

## Declining Rates of High-Grade Cervical Lesions in Young Women in Connecticut, 2008–2011

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### Abstract

Vaccines that prevent infection with human papillomavirus (HPV) types 16 and 18 that are known to cause cervical cancer have been available in the United States since 2006. High-grade cervical lesions are important for monitoring early vaccine impact because they are strong surrogates for cancer yet can develop within years after infection as opposed to decades. Trends in high-grade cervical lesions including cervical intraepithelial neoplasia grades 2, 2/3, and 3 and adenocarcinoma *in situ* among women ages 21 to 39 years old were examined using a statewide surveillance registry in Connecticut from 2008 to 2011. During this time period, HPV vaccine initiation increased among adolescent females from 45% to 61%. Analyses were stratified by age, according to census tract measures of proportion of population Black, Hispanic, living in poverty, and by urban/nonurban counties. The annual rate per 100,000 females ages 21 to 24 years declined from 834 in 2008 to 688 in 2011 ( $P_{\text{trend}} < 0.001$ ). No significant declines were observed among women ages 25 to 39 years. Significant declining trends also occurred in census tracts with lower proportions of the population being Black, Hispanic, or living below the federal poverty level. Declines in high-grade cervical lesions have occurred among young women during 2008 to 2011. This is the first report of declines in cervical neoplasia in the United States since HPV vaccines became available. Continued surveillance is needed to measure vaccine impact and monitor health disparities. *Cancer Epidemiol Biomarkers Prev*; 22(8); 1446–50. ©2013 AACR.

### Introduction

Human papillomavirus (HPV) is a known cause of cervical cancer and associated with other genital cancers (e.g., anal, penile, vaginal, vulvar) and cancers of the head, neck, and mouth. Vaccines that prevent infection with HPV types 16 and 18, associated with approximately 50% of precancerous high-grade cervical lesions and approximately 70% of cervical cancers (1), are now available in the United States (U.S.) and recommended for routine use among 11- to 12-year-old adolescents and for catch-up or permissive vaccination through the age of 26 years (2). High vaccine efficacy (3, 4) coupled with increasing rates of vaccine uptake indicates the potential for these vaccines to have substantial impact on reducing HPV-associated diseases. During 2007 to 2011, estimates from the National Immunization Survey-Teen indicate that vaccine coverage among females ages 13 to 17 years increased from 25% to 53% (5, 6). Among women ages 19 to 26 years who are eligible for catch-up vaccination, rates increased from 11% in 2008 to 21% in 2010 based on estimates from the National Health Interview Survey (7).

Recently reported declines in genital warts and vaccine-type HPV infections in the United States may reflect early vaccine impact. Bauer and colleagues showed a 35% decrease in genital warts among women younger than 21 years of age (from 0.94%–0.61%) between 2007 and 2010 using a family planning administrative database in California (8). Kahn and colleagues estimated a reduction in prevalence of vaccine-type HPV infections from 32% to 13% during 2006 to 2010 among young women recruited from primary care clinics (9). Similar findings have been reported from other countries (10–12).

High-grade cervical lesions including cervical intraepithelial neoplasia grades 2 and 3 and adenocarcinoma *in situ* (CIN2<sup>+</sup>/AIS) are important for monitoring early vaccine impact because they are intermediate stages in progression to cancer and develop within years after infection as opposed to decades for invasive carcinoma (13–15). High-grade cervical lesions are also important to monitor because of their own public health significance. More than one million women are diagnosed with these conditions every year in the United States, and these diagnoses are associated with high subsequent health care usage, costs, and psychosocial harms for the patient (16–18). The purpose of this analysis was to analyze trends in high-grade cervical lesions in Connecticut in 2008 to 2011. Estimates of HPV vaccination among adolescent females in Connecticut are above the national average and increased from 45% to 61% during this time period (5, 6). This analysis is based on statewide surveillance data collected from mandatory reporting enacted in 2008.

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## Materials and Methods

In 2008, the Centers for Disease Control and Prevention began to monitor the impact of HPV vaccination through population-based surveillance of CIN2<sup>+</sup>/AIS conducted by the Emerging Infections Program network (19). To facilitate implementation of this surveillance system in Connecticut, the Department of Public Health added CIN2<sup>+</sup>/AIS (subsequently referred to as high-grade cervical lesions) to the list of mandatory reportable diseases, effective January 1, 2008; this system has been previously described (20). Briefly, all 34 pathology laboratories in the state are currently in compliance with the reporting requirement. Reports contain diagnostic information as well as patient demographics, including residential address. All labs are regularly contacted to ensure ongoing, complete, and timely reporting, and quality assurance protocols include logic and range checks and double data entry for a subset of cases. This work has been deemed public health surveillance by university, state, and federal Institutional Review Boards and thus exempt from the need for human subjects approval.

