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Human papillomavirus vaccination and subsequent cervical cancer screening in a large integrated healthcare system

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Abstract

Background—Human papillomavirus vaccination may result in lowered intention to be screened for cervical cancer, potentially leading to gaps in screening coverage and avoidable cervical cancer diagnoses.

Objective—To examine the association between human papillomavirus vaccination and subsequent cervical cancer screening initiation and adherence to recommended screening intervals to detect gaps in screening coverage and inform future prevention efforts.

Study Design—A retrospective cohort study was conducted in two distinct cohorts of female members of Kaiser Permanente Southern California, a large integrated healthcare delivery system. Pap screening initiation was evaluated in women who reached age 21 years between 2010 and 2013. Adherence to recommended screening intervals was evaluated in women between ages 25–30 years in 2010. All women were followed to the end of 2013 for the evaluation of their screening behaviors. History of human papillomavirus vaccination and Pap screening were obtained from electronic medical records. Adherence to recommended screening intervals was measured as ≥85% vs. <85% of the observed "screening up-to-date" person-time. Multivariable Cox and logistic regression models were used to examine associations between vaccination history and screening initiation and interval adherence. Demographic characteristics, gynecological health history, healthcare utilization, and characteristics of women's primary care providers were included as potential confounders in analyses.

Results—There were 27,352 and 41,328 women included in the screening initiation and screening interval adherence analyses, respectively. In comparison to unvaccinated women,

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Conflict of Interest

Conflict of Interest: Chao C received research funding from Merck, Co. for other studies related to the Gardasil vaccine. The other authors have no conflict of interest to disclose.

adjusted hazard ratios [95% confidence intervals (CIs)] for screening initiation among human papillomavirus vaccinated women were 1.19 (1.11–1.28), 1.44 (1.34–1.53) and 1.57 (1.50–1.65), for 1, 2 and 3+ doses, respectively. Adjusted odds ratios (and CIs) for screening interval adherence were 0.93 (0.83–1.04), 1.73 (1.52–1.97) and 2.29 (2.05–2.56), for 1, 2 and 3+ dose, respectively.

Conclusion—Human papillomavirus vaccinated women in this community-based, integrated healthcare setting were more likely to be screened for cervical cancer than were unvaccinated women. Our findings underscore the need for targeted interventions among unvaccinated women, who may be disproportionally affected by cervical cancer despite the presence of population-based screening programs.

Keywords

cervical cancer; health behavior; human papillomavirus vaccine; papanicolaou test; screening

Introduction

Immunization with the human papillomavirus (HPV) vaccine does not eliminate the need for routine cervical cancer screening since currently available HPV vaccines do not offer complete protection against all oncogenic HPV types. Also, vaccination does not always occur at the recommended ages (i.e., 11–12 years old)[1], increasing the chance of exposure to oncogenic HPV prior to vaccination. Furthermore, many of those who receive the vaccine are not vaccinated according to the recommended dosing schedule, raising concerns of compromised protection[2]. As a consequence of these factors, it remains important for women, regardless of their vaccination status, to continue to undergo cervical cancer screening.

A study reported that almost all women (96%) who participated in the 2008 US Health Information National Trend Survey were aware of the need for continuing cervical cancer screening after HPV vaccination[3]. However, a previous report suggested that vaccination may lower women's perception of their risk for developing HPV-related diseases, and thus their motivation to be screened for cervical cancer after vaccination[4]. This is concerning because a recent simulation study suggested that missed cervical intraepithelial neoplasia II–III cases could progress to cancer if vaccinated women are less likely to get screened[5]. While the findings of several surveys suggest that vaccination is generally not associated with a reduced willingness for screening[3,6–8], actual screening behaviors after receipt of the HPV vaccine have not been comprehensively examined. Two studies in the United States (US) reported a positive association between vaccination and subsequent screening, but these studies were not designed to elucidate the nature of this relationship, which requires accounting for important differences in clinical and utilization histories between women with and without vaccination[9,10]. To address these gaps in the literature, we examined the relationship between HPV vaccination and subsequent screening initiation and adherence to recommended screening intervals among female members of Kaiser Permanente Southern California (KPSC). We took advantage of KPSC's comprehensive electronic medical records to assess women's vaccination and screening behaviors, as well as their detailed relevant clinical characteristics.

