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Short communication

Differences between vaccinated and unvaccinated women explain increase in non-vaccine-type human papillomavirus in unvaccinated women after vaccine introduction

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ABSTRACT

The aim of this study was to determine whether an observed increase in non-vaccine-type human papillomavirus (HPV) in unvaccinated women during the first eight years after vaccine introduction may be explained by differences in demographics or sexual behaviors, instead of type replacement. We analyzed data from three cross-sectional surveillance studies of 13–26 year-old women (total N = 1180). For women recruited from a health department clinic, older age (OR = 1.4, 95% CI: 1.2–1.6) and consistent condom use with main partner in the past 3 months (OR = 11.6, 95% CI: 3.4–40) were associated with being unvaccinated. For women recruited from a teen health center African American race (OR = 0.2, 95% CI: 0.07–0.7) and having Medicaid health insurance (OR = 0.3, 95% CI: 0.1–0.7) were inversely associated with being unvaccinated. The observed increase in non-vaccine-type HPV prevalence in unvaccinated women may be explained by differences between unvaccinated and vaccinated women.

1. Background

Human papillomavirus (HPV) infection is a common sexually transmitted infection that may cause anogenital and oropharyngeal cancers. Surveillance studies after introduction of prophylactic HPV vaccines have demonstrated that vaccine introduction has led to a substantial decline in vaccine-type HPV prevalence in vaccinated individuals [1], supporting vaccine effectiveness, and a decline in vaccine-type HPV among unvaccinated individuals in regions where vaccination rates are high, supporting herd protection [1,2].

Studies have also examined trends in non-vaccine-type HPV after vaccine introduction to identify if cross protection or type replacement is occurring. Cross-protection against HPV types genetically related to vaccine-type HPV may lead to a decrease in non-vaccine-type HPV and increase vaccine effectiveness [3–6]. Type-replacement, defined as an increase in non-vaccine-type HPV due to an ecological niche created by a reduction in vaccine-type HPV, could lead to an increase in cancers caused by non-vaccine HPV types, but is thought to be very unlikely given that HPV is a genetically stable virus and competition between HPV types has not been observed [7,8]. Recent studies have not demonstrated evidence of type replacement [9], but findings are inconsistent [4,5,10].

In our ongoing study in which three unique cohorts of young women were recruited before and after HPV vaccine introduction, we found a significant increase in non-vaccine-type HPV prevalence among unvaccinated, but not vaccinated, women [11]. In that study, non-vaccine-type HPV was comprised of types genetically related and unrelated to vaccine-type HPV, and therefore we did not take into account the effects of cross-protection, which could decrease non-vaccine-type HPV prevalence. We hypothesized that a possible mechanism for the increase in non-vaccine-type HPV prevalence might be differences in demographic characteristics or behaviors between unvaccinated and vaccinated women that are associated with the risk of HPV acquisition, such as race, insurance status, and sexual behaviors [12–19]. Therefore, the first aim of this study was to examine changes in non-vaccine-type HPV genetically unrelated to vaccine-type HPV, in order to take into account the possible effects of cross-protection, over first 8 years after vaccine introduction in vaccinated and unvaccinated women. The second aim was to examine whether there were any differences between unvaccinated and vaccinated women; we hypothesized that unvaccinated women would be more likely to have demographic and behavioral characteristics that have been associated with HPV infection in previous studies [12–19].

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2. Methods

We conducted three cross-sectional studies before (2006–2007, n = 371) and during the 8 years after (2009–2010, n = 409, and 2013–2014, n = 400) widespread HPV vaccine introduction [1]. A total of 1180 young women 13–26 years of age were recruited sequentially from a hospital-based teen health center and health department clinic in Cincinnati, Ohio. Participants completed a survey immediately after enrollment which assessed sociodemographic characteristics, gynecological history and behaviors, and vaccination status, defined as having received at least one HPV vaccine dose before enrollment and verified by medical record. The survey was developed and validated in several studies [20]. Cervicovaginal swabs were obtained and were tested for 36 HPV types using the Roche Linear Array test (Roche Molecular Systems, Alameda, CA) [1,21]. The study was approved by the Institutional Review Boards of the hospital and health department, and written informed consent was obtained from participants.

All vaccinated women had received the 4-valent vaccine. The four outcome variables were: (1) non-vaccine-type HPV, (2) non-vaccine-type HPV genetically related to HPV16 (HPV31, 33, 35, 52, 58, 67), (3) non-vaccine-type HPV genetically related to HPV18 (HPV39, 45, 59, 68, 70), and (4) non-vaccine-type HPV genetically unrelated to HPV16 or HPV18. Propensity score analysis as previously described [1] was carried out to balance baseline covariates across the 3 study waves by vaccination status. We previously examined changes in prevalence of the first three outcome variables between waves 1 and 3 in vaccinated and unvaccinated women, not stratified by recruitment site [11]. In this study, we examined changes in prevalence of the fourth outcome variable, and also stratified analyses for all four outcomes by recruitment site. We then determined whether there were any differences in demographics or sexual behaviors between the vaccinated and unvaccinated women between waves 1 and 3, using *t*-test or Wilcoxon rank-sum test for continuous variables, and Chi-square test or Fisher's exact test for categorical variables. For factors that were different between vaccinated and unvaccinated women in univariable analysis at $p < .10$, multivariable logistic regression analysis with stepwise variable selection was used to determine if any of these factors were independently associated with HPV vaccination status. In addition, univariable logistic regression models were run to examine the associations between those factors that differed significantly by vaccination status ($p < .05$) and non-vaccine-type HPV infection. We stratified all above analyses by recruitment site because the populations recruited from the two sites differed demographically. For example, women recruited from the health department were older, more likely to be Hispanic, more likely to be married, and more likely to be uninsured (vs. having private or public insurance) compared to women recruited from the teen health center. All analyses were done with inverse propensity score weighting. SAS version 9.3 (Cary, NC) was used for all analyses.

