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Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results

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ABSTRACT

Women previously vaccinated against human papillomavirus (HPV) type 16 and 18 are now reaching the age (21 years) at which cervical-cancer screening is recommended in the U.S. The impact of HPV vaccination on risks of cervical precancer following a positive and negative screen among women aged 21–24 years who just started routine cervical screening are not well described. Therefore, three-year absolute and relative (RR) cumulative risks of cervical intraepithelial neoplasia grade 2 or more severe diagnoses (≥CIN2) and grade 3 or more severe diagnoses (≥CIN3) were estimated for women undergoing cervical screening at Kaiser Permanente Northern California. Risks were estimated in women aged 21–24 years (n = 75,008) undergoing cervical screening since late 2006, 6 months after HPV vaccination became available; women were categorized vaccinated at ages < 18, 18–20, and 21–24 years and compared to those who were unvaccinated. Three-year risks were estimated for normal, low-grade, and high-grade cytology results. Three-year risks of ≥CIN2 and ≥CIN3 for unvaccinated women following low-grade cytology were 10.89% for and 3.70%, respectively. By comparison, Three-year risks of ≥CIN2 and ≥CIN3 were 5.26% (RR = 0.48, 95%CI = 0.24–0.99) and 0.99% (RR = 0.27, 95%CI = 0.06–1.13), respectively, for women vaccinated under the age of 18 years. Three-year ≥CIN2 and ≥CIN3 risks were lower for those HPV vaccinated at younger age for any screening result ($p_{trend} \leq 0.01$ for all comparisons). These data support initiating cervical screening at an older age or changing the management of a low-grade cytology result in women aged 21–24 years who were vaccinated against HPV younger than age of 18 years.

1. Introduction

Human papillomavirus (HPV) vaccines have been shown to be highly effective in preventing cervical intraepithelial neoplasia grade 2 (CIN2) or more severe diagnoses (≥CIN2) (Drolet et al., 2015; Crowe et al., 2014; Baldur-Felskov et al., 2014). The predominate HPV vaccine used over the past decade in the US, Gardasil (Merck, Whitehouse Station, NJ, USA), prevents HPV16 and HPV18 infections that cause approximately 70% of cervical cancer, and HPV6 and HPV11, which cause approximately 90% of genital warts (Stokley et al., 2014). Gardasil was first approved by the U.S. Food and Drug Administration (FDA) in mid-2006 for females ages 9–26 years (Merck, 2011; Markowitz et al., 2007), and cohorts of women, some of whom have been HPV vaccinated, are now reaching the age to start cervical screening (21 years and older). HPV-vaccinated women still need screening because Gardasil does not protect against other high-risk HPV types that cause approximately 30% of cervical cancer and does not treat pre-existing HPV16 and HPV18 infections and related conditions.

However, predictive values or risks for high-grade cervical abnormalities following a positive cervical screening result, non-normal cytology (atypical squamous cells of undetermined significance [ASC-US] or more severe cytologic interpretations (ASC-US+)) and/or testing high-risk HPV positive, are expected to decrease following vaccination against HPV16 and HPV18 (Castle et al., 2008a). This is due to vaccination reducing the proportion of these events that relate to the two most carcinogenic HPV types. One report from Scotland found a

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significant reduction in predictive values (risks) for ≥CIN2 following abnormal and normal cytology (Palmer et al., 2016). That study used a different cytology classification system (Palmer et al., 2016) than the one used in the U.S. (Solomon et al., 2002), and cytologic interpretation differs between countries (Scott et al., 2002). Nonetheless, these results raise concern over the recent draft recommendations by the U.S. Preventive Services Task Force (U.S. Preventive Service Task Force, 2017) that women aged 21–24 continue to undergo cytology screening every three years, without consideration of vaccine status. We therefore examined the impact of HPV16 and HPV18 vaccination on three-year risks of ≥CIN2 following abnormal and normal cytology and high-risk HPV testing among young women who just started to undergo routine cervical screening at Kaiser Permanente Northern California (KPNC). As HPV vaccination is thought to be most efficacious when administered at a younger age, we examined the impact of age at vaccination on screening performance (Munoz et al., 2010; Kjaer et al., 2009; Lehtinen et al., 2012; Silverberg et al., 2018).

