Cervical Cancer Incidence in Young U.S. Females After Human Papillomavirus Vaccine Introduction

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Introduction: Since 2006, human papillomavirus vaccine has been recommended for young females in the U.S. This study aimed to compare cervical cancer incidence among young women before and after the human papillomavirus vaccine was introduced.

Methods: This cross-sectional study used data from the National Program for Cancer Registries and Surveillance, Epidemiology, and End Results Incidence–U.S. Cancer Statistics 2001–2014 database for U.S. females aged 15–34 years. This study compared the 4-year average annual incidence of invasive cervical cancer in the 4 years before human papillomavirus vaccine was introduced (2003–2006) and the 4 most recent years in the vaccine era (2011–2014). Joinpoint regression models of cervical incidence from 2001 to 2014 were fitted to identify the discrete joints (year) that represent statistically significant changes in the direction of the trend after the introduction of human papillomavirus vaccination in 2006. Data were collected in 2001–2014, released, and analyzed in 2017.

Results: The 4-year average annual incidence rates for cervical cancer in 2011–2014 were 29% lower than that in 2003–2006 (6.0 vs 8.4 per 1,000,000 people, rate ratio=0.71, 95% CI=0.64, 0.80) among females aged 15–24 years, and 13.0% lower among females aged 25–34 years. Joinpoint analyses of cervical cancer incidence among females aged 15–24 years revealed a significant joint at 2009 for both squamous cell carcinoma and non–squamous cell carcinoma. Among females aged 25–34 years, there was no significant decrease in cervical cancer incidence after 2006.

Conclusions: A significant decrease in the incidence of cervical cancer among young females after the introduction of human papillomavirus vaccine may indicate early effects of human papillomavirus vaccination.
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INTRODUCTION

Cervical cancers are caused by human papillomavirus (HPV) infections.[1] HPV vaccination was introduced in the U.S. in 2006. Currently, there are three types of HPV vaccines available: bivalent,[2] quadrivalent,[3] and nonavalent.[4] The bivalent and quadrivalent vaccines protect against HPV 16 and 18, which are responsible for approximately 70% of cervical cancers.[1] The nonavalent vaccine covers an additional five oncogenic types responsible for another 20% of cervical cancers.[5] HPV vaccination is recommended for girls aged 11–12 years, with catchup vaccination up to 26 years. Nationwide in 2015, a total of 63% of girls aged 13–17 years had received at least one dose of the HPV vaccine.[6]

Prior studies on the HPV vaccine have investigated the vaccine's impact on the prevalence of the virus and high-grade cervical lesions.[7–11] To date, no study has examined trends in cervical cancer incidence before and after the HPV vaccination was introduced among young females who may have been vaccinated. An ecologic

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study comparing cervical cancer incidence among young females before and after HPV vaccine introduction provides insight into whether HPV vaccination has contributed to potential changes in cervical cancer incidence, particularly among younger girls who may not routinely undergo screening to detect cervical lesions.[12–14] The objective of this study is to compare cervical cancer incidence by histology between the pre-vaccine and vaccine eras among young women (aged 15–24 years and 25–34 years) using data from U.S. Cancer Statistics (USCS), the combined data from the Centers for Disease Control and Prevention (CDC) National Program for Cancer Registries (NPCR) and the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program. To explore the relationship between HPV vaccination and changes in cervical cancer incidence, as secondary aims, this study also assesses HPV vaccine uptake, HPV infections, and changes in cervical cancer screening guidelines.

METHODS

Study Sample

This study included data on young females (aged 15–34 years) from USCS.[15] USCS 2001–2014 database combines data from NPCR and SEER, including cancer incidence and population data for all 50 states, and the District of Columbia. Hospitals, physicians, and laboratories across the nation report data on demographic and tumor characteristics to central cancer registries supported by CDC and NCI. The NPCR and SEER Incidence–USCS Public Use Database (2001–2014 database) covered essentially all of the young female population (aged 15–34 years) between 2001 and 2014 in the U.S. (Puerto Rico not included). This study was not considered human subjects research by the IRB at The University of Texas Medical Branch, Galveston, TX.

