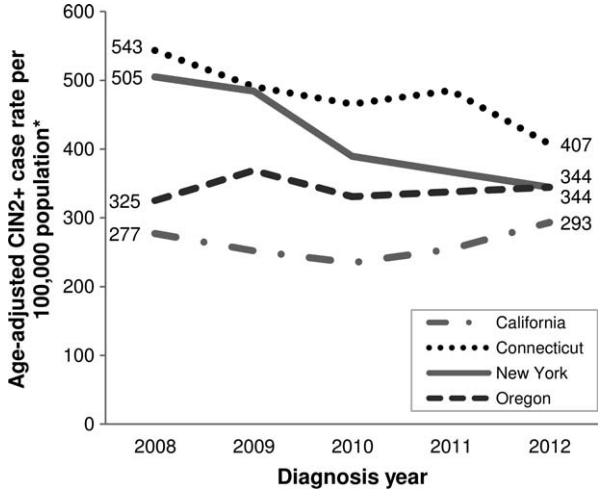

Figure 1. Age-adjusted CIN2+ incidence (per 100,000) among adult women aged 18 to 39 years by catchment area and year (HPV-IMPACT, 2008-2012). *Rates were age-adjusted to the 2010 US Census female population in 5-year age groups (18-19, 20-24, 25-29, 30-34, and 35-39 years). CIN2+ indicates cervical intraepithelial neoplasia grade 2, 3, and adenocarcinoma in situ.

Screening rates decreased among women aged 21 to 29 years during the same time period, but to a smaller degree. Relative decreases were 13% in Oregon, 26% in New York, and 27% in California. In New York, there was a corresponding and larger decline (40%) in the CIN2+ incidence during the 5-year period. No CIN2+ decreases were observed in California or Oregon in this age group. In the 30- to 39-year-old age group, there were inconsistent changes in both CIN2+ and screening rates. Overall, screening decreased in all 3 catchment areas (3% in California, 18% in New York, and 21% in Oregon), whereas the CIN2+ incidence remained largely unchanged.

DISCUSSION

This population-based study describes the CIN2+ incidence in women across multiple geographic areas in the United States and examines CIN2+ incidence trends in the first few years since the introduction of HPV vaccine. We found striking differences in the baseline incidence of CIN2+ diagnoses across the 4 catchment areas. In the first year of the study, the CIN2+ burden in Connecticut and New York was approximately twice that in Oregon and California. Site differences diminished over the next 4 years as CIN2+ rates significantly decreased in Connecticut and New York but remained the same or slightly increased in the other 2 catchment areas. Differences in screening utilization among health care providers may be partially responsible for the large geographic variability in CIN2+ rates. California and Oregon, areas with the lowest CIN2+ incidence and lower screening rates, tended to have higher population enrollment in managed care

TABLE 2. Incidence of CIN2+ (per 100,000) by Age Group, Year, and Catchment Area (HPV-IMPACT, 2008-2012)

	2008		2009		2010		2011		2012		
Age	n	Rate	n	Rate	n	Rate	n	Rate	n	Rate	% Change (2008-2012): % (95% Confidence Interval)
18-20 y											
California	18	94	10	52	3	16	2	10	1	5	−94 (−99, −58)
Connecticut	87	450	39	202	22	114	14	72	11	57	−87 (−93, −76)
New York	56	299	42	224	32	171	12	64	8	43	−86 (−93, −70)
Oregon	22	202	20	183	10	92	4	37	4	37	−82 (−94, −47)
21-29 y											
California	192	348	173	314	176	319	180	326	216	392	13 (−7, 37)
Connecticut	397	762	367	704	342	656	369	708	307	589	−23 (−33, −10)
New York	363	770	350	743	276	586	260	552	219	465	−40 (−49, −29)
Oregon	232	447	252	486	237	457	232	447	260	501	12 (−6, 34)
30-39 y											
California	160	270	153	258	133	224	157	265	174	293	9 (−12, 35)
Connecticut	198	368	204	379	212	394	217	403	185	343	−7 (−24, 14)
New York	142	321	146	330	122	276	129	291	144	325	1 (−20, 28)
Oregon	137	241	180	317	163	287	187	330	159	280	16 (−8, 46)

Abbreviation: CIN2+, cervical intraepithelial neoplasia grade 2, 3, and adenocarcinoma in situ.