2. Methods

2.1. Population

From December 12, 2006 to December 13, 2016, a HPV vaccination-eligible cohort of 75,008 women aged 21–24 years underwent cervical cancer screening at KPNC. The start date for this analytic cohort of HPV vaccination-eligible women was approximately 6 months after Gardasil was U.S. FDA approved. Women aged 25 years and older before December 12, 2006 were excluded. Women who had no record of HPV vaccination at KPNC were considered unvaccinated although they may have received HPV vaccination prior to join the KPNC system. As a second comparison group, a cohort of 36,796 women aged 21–24 years that underwent cervical cancer screening at KPNC from January 1, 2003 to December 11, 2006, prior to when HPV vaccination was generally available ("pre-vaccination"), was included. Cervical histopathology outcomes were collected for women through May 22, 2017. The KPNC institutional review board (IRB) approved use of the data, and National Institutes of Health Intramural Research Program (IRP) Human Research Protections Program (HRPP) and Albert Einstein College of Medicine IRBs deemed the use of these de-identified data exempt from review.

2.2. Screening and clinical management

During this period of a decade (2006–2016), cervical screening of women aged 21–29 years (inclusive of women aged 21–24 years who had been HPV vaccinated) at KPNC evolved: cytology every one to three years (2005–8), cytology every three years (2008–12), and cytology every three years for ages 21–24 years and HPV and cytology cotesting every three years for ages 25–29 years (2012–currently). The Bethesda System has been used consistently for cytology classification (Solomon et al., 2002). Starting in 2001, a pooled DNA test targeting 13 types high-risk HPV types, Hybrid Capture 2 (HC2; Qiagen, Germantown, MD), is used for triage women with atypical squamous cells of undetermined significance (ASC-US) cytology, which is the most common non-normal result, representing equivocally abnormal results. HPV-positive ASC-US has a risk of ≥CIN2 and ≥CIN3 similar to that of LSIL and is similarly referred to colposcopy (Solomon et al., 2001; Katki et al., 2013a; Katki et al., 2013b; Katki et al., 2013c). HPV-negative ASC-US has a similar risk of ≥CIN2 and ≥CIN3 to that of normal cytology and is similarly re-screened in three years. Women are followed according to internal Kaiser guidelines, which were generally concordant with national standards at the time of this study (Wright et al., 2002; Wright et al., 2007a; Wright et al., 2007b).

2.3. Statistical analyses

We estimated three-year absolute and relative (RR) cumulative risks of ≥CIN2 and ≥CIN3 (including adenocarcinoma in situ), as a measure of predictive values, by HPV vaccination status for following categories of cytology results: 1) normal cytology (negative or HPV-negative ASC-US cytology), 2) low-grade cytology (HPV-positive ASC-US or low-grade squamous intraepithelial lesion [LSIL] cytology), or 3) high-grade cytology (high-grade squamous intraepithelial lesion [HSIL] or more severe, atypical squamous cells, cannot rule out HSIL, or atypical glandular cells cytology). Analyses were restricted to women aged 21–24 years who underwent cervical screening. We distinguished those women without a medical record of HPV vaccination as "unvaccinated" if they were screened on December 12, 2006 (6 months after HPV vaccination became available) or more recently, when HPV vaccination was generally available from "prevaccination" who were screened prior to December 12, 2006 when HPV vaccination was not available. Among those who could have been vaccinated against HPV using Gardasil, HPV vaccination status of women was defined using KPNC electronic medical records as having received HPV vaccination at ages < 18 years, 18–20 years, or 21–24 years (but prior to being screened) and was compared to women who were unvaccinated as the reference.