Measures

The information collected about each incident of cancer diagnosis included demographic characteristics, date of diagnosis, and cancer histology. Patients were divided into the following groups according to age: 15–19, 20–24, 25–29, and 30–34 years. Histology of invasive cervical cancer was classified using the International Classification of Disease for Oncology, 3rd edition, topography, and morphology codes. Cervical cancer was stratified by histology, as adenocarcinoma can progress from a normal Pap smear to invasive cancer faster than squamous cell cancer.[16] Thus, changes in the incidence of these two cancers may differ. Invasive cervical cancers were grouped into squamous cell carcinoma (SCC) and non-SCC. SCC was defined as International Classification of Disease for Oncology, 3rd edition codes 8050–8084. Non-SCC was defined as all other types, excluding SCC, and was composed mainly of adenocarcinoma (codes 8140–8149, 8160–8162, 8190–8221, 8260–8337, 8350–8551, and 8570–8576). Hispanic ethnicity for all cancer cases was identified by the North American Association of Central Cancer Registries National Hispanic/Latino Identification Algorithm.[17]

Statistical Analysis

All data analyses were carried out in 2017 using the SEER*Stat statistical software package, version 8.3.4 or SAS software, version 9.4. Statistical significance was determined as two-sided p-values < 0.05. Cervical cancer incidence rates were calculated as cases per 1,000,000 people and age-adjusted to the 2000 U.S. standard population. CIs were calculated using the Tiwari method.[18] The 4-year average annual incidence rates were calculated for 4 years before the introduction of HPV vaccination (2003–2006) and the 4 most recent years in the vaccine era (2011–2014). Differences in age-adjusted rates were evaluated using rate ratio (RR) and the corresponding 95% CI. Considering lag time between the introduction of HPV vaccination in 2006 and the subsequent impact on cervical cancer incidence, joinpoint regression models[19] were fitted to identify the joinpoints (year) when annual percentage changes (APC) changed significantly, using the NCI's Joinpoint Regression Analysis program, version 4.5.0.[20] APC statistics were used to characterize the magnitude and direction of trends. APC was calculated as $(exp[\beta]-1)X100$, where the regression coefficient (β) was estimated by fitting a least squares regression line to the natural logarithm of the rates, using the calendar year as a regressor variable. Joinpoint regression uses least squares regression to fit line segments to the natural log of the age-standardized incidence rates, joined at discrete points that represent statistically significant changes in direction of the trend.[20] Subgroup analyses were performed in age groups, races/ethnicities, and cervical cancer histologic subtypes (SCC and non-SCC).

This study also examined the trends in HPV vaccine coverage among girls aged 13–17 years using data from the National Immunization Survey–Teen 2008–2014, and among women aged 18–24 or 25–34 years using data from National Health Interview Survey 2008–2015, the trends in prevalence of high-risk vaccine type HPV (16 and 18) among females aged 18–24 or 25–34 years using test results of HPV DNA from vaginal swabs in the National Health and Nutrition Examination Survey 2003–2014, and changes in cervical cancer screening recommendations from major national guidelines during the study period in the U.S. Details of National Immunization Survey–Teen, National Health Interview Survey, and National Health and Nutrition Examination Survey are available at each study's websites at the CDC.[21] As HPV vaccination data from National Immunization Survey–Teen and National Health Interview Survey were recall data, the estimates were plotted 1 year prior to the interview date.

RESULTS

In USCS, there were 25,427 cases of invasive cervical cancer among young females aged 15–34 years during 2001–2014 (Appendix Table 1, available online). During the pre-vaccine era (2001–2006), there were 1,056 cases among females aged 15–24 years and 10,498 cases among women aged 25–34 years for any histologic type. During the vaccine era (2007–2014), there were 1,171 cases in females aged 15–24 years and 12,702 cases in women aged 25–34 years for any histologic type.

Comparing the pre-vaccine era (2003–2006) to the vaccine era (2011–2014), the 4-year average annual incidence rate decreased by 29%, from 8.4 to 6.0 per