Materials and Methods

Study setting and population

KPSC is the largest integrated health care delivery system in Southern California, serving over 4 million members who are broadly representative of the racial/ethnic and socioeconomic diversity of the population in this geographical area[11]. KPSC provides comprehensive health care services to its members and by nature of the prepaid managed care system, members have comparable access to health care. Preventive measures, including HPV vaccination and cervical cancer screening are offered without additional out-of-pocket cost. KPSC's cervical cancer screening guidelines generally follow the national guidelines that recommend initiation at age 21. In 2004, KPSC adopted HPV co-testing for women ages 30 and older and HPV reflex testing for women between ages 21–29. Subsequent screening is recommended every three years. This study was approved by the KSPC Institutional Review Board. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements were followed for the preparation of this manuscript[12].

A retrospective cohort study design was used to examine the association between HPV vaccination and subsequent cervical cancer screening initiation and adherence to recommended screening intervals. Two separate, non-overlapping cohorts of women were identified to examine these behaviors between calendar years 2010 and 2013. The eligibility requirements for entry into the two cohorts were guided by age-related cervical cancer screening recommendations and the timing of the approval and subsequent availability of the HPV vaccine.

For the evaluation of screening initiation, all female KPSC members who reached age 21 between 2010 and 2013 were eligible for inclusion. Follow-up started for these women at age 21 (study baseline), the age for screening initiation as recommended by current clinical guidelines[13]. To ensure complete capture of vaccination history, women were excluded if they did not have continuous KPSC membership between June 2006 when the HPV vaccine was first approved by the US Food and Drug Administration[14] and the study baseline. Women were also excluded if, prior to baseline, they had a hysterectomy in which the cervix was removed, cervical cancer, or if they had initiated cytology-based screening prior to the guideline-recommended age of 21. Women were followed from study baseline to the initiation of Pap screening, 12/31/2013, or a censoring event (i.e., HPV vaccination after baseline, hysterectomy, termination of KPSC membership, or death), whichever came first.

For the evaluation of adherence to recommended screening intervals, all female KPSC members who reached any age between 25 and 30 years in 2010 were eligible for inclusion. This age range was chosen to ensure all subjects were screening eligible (i.e., ≥ age 21) and vaccine eligible (i.e., ≤ age 26) at the time when the vaccine was introduced. Follow-up started for these women in year 2010 (study baseline). The same exclusion criteria described above were also applied to this cohort, except that women with Pap screening prior to baseline were not excluded. Women were followed from study baseline to 12/31/2013, or censoring events [i.e., HPV vaccination after baseline, an abnormal Pap result (which would

place the woman on a surveillance schedule instead of a screening schedule), hysterectomy, termination of KPSC membership, or death], whichever came first.

Data collection

The exposure of interest was HPV vaccination, including number of doses received. The outcomes of interest were initiation of Pap screening and adherence to screening interval. In addition, information on the following potential confounders was collected: race/ethnicity; census block-level education and income level; Medicaid enrollment; primary care provider's specialty and sex; health care utilization in the year prior to baseline including number of office visits, any emergency room visit or hospitalization, and influenza vaccination; gynecological history including history of oral contraceptive use, pregnancy, and sexually transmitted infections (STIs), specifically chlamydia, gonorrhea, syphilis and herpes; and primary medical center. All data were obtained from KPSC's electronic medical records which include clinical databases on immunization, laboratory tests, diagnoses, procedures, pharmacy, utilization, and providers.

Statistical analysis

The distributions of demographic and clinical characteristics of the study cohorts were calculated by HPV vaccination status; differences were assessed using the t-test or chi-square test. The incidence rate of screening initiation was calculated by HPV vaccination status. The associations between HPV vaccination status (yes vs. no, and by dose) and screening initiation were examined using bivariate and multivariable Cox models adjusted for all potential confounders described above [categories/forms of each confounder adjusted for are shown in Table 1]. Stratified analyses by race/ethnicity were also conducted.

Although current cervical cancer screening guidelines recommend screening initiation at age 21[13], earlier guidelines also recommended screening for those sexually active for 3 years before age 21[15]. Thus, in a sensitivity analysis, screening initiation at age 18 was examined in a separate cohort of women who reached age 18 between 2010 and 2013. The same exclusion criteria were applied to this cohort as in the primary analysis. Furthermore, because the requirement of continuous membership from 2006 led to exclusion of a large proportion of initially eligible women, an additional sensitivity analysis including all women regardless of their length of membership was also conducted.