The event time was defined as the time from 1) the first screening visit for those who were never vaccinated in the study or the first screening visit after the first vaccination for those who were vaccinated to 2) the midpoint between the last screening visit without event and the first visit with event, or the last screening visit for those who never had an event. As a measure of absolute risks, we calculated cumulative ≥CIN2 or ≥CIN3, including prevalent ≥CIN2 or ≥CIN3, as one minus the Kaplan-Meier survival estimate. Log-log transformation was used to get 95% confidence intervals (95%CI) on cumulative risks. The log-rank trend test was used to compare cumulative ≥CIN2 or ≥CIN3 in the populations by HPV vaccination status. RRs were calculated, and the normal approximations with log transformation on the RRs were used to calculate the confidence intervals and p-values.

Sensitivity analysis was conducted to determine whether limiting to the first screening visit, or the number of HPV vaccine doses received (2 or more vs. 1 doses), altered any findings. To assess any time period effects, a *post-hoc* analysis three-year risks of ≥CIN2 following low-grade cytology were stratified on early and late periods of screening, defined (retrospectively) on the date (January 2, 2013) when first 50% of ≥CIN2 were diagnosed among the women vaccinated younger than 18 years of age to maximize the power for the group with the fewest ≥CIN2.

Racial/ethnicity distribution across all five sub-cohorts was assessed for differences using Pearson chi-square test. All tests were two-sided. A p value < 0.05 was considered statistically significant. SAS (version 9.3; Cary, NC, USA) and STATA (version 12.1; College Station, TX, USA) were used for the statistical analyses.

3. Results

Table 1 shows the racial/ethnic distribution by sub-cohorts defined by HPV vaccination status. While qualitatively similar, there was a small but significant difference in race/ethnicity across all sub-cohorts defined by HPV vaccination status ($p < 0.001$). Notably, the percentage of unvaccinated who were White was lower than among those who were HPV vaccinated (at any age) (32.5% vs. 38.4%, respectively) and more likely to be Hispanic (18.8% vs. 14.6%, respectively).

For any cytology result from screening women aged 21–24 years, those who were vaccinated against HPV under the age of 18 years had less than half the risk of ≥CIN2 (Table 2) and ≥CIN3 (Table 3) compared to the unvaccinated women or the pre-vaccination cohort. A history of HPV vaccination at progressively older ages was less effective in reducing risks of ≥CIN2 ($p_{trend} < 0.01$) and ≥CIN3 ($p_{trend} < 0.01$) following any cytology result.

Table 1
Distribution of race/ethnicity for sub-cohorts defined if and at what age at HPV vaccination occurred for a cohort of women aged 21–24 years and undergoing screening between January 1, 2003 and December 13, 2016.

	HPV vaccination status/age at HPV vaccination											
Race/ethnicity	Pre-vaccination[a]		Unvaccinated [b]		< 18 years		18–20 years		21–24 years		All	
	N	%	N	%	N	%	N	%	N	%	N	%
White	13,303	36.1%	19,638	32.5%	1489	37.3%	2320	38.5%	2065	39.2%	5874	38.4%
Black	2076	5.6%	4483	7.4%	297	7.4%	449	7.4%	373	7.1%	1119	7.3%
Hispanic	5680	15.4%	11,361	18.8%	657	16.4%	900	14.9%	679	12.9%	2236	14.6%
Other	4864	13.2%	9594	15.9%	490	12.3%	714	11.8%	720	13.7%	1924	12.6%
Missing/unknown	10,966	29.7%	15,283	25.3%	1062	26.6%	1650	27.3%	1425	27.1%	4137	27.1%
Total	36,889	100.0%	60,359	100.0%	3995	100.0%	6033	100.0%	5262	100.0%	15,290	100.0%

[a] Screened prior to December 12, 2006 before HPV vaccination became available.
[b] Screened on December 12, 2006 or more recently when HPV vaccination was available.

