Population-Based Incidence Rates of Cervical Intraepithelial Neoplasia in the Human Papillomavirus Vaccine Era

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**IMPORTANCE** A substantial effect of human papillomavirus (HPV) vaccines on reducing HPV-related cervical disease is essential before modifying clinical practice guidelines in partially vaccinated populations.

**OBJECTIVE** To determine the population-based cervical intraepithelial neoplasia (CIN) trends when adjusting for changes in cervical screening practices that overlapped with HPV vaccination implementation.

**DESIGN, SETTING, AND PARTICIPANTS** The New Mexico HPV Pap Registry, which captures population-based estimates of both cervical screening prevalence and CIN, was used to compute CIN trends from January 1, 2007, to December 31, 2014. Under New Mexico Administrative Code, the New Mexico HPV Pap Registry, a statewide public health surveillance program, receives mandatory reporting of all cervical screening (cytologic and HPV testing) and any cervical, vulvar, and vaginal histopathological findings for all women residing in New Mexico irrespective of outcome.

**MAIN OUTCOME MEASURES** Prespecified outcome measures included low-grade CIN (grade 1 [CIN1]) and high-grade CIN (grade 2 [CIN2] and grade 3 [CIN3]).

**RESULTS** From 2007 to 2014, a total of 13 520 CIN1, 4296 CIN2, and 2823 CIN3 lesions were diagnosed among female individuals 15 to 29 years old. After adjustment for changes in cervical screening across the period, reductions in the CIN incidence per 100 000 women screened were significant for all grades of CIN among female individuals 15 to 19 years old, dropping from 3468.3 to 1590.6 for CIN1 (annual percentage change [APC], −9.0; 95% CI, −12.0 to −5.8; \( P < .001 \)), from 896.4 to 414.9 for CIN2 (APC, −10.5; 95% CI, −18.8 to −1.2; \( P = .03 \)), and from 240.2 to 0 for CIN3 (APC, −41.3; 95% CI, −65.7 to 0.3; \( P = .05 \)). Reductions in the CIN2 incidence were also significant for women 20 to 24 years old, dropping from 1027.7 to 627.1 (APC, −6.3; 95% CI, −10.9 to −1.4; \( P = .02 \)).

**CONCLUSIONS AND RELEVANCE** Population-level decreases in CIN among cohorts partially vaccinated for HPV may be considered when clinical practice guidelines for cervical cancer screening are reassessed. Evidence is rapidly growing to suggest that further increases in raising the age to start screening are imminent, one step toward integrating screening and vaccination.

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Persistent infection with human papillomavirus (HPV) can cause high-grade cervical intraepithelial neoplasia (CIN), which can progress to invasive cervical cancer if left untreated. Randomized trials have shown that HPV vaccines are efficacious in preventing HPV infection and low-grade and high-grade CIN, and cervical cancer reductions of 70% to 90% are envisioned to be possible through population vaccination during the next 25 years. Reductions in cervical cancer precursors will be observed much earlier as successive cohorts of women with greater vaccination coverage move into cervical screening. However, a coincident decreasing predictive value of current clinical approaches to cervical cancer screening is expected as a consequence of the absence of HPV, and as CIN prevalence decreases, the residual cases identified by screening could result in unnecessary clinical management and follow-up.

The New Mexico HPV Pap Registry (NMHPVPR) is the only surveillance system in the United States that has captured population-based estimates of both screening prevalence and CIN since the beginning of the vaccine introduction (in 2007) to 2014. All data were reported to the NMHPVPR under New Mexico Administrative Code regulation (NMAC 7.4.3.). The NMHPVPR data were examined to estimate the HPV vaccine effect on CIN rates when adjusting for cervical screening.

**Methods**

Under state regulations, all cytologic and HPV testing and histopathologic findings ascertained as part of clinical cervical screening are reported to the NMHPVPR. Ongoing evaluations of cervical screening, diagnosis, and treatment by the NMHPVPR have been reviewed and approved under exempt status by the University of New Mexico Human Research Review Committee. There were 658,093 women residing in New Mexico with cervical cytologic testing from 2007 to 2014, and 219,797 women (33.4%) were younger than 30 years at the time of screening. Cervical biopsy results were classified as CIN grade 1 (CIN1), CIN grade 2 (CIN2), CIN grade 3 (CIN3), carcinoma in situ, and adenocarcinoma in situ. Invasive cervical cancers were not included in the analyses.

The CIN incidence rates are presented per women with a cervical cytologic test in a given year to adjust the rates for changes in cervical cancer screening. The number of women tested per year is used as the denominator because CIN can only be detected in women who are screened. For the annual CIN incidence for a given age group, the numerator is the number of women diagnosed as having CIN1, CIN2, or CIN3, and the denominator is the total number of women with cervical cytologic testing. For the annual cervical cytologic testing rates for a given age group, the numerator is the number of women with cervical cytologic screening tests, and the denominator is the total number of women in the state’s population estimated from the US Census. For women with more than 1 biopsy per year, the first instance of the worst diagnosis was selected for that year. A woman can contribute to only one end point (CIN1, CIN2, or CIN3) in any given year within a given age category.

**Results**

Among female individuals 15 to 29 years old, there were 13,520 CIN1, 4,296 CIN2, and 2,823 CIN3 lesions diagnosed from January 1, 2007, to December 31, 2014. After adjusting for changes in cervical screening across the period, the CIN incidence showed significant reductions for all grades of CIN among females 15 to 24 years old and for CIN grade 2 among women 20 to 24 years old. Based on vaccination coverage, reductions were greater than anticipated, supporting vaccine cross-protection, efficacy of less than 3 vaccine doses, and herd immunity contributions.