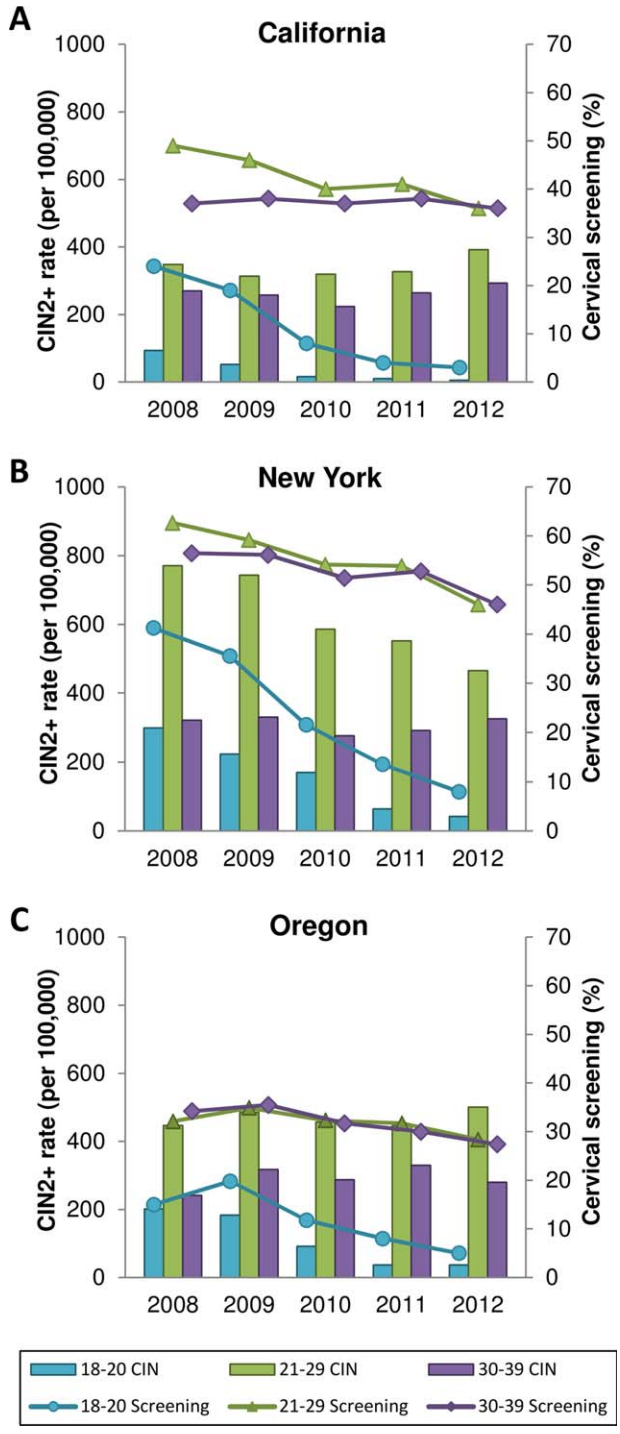

Figure 2. CIN2+ incidence (per 100,000 women) and proportions screened by age group, year, and catchment area (HPV-IMPACT, 2008-2012). CIN indicates cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2, 3, and adenocarcinoma in situ.

organizations, which were among the first to implement new recommendations to extend screening intervals.[9] The gradual adoption of new screening guidelines by a wider array of providers may explain the narrowing gap in rates and larger declines in Connecticut and New York, where traditional fee-for-service health systems predominated. Another possible reason for the observed variability in CIN2+ incidence across sites could be differences in population characteristics such as sexual behaviors and smoking, which may differentially influence the risk for CIN2+ in these populations. Finally, differences in vaccination coverage may also play a role, although this is unlikely because the greatest variability in incidence was in the first year when few adult women with CIN2+ would have been vaccinated, and site differences diminished over time as vaccination coverage increased in this population.