The three-year ≥CIN2 risk following normal cytology (Table 2) in the unvaccinated women was 0.46% (95%CI = 0.41–0.52%). In comparison to the unvaccinated women, three-year ≥CIN2 risks following normal cytology for women who received HPV vaccination under 18, 18–20, and 21–24 years of age were 0.20% (95%CI = 0.10–0.42%) (RR = 0.44, 95%CI = 0.21–0.92), 0.37% (95%CI = 0.24–0.58%) (RR = 0.81, 95%CI = 0.51–1.27), and 0.80% (95%CI = 0.58–1.11%) (RR = 1.73, 95%CI = 1.22–2.46), respectively. Among those who received HPV vaccination, three-year ≥CIN2 risks following low-grade cytology were lower with the younger the age at HPV vaccination ($p_{trend} < 0.001$). By comparison, the three-year ≥CIN2 risk among the pre-vaccination cohort was 0.50% (95%CI = 0.43–0.58%) (RR = 1.09, 95%CI = 0.89–1.32).

The three-year ≥CIN2 risk following low-grade cytology (Table 2 and Fig. 1A), the traditional clinical threshold for referral to colposcopy (Katki et al., 2013a; Wright et al., 2002; Wright et al., 2007a; Wright et al., 2007b), in the unvaccinated women was 10.89% (95%CI = 9.63–12.30%). In comparison to the unvaccinated women, three-year ≥CIN2 risks following low-grade cytology for women who received HPV vaccination under 18, 18–20, and 21–24 years of age were 5.26% (95%CI = 2.58–10.54%) (RR = 0.48, 95%CI = 0.24–0.99), 6.83% (95%CI = 4.40–10.53%) (RR = 0.63, 95%CI = 0.40–0.99), and 16.60% (95%CI = 12.64–21.64%) (RR = 1.52, 95%CI = 1.13–2.05), respectively. Among those who received HPV vaccination, three-year ≥CIN2 risks following low-grade cytology were lower with younger age at HPV vaccination ($p_{trend} < 0.001$). The three-year ≥CIN2 risk among the pre-vaccination cohort was 17.67% (95%CI = 14.76–21.07%) (RR = 1.62, 95%CI = 1.31–2.01).

No cases of ≥CIN2 were diagnosed among the eight women who had a high-grade cytology and were HPV vaccinated before the age of 18 years. Among those who received HPV vaccination, three-year ≥CIN2 risks following high-grade cytology were lower with younger age at HPV vaccination ($p_{trend} = 0.002$).

An even greater impact of HPV vaccination on risks was observed on ≥CIN3, a more rigorous definition of high-grade cervical abnormalities (Table 3). Notably, three-year ≥CIN3 risks among women vaccinated before the age of 18 years were approximately one-quarter of risks for the same cytologic results as those for unvaccinated women albeit not significantly different; Fig. 1B shows the ≥CIN3 risks following a low-grade cytology result. Again, among those who received HPV vaccination, three-year ≥CIN3 risks following normal ($p_{trend} = 0.009$), low-grade ($p_{trend} < 0.001$), and high-grade cytology ($p_{trend} = 0.004$) were lower with younger age at HPV vaccination.

Restricting the analysis to the first cytology results available (vs. any cytology available) during ages 21–24 years did not appreciably change the resultant risks for the ≥CIN2 endpoint (Supplemental Table 1). Similar patterns of ≥CIN2 risks related to if and at what age women were vaccinated were observed for those women who received two or more doses of HPV vaccine (Supplemental Table 2) or a single dose of HPV vaccine (Supplemental Table 3). Similar effects were observed in these restricted analyses using a ≥CIN3 endpoint (data not shown).

Finally, three-year ≥CIN2 risks following low-grade cytology were stratified on time period (Table 4). Most notably, three-year ≥CIN2 risks in the unvaccinated populations in the early period were approximately twice (12.30%, 95%CI = 10.84–13.93%) those in the late period (6.75%, 95%CI = 3.80–11.86%). There were no appreciable differences in risks in the vaccinated sub-groups defined by the age at HPV vaccination.

4. Discussion

HPV vaccination, especially under the age of 18 years, changes the meaning of subsequent cervical screening results, reducing the risk associated with each result, for women aged 21–24 years who are starting to undergo screening. That is, negative cytology becomes more reassuring against, and abnormal cytology less predictive of, ≥CIN2 and ≥CIN3. Risks for ≥CIN3 were very low. The value of screening at this age, in vaccinated women, can be questioned, as previously suggested (Palmer et al., 2016).