3. Results

We enrolled 1180 young women in the three study waves: none were vaccinated in wave 1 and 71.5% (286/400) were vaccinated in wave 3. Participant sociodemographic characteristics, gynecological history and behaviors were described in previous publications [1]. Table 1 and Fig. 1 demonstrate non-vaccine-type HPV prevalence in waves 1 and 3 after inverse propensity score weighting. As previously reported [11], in vaccinated women, there was no change in all non-vaccine type HPV, no change in non-vaccine-type HPV genetically related to HPV18, and a 36.1% ($p = .01$) decrease in non-vaccine-type HPV genetically related to HPV16. In these analyses, we also noted a small (3.9%) but nonsignificant increase in non-vaccine-type HPV genetically unrelated to vaccine types. In unvaccinated women, as previously reported [11], there was a 24.5% ($p = .01$) increase in all non-vaccine type HPV, a 55.2% ($p = .022$) increase in non-vaccine-type HPV genetically related to HPV18, and no significant change in non-vaccine-type HPV genetically related to HPV16. In these analyses, we also noted a 24.3% ($p = .042$) increase in non-vaccine-type HPV genetically unrelated to vaccine-type HPV. In analyses stratified by recruitment site, the direction of the changes in non-vaccine-type HPV were similar except for non-vaccine-type HPV genetically related to HPV16: among unvaccinated women from the health department, prevalence decreased 24.9% ($p > .05$), but among women from the teen health center, prevalence increased by 74.7% ($p = .012$). The increase in all non-vaccine-type HPV, non-vaccine-type HPV genetically related to HPV18, and non-vaccine-type HPV genetically unrelated to HPV16 or HPV18 noted among unvaccinated women in analyses that were not stratified by site were also noted in analyses stratified by site, but the increases were not all statistically significant, likely due to smaller sample sizes in stratified analyses.

Differences in demographics and sexual behaviors between unvaccinated and vaccinated women in wave 3 are shown in Table 2. Among women recruited from the health department, unvaccinated vs. vaccinated women were more likely to lack health insurance; to use condoms consistently with one's main male partner over the past 3 months; and to be older. In multivariable analyses, older age (OR = 1.4, 95% CI: 1.2–1.6) and consistent condom use with main partner in the past 3 months (OR = 11.6, 95% CI: 3.4–40.0) were associated with being unvaccinated. Among women recruited from the teen health center, unvaccinated women were less likely to be African-American; less likely to have Medicaid; more likely to have at least one new sexual partner in past 3 months; and less likely to have had anal sexual intercourse. In multivariable analysis, African American race (OR = 0.2, 95% CI: 0.07–0.7) and having Medicaid health insurance (OR = 0.3, 95% CI: 0.1–0.7) were inversely associated with being unvaccinated.

Logistic regression analysis examining the association between the variables that differed significantly by vaccination status and non-vaccine-type HPV infection, by recruitment site, demonstrated the following. Among women recruited from the health department, lack of health insurance was associated with overall non-vaccine-type HPV infection (OR = 2.3, 95% CI: 1.1–4.8) and non-vaccine-type HPV genetically unrelated to HPV 16 or 18 (OR = 2.3, 95% CI: 1.2–4.6); and consistent condom use with main partner in the past 3 months was associated with non-vaccine-type HPV types that are genetically related to HPV 18 (OR = 4.7, 95% CI: 2.0–10.9). Among women recruited from the teen health center, one or more new male sexual partners in past 3 months was associated with overall non-vaccine-type HPV infection (OR = 2.4, 95% CI: 1.3–4.2), non-vaccine-type HPV types genetically unrelated to HPV 16 or 18 (OR = 2.7, 95% CI: 1.5–4.7), and non-vaccine-type HPV types genetically related to HPV 16 (OR = 2.4, 95% CI: 1.2–4.8).

4. Discussion

In this study, we examined mechanisms for observed increases in non-vaccine type HPV infections among unvaccinated women after HPV vaccine introduction. We previously reported an increase in all non-vaccine-type HPV and non-vaccine-type HPV genetically related to HPV18 [11], and in this study found an increase in non-vaccine types genetically unrelated to HPV16 and HPV18, indicating that the increase in non-vaccine-type HPV was present even after accounting for the non-vaccine types that might be expected to decrease in prevalence due to cross-protection.