Cases were geocoded to the census tract level using ArcGIS version 9.2 software (ESRI) and the Federal Financial Institutions Examination Council website (21). Cases were then linked to measures of race, ethnicity, and federal poverty levels from the U.S. Census 2010 and 2006 to 2010 American Community Survey. Census tract level measures of race and ethnicity were obtained from U.S. Census 2010 data as percentages of the population in each census tract that were Black and Hispanic, respectively. The poverty measure was obtained from the U.S. Census 2006 to 2010 American Community Survey 5-year estimates as the percentage of population in each census tract living below the federal poverty level as determined by family income, size, and composition. We used the 4 categories for the area-based measures of race, ethnicity, and poverty recommended by the Public Health Disparities Geocoding Project of less than 5.0%, 5.0% to 9.9%, 10.0% to 19.9%, and 20% or more (22, 23). We examined cases by county type designated as urban if it contained a city of more than 100,000 population (3 out of 8 counties in the state).

Statistical analyses were restricted to women ages 21 to 39 years. Age was obtained from surveillance reports and examined in 5-year categories that correspond to national surveillance reports with the exception of the youngest age group that was classified as 21 to 24 years because of screening guidelines that now recommend first Pap test not be conducted before the age of 21 years (24–26). We used population estimates from 2010 U.S. Census data to compute the annual number of cases per female population overall, for each age group, and for each level of the area-based sociodemographic measures. We estimated 95% confidence intervals (CI) for differences between 2008 and 2011 and  $P_{\text{trend}}$  tests during the 4-year period.

## Results

During 2008 to 2011, 8,435 cases of high-grade cervical lesions among women ages 21 to 39 years were reported

and 8,146 (97%) were successfully geocoded and included in all subsequent analyses. The number of cases declined from 512 in 2008 to 476 in 2011 per 100,000 females ( $P_{\text{trend}} = 0.002$ ; Table 1). The largest decline and the only statistically significant trend were observed among women ages 21 to 24 years from 834 to 688 cases ( $P_{\text{trend}} < 0.001$ ). The 4-year declines were significant in areas with less than 5.0% of the population Black ( $P_{\text{trend}} = 0.006$ ), Hispanic ( $P_{\text{trend}} = 0.002$ ), in poverty ( $P_{\text{trend}} = 0.003$ ), and in nonurban counties ( $P_{\text{trend}} = 0.002$ ). Because of the strong and significant declines among women ages 21 to 24 years, we examined trends by area-based measures restricted to this age group (Fig. 1). Declines were observed across all levels of each measure and were statistically significant in areas with less than 5.0% and 5.0% to 9.9% of the population Black ( $P_{\text{trend}} < 0.001$  and  $P_{\text{trend}} = 0.009$ , respectively); less than 5.0%, 5.0% to 9.9%, and 10.0% to 19.9% of the population Hispanic ( $P_{\text{trend}} = 0.001$ ,  $P_{\text{trend}} < 0.015$ , and  $P_{\text{trend}} = 0.004$ , respectively); and less than 5.0% and 5.0% to 9.9% of the population living in poverty ( $P_{\text{trend}} = 0.001$  and  $P_{\text{trend}} = 0.035$ , respectively). Declines were statistically significant in both urban and nonurban counties ( $P_{\text{trend}} \leq 0.001$  for both).

## Discussion

In Connecticut, a significant decline in high-grade cervical lesions was observed between 2008 and 2011 among women ages 21 to 24 years. A decline in women younger than 25 years but not women ages 25 years and older may reflect HPV vaccine impact because of routine recommendations for vaccination during adolescence and higher rates of coverage among adolescents compared with young adults (5–7). Furthermore, the strongest and most significant declines occurred in areas with lower proportions of the population Black, Hispanic, and living in poverty and in nonurban counties. Though reasons for this are not clear, it is possible that these differences reflect the higher prevalence of HPV 16/18 targeted by the vaccine among White women and women living in low poverty areas (27, 28). This finding suggests that ongoing monitoring of vaccine impact and health disparities will be critical.