In the U.S., LSIL cytology has been the benchmark for referral to colposcopy (Katki et al., 2013a; Wright et al., 2002; Wright et al., 2007a; Wright et al., 2007b) in order to find treatable precancerous lesions and thus prevent cancer. In fact, LSIL cytology, and the risk-equivalent of HPV-positive ASC-US cytology (combined into a category of low-grade cytology in this analysis), are by far the most common screening result that leads to colposcopy referral (Eversole et al., 2010). However, these same test results following HPV vaccination, especially before the age of 18 years, conveyed so little risk that they must be re-interpreted accordingly.

Recently released draft recommendations from the US Preventive Services Task Force recommend cervical cytology every three years starting at age 21 years (U.S. Preventive Service Task Force, 2017). There is no recognition of the impact of HPV vaccination, now increasingly common at this age, on screening performance. These data highlight not only the importance of integrating HPV vaccination status into cervical screening and management guidelines but also age at which women receive HPV vaccination. Guided by the principle of "equal management for equal risk" (Katki et al., 2013a; Castle et al., 2008b), low-grade cytologic abnormalities among those who first start getting screened (age 21 years) and who have been vaccinated against HPV before the age of 18 years likely do not require immediate colposcopy. Given lower risks due to the reduced presence of HPV16 and HPV18, it might be rational to wait for evidence of persistent cytologic abnormalities (proxy for persistent HPV infection) that is the necessary cause of cervical cancer and strongly associated with ≥CIN2 and ≥CIN3 (Schiffman et al., 2007), prior to sending these young women to colposcopy. Alternatively, screening initiation might be deferred for

Table 2
Three-year absolute and relative (RR) cumulative risks with 95% confidence intervals (95%CI) of cervical intraepithelial neoplasia grade 2 or more severe diagnoses (≥CIN2) in women who were screened between ages 21–24 years, stratified by whether they were vaccinated against HPV and the cytology result. This analysis was *for any screening following vaccination* (if vaccinated) results during ages 21–24 years. A test of trend was used to test the statistical differences in risks among those women who were vaccinated under the age of 18, 18–20, and 21–24 years (p_{trend}). Bold type indicates statistical difference ($p < 0.05$) from the unvaccinated (reference) group. Abbreviations: N_{women}, number of women; $N_{\geq CIN2}$, number of women diagnosed with ≥CIN2; PY, person years.

Age at vaccination	Normal cytology[c]					Low-grade cytology[d]					High-grade cytology[e]				
	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)
Pre-vaccination[a]	36,143	99,972	165	0.50 (0.43–0.58)	1.09 (0.89–1.32)	624	1419	102	17.67 (14.76–21.07)	**1.62 (1.31–2.01)**	29	52	12	42.97 (26.93–63.40)	0.85 (0.54–1.36)
Unvaccinated[b]	56,824	159,910	243	0.46 (0.41–0.52)	1 (reference)	2889	5787	253	10.89 (9.63–12.30)	1 (reference)	147	200	71	50.42 (42.32–59.13)	1 (reference)
< 18 years	3628	10,134	7	0.20 (0.10–0.42)	**0.44 (0.21–0.92)**	275	533	10	5.26 (2.58–10.54)	**0.48 (0.24–0.99)**	8	19	0	0.00 (0.00–0.00)	0.00 (0.00–0.00)
18–20 years	5628	16,112	20	0.37 (0.24–0.58)	0.81 (0.51–1.27)	354	773	20	6.83 (4.40–10.53)	**0.63 (0.40–0.99)**	17	26	9	52.94 (32.03–77.04)	1.05 (0.65–1.69)
21–24 years	4890	13,725	36	0.80 (0.58–1.11)	**1.73 (1.22–2.46)**	331	705	46	16.60 (12.64–21.64)	**1.52 (1.13–2.05)**	17	12	11	66.39 (44.00–87.12)	1.32 (0.89–1.94)
	$p_{Trend} < 0.001$					$p_{Trend} < 0.001$					$p_{Trend} = 0.002$				

[a] Screened prior to December 12, 2006 before HPV vaccination became available.
[b] Screened on December 12, 2006 or more recently when HPV vaccination was available.
[c] Normal or HPV-negative atypical squamous cells of undetermined significance (ASC-US) cytology.
[d] HPV-positive ASC-US or low-grade squamous intraepithelial lesion cytology.
[e] Cancer, adenocarcinoma in situ, high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells, cannot rule out HSIL, or atypical glandular cells cytology.