A person-time based approach for measuring adherence to preventive services called the Prevention Index (PI) was used to evaluate adherence to cervical cancer screening intervals. Details of the PI methodology have been described elsewhere[16,17]. Briefly, the PI represents the proportion (ranging from 0–100%) of "screening up-to-date" person-time in the study period. For example, Pap screening is recommended every 3 years[13]. Thus, for a study subject, the 36 months after a Pap test is considered "up-to-date" person-time, and the time between month 37 and receipt of the next Pap test is considered "not up-to-date" person-time. For this study, the PI for Pap screening was calculated for each woman in the interval adherence cohort between 2010 and 2013, taking into account the date of their Pap screening prior to study baseline. The distribution of the PI was then calculated by HPV vaccination status. Because the distribution of the PI was highly skewed toward 100%, a dichotomized

outcome of 85% was used as the cutoff in the analysis, which was the mean among unvaccinated women. The association between HPV vaccination (yes/no and by dose) and screening adherence was evaluated using bivariate and multivariable logistic regression, adjusting for potential confounders as shown in Table 3. Stratified analyses by race/ethnicity were also conducted. In a sensitivity analysis, the analyses were repeated restricted to women who did not have an abnormal Pap screening result prior to study baseline to exclude those women who might have received a Pap test for surveillance rather than screening. Furthermore, an additional sensitivity analysis including all women regardless of their length of membership was also conducted. All analyses were conducted using SAS version 9.3, Cary, North Carolina, USA.

Results

A total of 27,352 women were included in the analysis examining HPV vaccination and initiation of Pap screening. Figure 1a details the study population inclusion and exclusion. A total of 28,262 person-years of follow-up were observed. Demographic and clinical characteristics of the study population are shown in Table 1. HPV vaccinated women were more likely to be of Hispanic ethnicity; have higher health care utilization; and have a history of oral contraceptive use, pregnancy, or STIs compared with those without HPV vaccination. Almost two-thirds of the HPV vaccinated women received 3 or more doses.

During the study period, 38% and 31% of women with and without any HPV vaccination initiated screening, respectively. The incidence of screening initiation was 439 and 239 per 1000 person-years among those with and without any HPV vaccination, respectively. Figure 2 shows the cumulative incidence of screening initiation after women reached age 21 by HPV vaccination dose. HPV vaccination was positively associated with screening initiation in both the bivariate and multivariable Cox models (Table 2): the adjusted hazard ratios (HR) for any vaccination was 1.46 (95% confidence interval 1.40–1.53). There was a positive dose-response relationship between number of HPV vaccine doses and screening initiation: HRs for 1, 2, and 3+ doses compared with none were 1.19 (1.11–1.28), 1.44 (1.34–1.53) and 1.57 (1.50–1.65), respectively. Similar associations between HPV vaccination and Pap screening initiation were found in analyses stratified by racial/ethnic groups, and in the sensitivity analyses evaluating screening initiation beginning at age 18 and when women were included regardless of length of membership.

A total of 41,328 women were included in the analysis evaluating HPV vaccination and adherence to recommended screening intervals. Figure 1b details the study population inclusion and exclusion. A total of 129,246 person-years of follow-up were observed. Table 3 shows the demographic and clinical characteristics of this cohort. HPV vaccinated women were more likely to have higher health care utilization in general (except hospitalization), and a history of oral contraceptive use and STIs.

The PI measure for Pap screening was high, with a median of 100% (range: 0% – 100%) in both vaccinated and unvaccinated women. The 25th percentiles for the PI were 94% and 84% in those with and without HPV vaccination, respectively. In the logistic regression evaluating the risk of PI ≥ 85% vs. PI < 85% (reference group), receipt of any HPV

vaccination was positively associated with a higher PI in both the crude and adjusted analyses [adjusted odds ratio (OR) =1.60 (1.49–1.72), Table 4]. Women who received 2 or 3+ doses, but not those who received only 1 dose, were more likely to have had a higher PI score compared with those with no HPV vaccination: adjusted ORs for 1, 2 and 3+ doses were 0.93 (0.83–1.04), 1.73 (1.52–1.97) and 2.29 (2.05–2.56), respectively. Similar results were obtained in the analyses stratified by racial/ethnic groups, and in the sensitivity analyses that excluded women who had an abnormal Pap test results prior to baseline or that included all women regardless of their length of membership (data not shown).