These findings are consistent with results from the studies in the United States and other countries that may reflect early vaccine impact (8–12). For example, Australia has observed dramatic declines in genital warts among women under 21 years of age from 18.6% to 1.9% during 2007 to 2011 and in high-grade cervical abnormalities among women under 18 years of age from 0.80% to 0.42% before and after 2007 (10, 11). Sweden has experienced a 17% decline in genital warts among women from 2006 to 2010, with the largest declines among women ages 17 to 18 years (12).

Although vaccine impact is one possible explanation for the observed decline, these data are ecological in nature and other reasons including changes in rates of cervical cancer screening need to be considered. High-grade lesions are diagnosed on cervical biopsies that are

**Table 1.** Annual rate of high-grade cervical lesions per 100,000 female population ages 21 to 39 years by age and area-level characteristics in Connecticut, 2008–2011

	Number of women	Number of cases	Rates (cases per 100,000 female population per year)				Difference 2008 to 2011 (95% CI)	<i>P</i> <sub>trend</sub>
			2008	2009	2010	2011		
TOTAL	411,624	8,146	512	517	475	476	−36 (−66 to −5)	0.002
Age								
21	87,507	2,657	834	849	665	688	−146 (−228 to −65)	<0.001
25	106,159	2,648	631	639	625	600	−31 (−98–35)	0.320
30	104,194	1,777	415	424	423	443	+29 (−27–85)	0.344
35	113,764	1,064	241	232	236	227	−14 (−54–26)	0.546
Proportion Black								
<5%	188,616	3,628	497	521	450	455	−42 (−86–2)	0.006
5%–9.9%	66,276	1,297	533	487	469	468	−65 (−141–11)	0.080
10%–19.9%	68,511	1,337	471	524	463	493	+22 (−51–95)	0.971
≥20%	88,221	1,884	558	524	542	512	−45 (−113–23)	0.283
Proportion Hispanic								
<5%	135,726	2,597	499	538	426	451	−48 (−100–4)	0.002
5%–9.9%	84,359	1,641	505	468	507	465	−40 (−107–26)	0.445
10%–19.9%	69,331	1,423	522	551	496	483	−39 (−113–36)	0.157
≥20%	122,208	2,485	525	507	494	507	−17 (−74–40)	0.477
Proportion in poverty								
<5%	162,490	3,161	510	521	463	451	−58 (−106 to −11)	0.003
5%–9.9%	89,288	1,738	503	507	447	489	−13 (−79–52)	0.333
10%–19.9%	90,033	1,776	494	513	478	488	−7 (−71–58)	0.595
≥20%	69,813	1,471	550	523	533	501	−49 (−125–27)	0.267
County								
Urban	315,190	6,235	503	511	484	479	−24 (−59–10)	0.076
Nonurban	96,434	1,911	539	534	443	466	−74 (−137 to −11)	0.002