Table 3
Three-year absolute and relative (RR) cumulative risks with 95% confidence intervals (95%CI) of cervical intraepithelial neoplasia grade 3 or more severe diagnoses (≥CIN3) in women who were screened between ages 21–24 years, stratified by whether they were vaccinated against HPV and the cytology result. This analysis was *for any screening following vaccination* (if vaccinated) results during ages 21–24 years. A test of trend was used to test the differences in risks among those women who were vaccinated under the age of 18, 18–20, and 21–24 years (p_{trend}). Bold type indicates statistical difference ($p < 0.05$) from the unvaccinated (reference) group. Abbreviations: N_{women}, number of women; $N_{\geq CIN3}$, number of women diagnosed with ≥CIN3; PY, person years.

Age at vaccination	Normal cytology[c]					Low-grade cytology[d]					High-grade cytology[e]				
	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	RR (95%CI)
Pre-vaccinationa	36,143	100,119	52	0.16 (0.12–0.21)	1.26 (0.87–1.81)	624	1555	32	5.74 (4.08–8.05)	**1.55 (1.04–2.32)**	29	67	4	14.61 (5.71–34.62)	0.72 (0.27–1.92)
Unvaccinated[b]	56,824	160,137	66	0.13 (0.10–0.16)	1 (reference)	2889	6086	84	3.70 (2.97–4.60)	1 (reference)	147	307	27	20.17 (14.23–28.15)	1 (reference)
< 18 years	3628	10,142	1	0.03 (0.00–0.20)	0.22 (0.03–1.59)	275	548	2	0.99 (0.24–4.08)	0.27 (0.06–1.13)	8	19	0		0.00 (0.00–0.00)
18–20 years	5628	16,133	4	0.08 (0.03–0.21)	0.61 (0.22–1.67)	354	795	7	2.43 (1.14–5.13)	0.66 (0.30–1.44)	17	39	4	23.53 (9.55–51.17)	1.17 (0.46–2.94)
21–24 years	4890	13,751	11	0.25 (0.14–0.46)	**1.99 (1.05–3.78)**	331	743	20	7.44 (4.83–11.35)	**2.01 (1.24–3.25)**	17	18	7	46.47 (25.03–74.22)	**2.30 (1.20–4.43)**
	$p_{Trend} = 0.009$					$p_{Trend} < 0.001$					$p_{Trend} = 0.002$				

[a] Screened prior to December 12, 2006 before HPV vaccination became available.
[b] Screened on December 12, 2006 or more recently when HPV vaccination was available.
[c] Normal or HPV-negative atypical squamous cells of undetermined significance (ASC-US) cytology.
[d] HPV-positive ASC-US or low-grade squamous intraepithelial lesion cytology.
[e] Cancer, adenocarcinoma in situ, high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells, cannot rule out HSIL, or atypical glandular cells cytology.