Comment

We found that HPV vaccinated women in this integrated healthcare setting were more likely than unvaccinated women to subsequently initiate cervical cancer screening, independent of demographics, gynecological history, provider type, and pattern of health care utilization. Vaccinated women were also more likely to adhere to the recommended cervical cancer screening interval. Our findings underscore a potential emerging disparity in protection from cervical cancer in the HPV vaccination era: unvaccinated women have a greater need for proper screening to help prevent cervical cancer; however, if they are both unvaccinated and less likely to adhere to screening, they risk being disproportionally affected by the disease. Thus, the results of this study suggest the need to prioritize interventions to improve vaccination rates and/or cervical cancer screening among this at-risk, unvaccinated population.

Several potential explanations exist for our findings. Women with a more positive attitude toward preventive services may be more likely to obtain both vaccination and screening[18]. It is also possible that women with primary care providers who emphasize preventive recommendations are more likely to utilize preventive services. In addition, if providers emphasized the need for screening while administering the vaccine, then the vaccination event would have served as an educational opportunity and prompted the increased uptake of screening. Qualitative studies to understand patient and provider perspectives about vaccination and screening may help further clarify areas for targeted intervention to prevent cervical cancer in subgroups that underutilize preventive services.

Of studies that examined screening behaviors following vaccination, Beer et al. found that vaccinated women were more likely to participate in cervical cancer screening than were unvaccinated women in the United Kingdom[19]. On the other hand, Budd et al. reported lower screening rates in vaccinated women than in unvaccinated women in Australia[20]. However, both the United Kingdom and Australia have nationwide HPV vaccination programs. Consequently, their findings may not generalize to women in the US. Paynter et al. reported a higher level of screening in vaccinated women than in unvaccinated women in a safety net health care system in Kansas City[10]. Using US administrative claim data, Hirth et al. reported a positive dose response by number of HPV vaccine received with subsequent Pap screening[9]. These observations are generally consistent with ours despite the differences in health care settings, i.e., safety net, diverse private insurance plans, and an integrated health care system with relatively equal access, suggesting that the phenomenon may be widespread across diverse US populations. However, none of the prior studies accounted for

important differences between vaccinated and unvaccinated women in their gynecological histories, STIs, health care utilization, and use of other preventive services. Our study adds to the literature by demonstrating that the association cannot be explained by confounding due to differences in encounters with the health care system, or history of gynecologic health. Instead, our results lend support to the influence of attitude/personal belief factors, as well as a potential causal role of HPV vaccination in the uptake of screening services, as discussed. These findings should further inform investigation into effective interventions to address under-vaccination and under-screening among women at risk for cervical cancer.

There are several potential limitations to be considered when interpreting the results of this study. First, although we controlled for some indicators of sexual activity, we do not know whether the women were sexually active or not. Those not sexually active may be less likely to obtain both vaccination and screening. However, the prevalence of HPV vaccination in our cohort was lower than the prevalence of sexually active young women reported on national surveys[21], suggesting this is unlikely to entirely explain our results. Second, we were unable to evaluate screening uptake among women who were vaccinated at age 11–12 years (the recommended age range for HPV vaccination) as these women had not yet become screening eligible in the study follow-up period. Because the vaccination decision for girls 11–12 years of age is primary made by parents, it is unclear whether the positive association between vaccination and screening behavior we observed here is generalizable to women who first received the vaccine at an earlier age. In fact, Paynter et al. reported that women vaccinated closer to age 21 were more likely to get screening than those vaccinated at age 14[10]. Thus, future studies are needed to confirm the association between vaccination in the recommended age range and subsequent screening behavior. Third, although we required continuous KPSC membership between 2006 and study baseline, it is possible that women obtained vaccination and/or cervical cancer screening outside of the health plan (e.g., in school/university medical facilities, Planned Parenthood). This could lead to misclassification and potential bias away from the null if those who received HPV vaccine outside of KPSC were also more likely to receive outside cervical cancer screening services. However, a recent member survey found that HPV vaccine and Pap screening use outside of KPSC is infrequent (unpublished data). Fourth, the requirement of continuous membership may lead to possible selection bias. Nevertheless, sensitivity analyses including all women regardless of their length of membership provided the same results; thus offering some assurance about our conclusions. Lastly, our 4-year study period (2010–2013) is relatively short for evaluating adherence, given cervical cancer screening intervals are 3 years long. However, this limitation is unlikely to affect the validity of our comparisons by vaccination status.