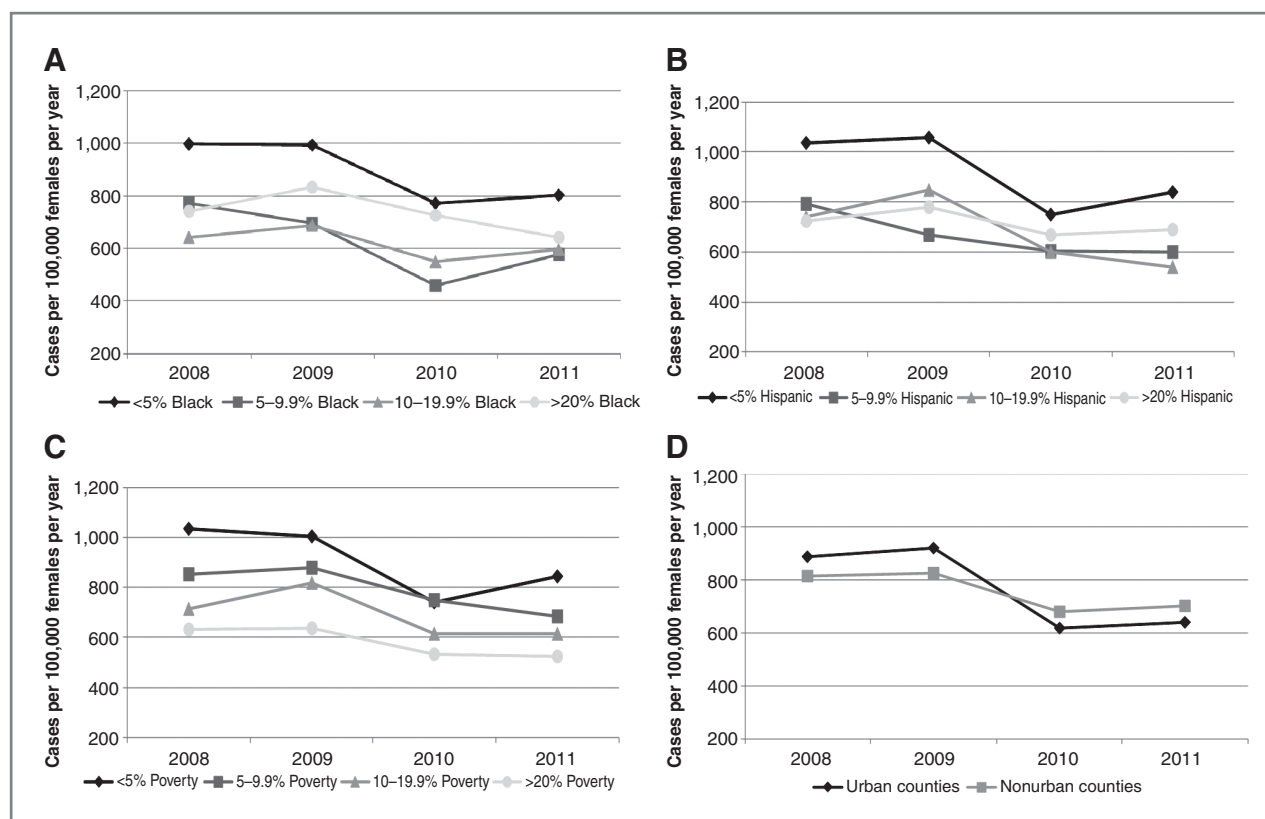
typically conducted as follow-up to abnormal Pap smears. Cervical cancer screening guidelines of the American Congress of Obstetrics and Gynecology (Washington, DC) changed in 2009 to recommend less frequent screening (24). Other organizations followed with similar recommendations (25, 26). This could also result in fewer cases of diagnosed high-grade cervical lesions. However, analysis of Behavioral Risk Factor Surveillance System data from Connecticut revealed steady cervical cancer screening with 73% of women ages 21 to 24 years reporting a Pap test in the previous year in both 2008 and 2010 (unpublished data). It is unclear at this time to what extent cervical cancer screening patterns will change, but this will be important to monitor to adequately assess vaccine impact on the diagnosis of high-grade cervical lesions.

Another possible explanation for these findings is changing treatment guidelines for abnormal cervical cytology or histology (29). Because a majority of HPV infections are transient, the American Society for Colposcopy and Cervical Pathology updated guidelines to more conservative management of adolescents with abnormal cytology or histology diagnoses (excluding CIN3) to avoid unnecessary treatment. Similar to possible changes in screening, these new guidelines could result in fewer

high-grade lesions being detected. The possible extent of this is unknown, but should be considered in future vaccine impact studies.

One limitation of this analysis is that the vaccination status of reported cases is unknown. However, the declines we observed in high-grade cervical lesions occurred during a time of increasing HPV vaccine uptake among adolescent females and young adult women nationally as well as adolescent females in Connecticut (5–7). Statewide estimates of vaccination rates among women ages 18 years and over are not available to the best of our knowledge. However, among women residing in New Haven County ages 25 to 29 years diagnosed with high-grade lesions (a subsample of women in the statewide surveillance), vaccination coverage increased from 9% to 25% during 2008 to 2011 (unpublished data). These data cannot be used to infer vaccine effectiveness because timing of vaccination in relation to diagnoses are not reported, but they do suggest an increase in vaccination rates among young adult women during the study period.

To the best of our knowledge, this is the first report of trends in high-grade cervical lesions since HPV vaccines were introduced in 2006 in the United States. Findings from this ongoing surveillance project add to a body of



**Figure 1.** Trends in annual rates of high-grade cervical lesions per 100,000 female population ages 21 to 24 years in Connecticut, 2008 to 2011 by census tract level area-based measures of (A) race, (B) ethnicity, (C) poverty, and (D) county type (urban vs. nonurban).

evidence that is consistent with vaccine impact on reducing HPV-related disease. However, continued and enhanced efforts to promote and monitor vaccine uptake will be necessary to maximize and measure their prevention potential for precancerous cervical lesions. Coverage has increased in each year since vaccine availability, yet current estimates that approximately half of adolescent females have received one or more doses are suboptimal and substantial room for improvement exists. Furthermore, efforts to monitor vaccine impact by vaccination history and for other HPV-related outcomes will also be important in addition to monitoring health disparities.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** L.M. Niccolai, J. Meek, J. Hadler, L. Sosa  
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