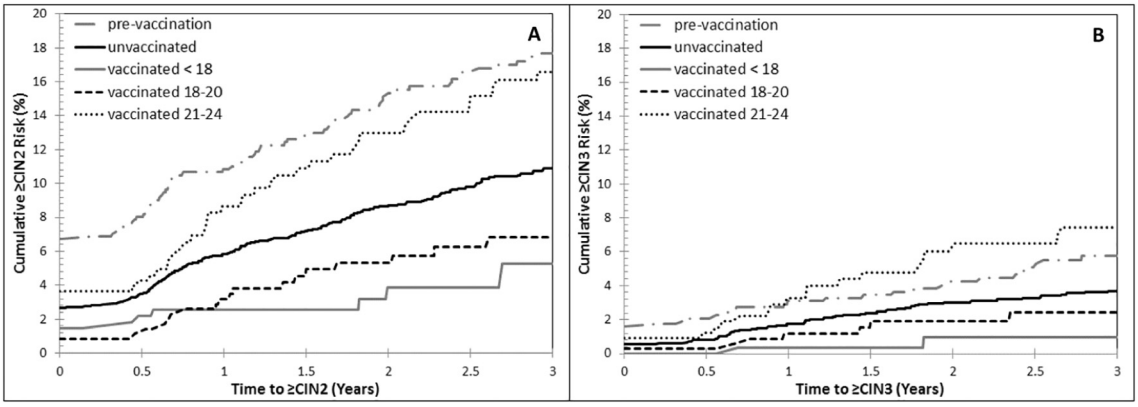

Fig. 1. Cumulative risk of ≥CIN2 (A) and ≥CIN3 (B) for women aged 21–24 years undergoing screening from January 1, 2003 to December 13, 2016 by HPV vaccination status following a low-grade cytology (low-grade squamous intraepithelial lesion or high-risk human papillomavirus-positive atypical squamous cells of undetermined significance) result.

Table 4
The impact of time period (before or after January 2, 2013) on the 3-year cumulative risk of cervical intraepithelial neoplasia grade 2 or more severe diagnoses (≥CIN2) in women who were screened between ages 21–24 years and had low-grade cytology, defined as HPV-positive atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion cytology.

	Early period				Late period			
Age at vaccination	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)	N_{women}	PY	$N_{\geq CIN2}$	Risk (95%CI)
Unvaccinated[a]	2048	4619	223	12.30 (10.84–13.93)	841	1168	30	6.75 (3.80–11.86)
< 18 years	120	265	5	5.04 (2.02–12.29)	155	269	5	4.86 (1.89–12.15)
18–20 years	294	658	18	7.06 (4.47–11.06)	60	116	2	7.75 (1.78–30.39)
21–24 years	309	677	40	15.27 (11.38–20.31)	22	28	6	49.62 (23.47–82.74)
	p = 0.4				p = 0.7			

[a] Screened on December 12, 2006 or more recently when HPV vaccination was available.

several years until the population risks for these women reach the "risk equivalent" of starting screening at 21 years of age in women who have not been vaccinated against HPV16 and HPV18. Even prior to the advent of HPV vaccination, benefits of population cervical screening under the age of 25 years were questionable (Sasieni et al., 2009), and guidelines in European countries recommended that cervical screening preferably not start before the age of 25 years (Arbyn et al., 2010).

Model-based analyses (Kim et al., 2016; Pedersen et al., 2018) have evaluated whether changes to cervical cancer screening for women vaccinated during adolescents are warranted. These studies have consistently found that cervical cancer screening will remain 'good value for money' (and continue to provide a reasonable balance between the harms and benefits) only if screening guidelines are modified to start at later ages and occur less frequently compared with current recommendations. For example, a US-based analysis conducted by Kim and colleagues (Kim et al., 2016) found that screening should be delayed until ages 25 or 30 years for women vaccinated with the bivalent/quadrivalent vaccines and delayed until age 35 years for women vaccinated with the nonavalent vaccine. In addition, the preferred strategies involved primary HPV testing every five to ten years. These modeling analyses were restricted to evaluating the optimal screening strategies for women who were fully vaccinated by the age of 12 years, while our current study demonstrates vaccination at least to the age of 18 years and perhaps even to 21 impacts the performance (and therefore the population benefits) of screening.

Future model-based studies should also evaluate how to modify screening schedules for women vaccinated up to age 26 years. Reassessing the intensity of screening for these women is important in reducing unnecessary referral of women to colposcopy, diagnosis of benign, highly regressive CIN2 (Tainio et al., 2018), and (over) treatment of CIN2 that is linked to pre-term delivery (Kyrgiou et al., 2016; Sasieni et al., 2016).

There were several limitations of this analysis. The population of HPV-vaccinated women may not be representative of the all women getting screened or being vaccinated against HPV at KPNC since they would have to be in the KPNC system for some duration to receive both interventions.