Our study has several important strengths, including the use of comprehensive electronic medical records to capture demographic and clinical characteristics that are important confounders; analyses conducted in a population with comparable access to care that eliminated the confounding due to differential health care access; and the fact that the study provided real world data in a community-based healthcare setting.

In conclusion, women who were HPV vaccinated in an integrated healthcare setting were more likely than unvaccinated women to be subsequently screened for cervical cancer. Our

data identify a potential emerging disparity in cervical cancer prevention efforts. The public health implications of these screening patterns need to be investigated further. Qualitative studies could identify motivations and barriers relevant to cervical screening and inform potential targets for future interventions. Finally, as called for in the recent statement from the American Society of Clinical Oncology, a significantly enhanced HPV vaccination rate in the US population may be the ultimate goal in order to reduce cervical cancer disparities and the human and economic burden of cervical cancer[22].

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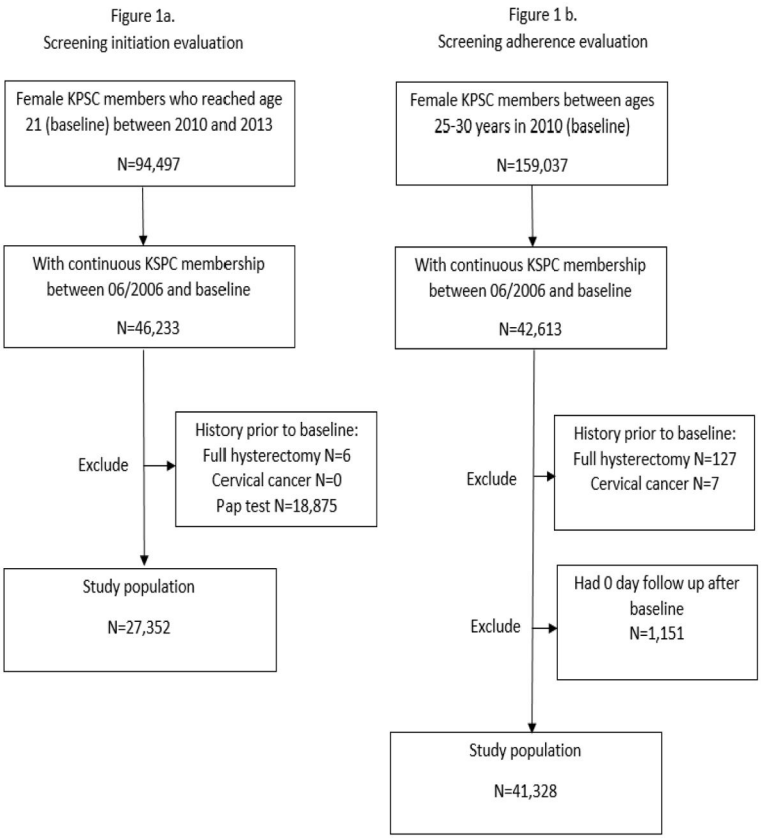

Figure 1.
Study population flow chart

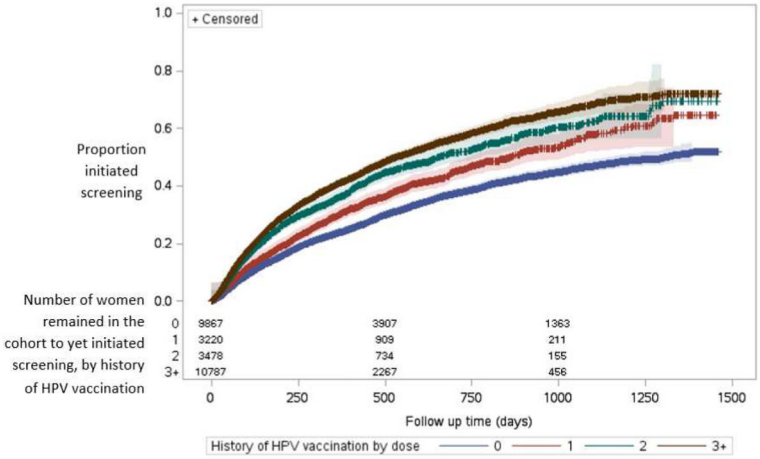

Figure 2.