Trends in CIN were characterized by the annual percentage change (APC) with 95% CIs. The APC was estimated by fitting a least squares regression line to the natural logarithm of the incidence using the calendar year as a regressor variable. P values tested if the slope of the fitted linear line is zero under the assumption that the estimate of the slope follows a t distribution, which in turn tests whether the APC is significant. In the Figure, the incidences over calendar years were fitted using a smoothing function with a local polynomial regression approach. Software programs (SAS, version 9.4; SAS Institute Inc and R, version 3.2.3; R Foundation for Statistical Computing) were used for the analyses.

### Key Points

**Question** What is the effect of human papillomavirus (HPV) vaccination on cervical intraepithelial neoplasia (CIN) rates when adjusting for cervical cancer screening?

**Findings** In this population-based registry study, after adjustment for changes in screening across 2007 to 2014, reductions in the population-based CIN incidence were significant for all grades (CIN 1, 2, and 3) among females 15 to 19 years old and for CIN grade 2 among women 20 to 24 years old. Based on vaccination coverage, reductions were greater than anticipated, supporting vaccine cross-protection, efficacy of less than 3 vaccine doses, and herd immunity contributions.

**Meaning** Significant population-level decreases in CIN among cohorts partially vaccinated for HPV suggests a rapidly approaching need to revisit guidelines for cervical cancer screening in the United States, including increasing the age to begin screening.

**Figure** The CIN incidences over calendar years were fitted using a smoothing function with a local polynomial regression approach. Software programs (SAS, version 9.4; SAS Institute Inc and R, version 3.2.3; R Foundation for Statistical Computing) were used for the analyses.
The proportion of vaccinated women increased within the cohorts. These data are summarized in eTable 2 and the eFigure in the Supplement.

Discussion

In New Mexico, the mean uptake of all 3 doses of HPV vaccine among female individuals (age range, 13-17 years) in 2014 was 40%.9 In earlier years, the uptake ranged from 17% (in 2008) to 38% (in 2013).10 We observed a significant population-level decrease in the incidence rate of all grades of CIN for female individuals 15 to 19 years old and in the incidence of CIN2 for women 20 to 24 years old. Reductions in the incidence were greater than anticipated based on HPV vaccination coverage in the population and the proportions of CIN attributable to HPV types directly targeted by the vaccine (HPV-6, HPV-11, HPV-16, and HPV-18). Cross-protection against nonvaccine HPV types, efficacy of less than 3 vaccine doses, and herd immunity may likely be contributing to these observations.

The primary goal of HPV vaccines is to prevent cervical cancer. Reductions in CIN2 and CIN3 precancers are early benchmarks for achieving this aim, but reductions in CIN1 are a direct measure of reductions in HPV infections requisite to the development of almost all invasive cervical cancer. Because CIN1 is the most common cervical neoplastic diagnosis that can lead to additional clinical follow-up, increased health care costs, and patient morbidities, reductions in CIN1 are an added benefit of HPV vaccination.

In the oldest age group (25-29 years), there were higher rates of all grades of CIN, with a pronounced increase observed in later years. This finding has been seen in other investigations11 and is believed to reflect longer intervals between screens and more HPV testing associated with increases in colposcopy referral and CIN detection within this age group.

For the CIN1, CIN2, and CIN3 incidence rates, the numerator is the number of women diagnosed as having CIN1, CIN2, and CIN3, respectively, in a year for an age category, and the denominator is the total number of women with cervical cytologic testing in each age category per year recorded in the New Mexico HPV (Human Papillomavirus) Pap Registry. For the cervical cytologic testing rate, the numerator is the number of women with cervical cytologic screening tests in a year for an age category, and the denominator is the total number of women in the population in each age category per year estimated from the US Census; intercensal estimates were used for 2007 to 2009, and postcensal estimates for 2010 to 2014 were obtained in November 2015 at http://www.census.gov. P values for each age group indicate whether the annual percentage change in rates is significant.

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Figure. Annual Incidence of Cervical Intraepithelial Neoplasia (CIN) and Cervical Screening Rates by 5-Year Age Groups, 2007 to 2014
Adjusting the incidence rates for screening takes into account changes in guideline recommendations, including a later age to start screening and lengthened intervals between screening episodes, leading to overall reductions in women who were screened each year. Using census-based denominators, we observed a significant decrease in the CIN incidence rates for all age groups between 15 and 29 years. When screening changes were accounted for, the decline was not as large and remained significant only in the younger age groups. These observations indicate the importance of adjusting for cancer screening when estimating the CIN incidence, and they highlight that CIN reductions attributed to the HPV vaccine effect will be overestimated when using census-based denominators.

Currently, cervical cancer screening guidelines do not differentiate between vaccinated vs nonvaccinated women, yet our findings of decreasing rates of CIN at the population level may warrant a review of the growing body of evidence in the near future. In particular, a later starting age for cervical screening among partially vaccinated populations of young women in the United States may be prudent given the already infrequent incidence of invasive cervical cancer for women younger than 25 years reported before HPV vaccination implementation.

Conclusions

Overall, our data demonstrate that clinical outcomes of CIN will be reduced among cohorts partially vaccinated for HPV, which will change clinical practice and reduce the cost-effectiveness of current clinical care that supports cervical cancer prevention. Most important, screening modalities and strategies, as well as clinical management algorithms, will need to evolve as we work toward a rational integration of HPV vaccination and cervical screening.

ARTICLE INFORMATION

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Author Contributions: Drs Lee and Wheeler had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Benard, Castle, Jenison, Wheeler. Acquisition, analysis, or interpretation of data: Benard, Castle, Hunt, Kim, Cuzick, Lee, Du, Robertson, Norville, Wheeler. Drafting of the manuscript: Benard, Castle, Wheeler. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Castle, Hunt, Cuzick, Lee, Du. Obtained funding: Wheeler.

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REFERENCES