In addition, this was not a randomized trial so we could not control for differences between sub-groups of women. We did not have data on income or education for these women or their parents, latter of which might difficult to collect accurately from young adults included in this analysis and might influence their likelihood of getting vaccinated. Nor did we have sexual history data that perhaps influenced their risks for CIN2/3. We therefore cannot rule out the possibility that confounding may explain partially or fully our findings.

However, there are several reasons why it is unlikely that these observations are due to confounding and are directly related to HPV vaccination. First, there only were statistically significant but small differences in race/ethnicities (e.g., < 5% difference between percentage of whites) that seem unlikely to explain the at least two-fold and four-fold differences in risk of ≥CIN2 and ≥CIN3, respectively, between the different groups of women. Second, to some extent, we have controlled for exposure to HPV, the cause of virtually all cervical cancer (Schiffman et al., 2007; Walboomers et al., 1999; Munoz et al., 2003), and cancer risk by stratifying on cytologic results and restricting the analysis to a narrow age range. Finally, the trend of lesser impact of HPV vaccination with older age of HPV vaccination is consistent with findings from the clinical trials (Munoz et al., 2010; Lehtinen et al., 2012) and population-based studies (Kavanagh et al., 2017).

Third, while a recent systematic review (Rambout et al., 2014) reported that the most common self-reported barrier to HPV vaccination was cost/access and the second was perception of low risk, it is worth noting that women included in this analysis were KPNC members who underwent cervical screening. That is, they had adequate financial

resources or means to become KNPC members and perceived themselves at sufficient risk of cervical cancer to undergo screening, thus controlling in part for those two modifying factors.

We observed that the unvaccinated women had lower risk of ≥CIN2 and ≥CIN3 following a normal or low-grade cytology result than women who were vaccinated at the ages of 21–24 and women of the pre-vaccination era. There are several possible explanations. First, some women in the unvaccinated group may have been vaccinated against HPV in a different health system and at earlier age prior to joining KPNC. Risks of ≥CIN2 in the unvaccinated sub-cohort were significantly greater in the early period than the late period (Table 4), suggesting that more women in this sub-cohort either were vaccinated against HPV prior to becoming KPNC members over time, which is consistent with the slow rise in the uptake of HPV vaccination in the U.S. during that period, and/or population impact of HPV vaccination i.e. herd immunity. We cannot distinguish between these two possibilities.

Second, women who were vaccinated at the ages of 21–24 years were at higher risk of ≥CIN2 and ≥CIN3 i.e., more sexually active women seeking to get vaccinated against HPV. Also of note, a previous study found that HPV DNA- and serology-positive women vaccinated by Gardasil had a higher risk of ≥CIN2 than women given a placebo but the increased ≥CIN2 risk was unexplained. However, if the effect is real, it is reasonable to expect the greatest increase in risk due to HPV vaccination in the older age group at vaccination since they would be more likely to be HPV DNA- and serology positive than a younger age group at vaccination (Haupt et al., 2011).

Finally, our small sample size limited our ability to look at the impact of HPV vaccination on risks following high-grade cytology and resulted wide confidence intervals for risks of ≥CIN3, a better proxy of cancer risk (Schiffman and Rodriguez, 2008; Castle et al., 2007; Carreon et al., 2007; Stoler et al., 2015), when it was used as an endpoint.

In conclusion, as women who are known to have received HPV vaccination younger than 18 years of age now reach the age for cervical screening, the impact of vaccination on population prevalence of CIN2/3 cannot be ignored. Recommendations on the age to initiate cervical screening and/or management of screen positives need to be changed to better balance the benefits-to-harms of screening overall. Regardless of whether getting vaccinated against HPV had a direct effect on reducing absolute risks of ≥CIN2 and ≥CIN3 following a cytology result or is a behavioral marker of a lower-risk population, these lower-risk women need to be screened and/or managed less aggressively (Katki et al., 2013a; Castle et al., 2008b). The impact of HPV vaccination on risk prediction by cytology and pooled HPV testing (e.g., HPV-positive ASC-US) is already being observed in this young population just beginning to be screened, and will expand to older ages as time passes and these cohorts age.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.10.001.

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