Cumulative incidence curve and 95% confidence interval band of screening initiation probability by dose history in the screening initiation evaluation cohort.

Table 1

Baseline demographic and clinical characteristics of the screening initiation cohort

	Women who reached age 21 between 2010–2013		
	Had HPV vaccine (N=17485)	**No HPV vaccine (N=9867)**	**p-value**
Race/ethnicity			
White	4989 (28.5%)	3081 (31.2%)	
Black	1827 (10.4%)	1315 (13.3%)	
Hispanic	7245 (41.4%)	2836 (28.7%)	<0.01
Asian/Pacific Islander	2129 (12.2%)	1070 (10.8%)	
Other/Unknown	1295 (7.4%)	1565 (15.9%)	
Census block income and education level			
Median annual household income in the census block			
<=$45,000	3825 (21.9%)	2046 (20.8%)	
$45,001–$80,000	8588 (49.1%)	4774 (48.3%)	<0.01
>$80,000	5072 (29.0%)	3047 (31.0%)	
Percent of adults in the census block with high school degree or higher			
0%–50%	1109 (6.3%)	536 (5.4%)	
51%–75%	4705 (26.9%)	2319 (23.6%)	<0.01
76%–100%	11671 (66.7%)	7012 (71%)	
Medicaid enrollment	264 (1.5%)	113 (1.1%)	0.01
Length of membership, yrs, mean (SD)	15.0 (5.3)	14.1 (5.6)	<0.01
PCP characteristics			
Specialty			
Pediatrics	282 (1.6%)	467 (4.7%)	
Family medicine	12967 (74.2%)	6993 (70.9%)	<0.01
Internal medicine	3811 (21.8%)	1986 (20.1%)	
Other/unknown	425 (2.4%)	421 (4.3%)	
Female	11762 (67.3%)	5898 (59.8%)	<0.01
Health care utilization within 12 months prior to baseline			
Any Hospitalization	412 (2.4%)	179 (1.8%)	0.03
Any ER visit	2323 (13.3%)	1054 (10.7%)	<0.01
Any outpatient visit	13719 (78.5%)	6140 (62.2%)	<0.01
Number of outpatient visits, mean (SD)	0.1 (0.7)	0.1 (1.0)	0.20
Flu vaccination within 12 months prior to baseline	4017 (23.0%)	986 (10.0%)	<0.01
Gynecological history prior to baseline			
Oral contraceptive use	5496 (31.4%)	1573 (15.9%)	<0.01
Pregnancy	419 (2.4%)	166 (1.7%)	<0.01
Sexually transmitted infections	657 (3.8%)	189 (1.9%)	<0.01
HPV vaccination history prior to baseline			
1 dose	3220 (18.4%)	-	
2 doses	3478 (19.9%)	-	

	Women who reached age 21 between 2010–2013		
	Had HPV vaccine (N=17485)	**No HPV vaccine (N=9867)**	**p-value**
3+ doses	10787 (61.7%)	-	

Table 2

Crude and adjusted associations between history of HPV vaccination and Pap screening initiation.

History of HPV vaccination	Crude	Adjusted[a]
	Screening Initiation after Age 21	
	Hazard ratio (95% confidence interval)	
No vaccination	Reference	Reference
Any dose	1.70 (1.63–1.77)	1.46 (1.40–1.53)
1 dose	1.29 (1.20–1.39)	1.19 (1.11–1.28)
2 doses	1.62 (1.52–1.73)	1.44 (1.34–1.53)
3+ doses	1.87 (1.78–1.96)	1.57 (1.50–1.65)

[a]Model adjusted for: race/ethnicity (white; black, Hispanic, Asian, other/unknown), census block income level (median household income <= $45,000, $45,001–$80,000, >$80,000) and education (% adults with high school degree or above: 0%–50%, 51%–75%, 76%–100%); Medicaid enrollment (yes/no); primary care provider's specialty (pediatrician, family medicine, internal medicine and others) and sex; health care utilization in the 12 months prior to baseline (number of office visits, any emergency room visit, any hospitalization); influenza vaccination in the 12 months prior to baseline; women's gynecological history prior to baseline (oral contraceptive use, pregnancy, and sexually transmitted infections - specifically chlamydia, gonorrhea, syphilis and herpes); and women's primary medical center.