We found a dramatic and consistent decrease in CIN2+ incidence in all catchment areas among 18- to 20-year-old women. By 2012, CIN2+ diagnoses in this age group had declined to 10 or fewer cases per 100,000 at all 4 sites. The observed declines in this age group were likely due to wide-scale implementation of new guidelines that recommend cervical cancer screening begin at the age of 21 years. This is reflected in the substantial decrease in cervical cancer screening that we found in this age group during the same time period. However, the larger decreases in CIN2+ incidence with respect to declines in screening suggest the possible impact of the vaccine on reducing the true burden of CIN2+ in this age group.

Trends in CIN2+ rates in the older age groups were inconsistent and more difficult to interpret. In particular, we did not observe any decreases in CIN2+ incidence in the 20- to 29-year-age groups in California and Oregon despite the sustained declining trends in screening. An analysis of more years of data is ongoing to determine any emerging trends. The impact of the vaccine on CIN2+ trends in this age group should become clearer over time as more women in this age group receive HPV vaccine at younger ages. However, decreases in the measured incidence due to vaccination may be confounded by continued changes in screening practices, such as the recent approval of an HPV-based test for the primary screening of women who are 25 years old or older. Among women aged 30 to 39 years, CIN2+ rates were similarly inconsistent with no discernible trends over the 5-year study period.

This analysis demonstrates the challenges in examining the ecologic effect of HPV vaccination on CIN2+ incidence trends during a time of concurrent changes to screening recommendations, even in geographically well-defined populations. Although our data suggest that less screening in the youngest age group likely had the largest impact on the observed declines in CIN2+ rates, some of the observed decreases may be attributable to vaccination.

However, it was not possible to quantify the relative contribution of vaccination in these populations. Although a complete and accurate vaccination history was not obtainable for the majority of this study population, national survey data indicate that self-reported HPV vaccination coverage (≥1 dose) in women aged 19 to 26 years was low during our study period and ranged from 11.6% in 2008 to 34.5% in 2012.[11]

To assist with the interpretation of observed CIN2+ trends, we identified all available data sources with which age-stratified annual screening rates in the catchment population could be estimated. However, there were insufficient data to allow estimation in one project area, and the use of disparate data sources and estimation methodologies prevented valid comparisons across the other 3 areas. Despite these limitations, the fact that our findings were similar to results obtained from the only population-based screening registry in the United States is reassuring.[12] In that study, Cuzick et al[12] found a significant 61% decrease in screening in females aged 15 to 20 years from 22.4% in 2008 to 8.7% in 2011. Finally, changes to CIN2+ terminology and coding that occurred during the study period may have also affected the completeness of the reporting. However, extensive audits of reporting laboratories using broad search criteria did not suggest differential or underreporting over time.

To our knowledge, this is the first examination of trends in CIN2+ diagnosis in multiple populations of US women in the new era of cervical cancer prevention. These results demonstrate large and uniform reductions in the CIN2+ incidence in young women aged 18 to 20 years as well as more variable declines in women aged 20 to 29 years, which may be due to a combination of new screening guidelines and HPV vaccine introduction. Importantly, our data illustrate the challenges in assessing HPV vaccine impact on cervical precancers in the United States and emphasize the importance of additional information such as the types of HPV detected in these lesions to assist in this determination.[13]

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CONFLICT OF INTEREST DISCLOSURES

Linda M. Niccolai reports personal fees from Merck outside the submitted work.

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