Table 3

Baseline demographic and clinical characteristics of the screening interval adherence cohort

	Women between age 25–30 in 2010		
	Had HPV vaccine (N=6951)	**No HPV vaccine (N=34377)**	**p-value**
Race/ethnicity			
White	2295 (33.0%)	9928 (28.9%)	
Black	528 (7.6%)	2889 (8.4%)	
Hispanic	2870 (41.3%)	16138 (46.9%)	<0.01
Asian/Pacific Islander	669 (9.6%)	2967 (8.6%)	
Other/Unknown	589 (8.5%)	2455 (7.1%)	
Census block income and education level			
Median annual household income in the census block			
<=$45,000	1545 (22.2%)	8652 (25.2%)	
$45,001–$80,000	3508 (50.5%)	17576 (51.1%)	<0.01
>$80,000	1898 (27.3%)	8149 (23.7%)	
Percent of adults in the census block with high school degree or higher			
0%–50%	581 (8.4%)	3686 (10.7%)	
51%–75%	1646 (23.7%)	8987 (26.1%)	<0.01
76%–100%	4724 (68%)	21704 (63.1%)	
Medicaid enrollment	248 (3.6%)	1248 (3.6%)	0.80
Length of membership, yrs, mean (SD)	10.3 (8.0)	8.4 (6.6)	<0.01
PCP characteristics			
Specialty			
Family medicine	5335 (76.8%)	24934 (72.5%)	
Internal medicine	1448 (20.8%)	8403 (24.4%)	<0.01
Other/unknown	168 (2.4%)	1040 (3.0%)	
Female	4311 (62.1%)	19576 (57.3%)	<0.01
Health care utilization within 12 months prior to baseline			
Any Hospitalization	525 (7.6%)	4345 (12.6%)	<0.01
Any ER visit	1306 (18.8%)	5922 (17.2%)	<0.01
Any outpatient visit	6606 (95.0%)	30629 (89.1%)	<0.01
Number of outpatient visits, mean (SD)	0.3 (1.2)	0.5 (1.7)	<0.01
Flu vaccination within 12 months prior to baseline	1933 (27.8%)	8677 (25.2%)	<0.01
Gynecological history prior to baseline			
Oral contraceptive use	4782 (68.8%)	18518 (53.9%)	<0.01
Pregnancy	1659 (23.9%)	15557 (45.3%)	<0.01
Sexually transmitted infections	932 (13.4%)	2903 (8.4%)	<0.01
Abnormal Pap results	404 (5.8%)	1396 (4.1%)	<0.01
HPV vaccination history prior to baseline			
1 dose	1709 (24.6%)	-	
2 doses	1810 (26.0%)	-	
3+ doses	3432 (49.4%)	-	

Table 4

Crude and adjusted associations between history of HPV vaccination and adherence to recommended Pap screening intervals.

History of HPV Vaccination	Crude	Adjusted[a]
	Odds ratio[b] (95% confidence interval)	
No vaccination	Reference	Reference
Any dose	1.77 (1.65–1.89)	1.60 (1.49–1.72)
1 dose	0.95 (0.86–1.06)	0.93 (0.83–1.04)
2 doses	1.86 (1.64–2.11)	1.73 (1.52–1.97)
3+ doses	2.63 (2.36–2.92)	2.29 (2.05–2.56)

[a] Model adjusted for: race/ethnicity (white; black, Hispanic, Asian, other/unknown), census block income level (median household income <= $45,000, $45,001–$80,000, >$80,000) and education (% adults with high school degree or above: 0%–50%, 51%–75%, 76%–100%); Medicaid enrollment (yes/no); primary care provider's specialty (pediatrician, family medicine, internal medicine and others) and sex; health care utilization in the 12 months prior to baseline (number of office visits, any emergency room visit, any hospitalization); influenza vaccination in the 12 months prior to baseline; women's gynecological history prior to baseline (oral contraceptive use, pregnancy, and sexually transmitted infections - specifically chlamydia, gonorrhea, syphilis and herpes); and women's primary medical center.

[b] Odds ratio for the Prevention Index (PI) outcome ≥ 0.85 vs. < 0.85 (reference group).