Catch-up HPV Vaccination and Subsequent Uptake of Papanicolaou Testing in A State-mandated Health System

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ABSTRACT

The objective of this study was to evaluate the association between human papillomavirus (HPV) vaccination and uptake of initial Papanicolaou (Pap) testing in Israel among women not previously vaccinated through the national immunization program. In this retrospective cohort we used health provider records of vaccinations and cancer screening attendance among female members of a state-mandated health provider in Israel (Maccabi Healthcare Services, MHS). All eligible female members ($N = 20{,}904$) immunized with at least one dose of HPV vaccine from the date of its introduction in Israel (June 2007) until December 31, 2018 were individually matched with nonvaccinated MHS members on one to one ratio by year of birth, residential area socioeconomic level, and district of residence. Data on the uptake of Pap smears until December 2018 were extracted from MHS central datasets, and the number of Pap smears for each woman during the study period was counted. During the observed follow-up period (mean, 6.6 years; interquartile range, 3.9–8.7 year), the cumulative uptake rate of Pap testing in vaccinated women (26.8%) was significantly ($P < 0.001$) greater than among unvaccinated (22.4%) women. In a multivariable model, HPV vaccination was associated with an HR of 1.34 [95% confidence interval (CI), 1.29–1.41] to perform Pap testing. Our findings suggest that uptake of catch-up HPV vaccine was positively correlated to increased uptake of Pap testing.

Prevention Relevance: We found that catch-up HPV vaccination was associated with increased attention to long-term cervical screening attendance. Whereas, those who are not vaccinated and unprotected from HPV, are more likely to abstain from secondary prevention screening tests too and further increase their cervical cancer risk.

Introduction

Cervical cancer is caused by oncogenic types of human papillomavirus (HPV; refs. 1, 2). The quadrivalent HPV vaccine (Gardasil, Merck) and the bivalent vaccine (Cervarix, GlaxoSmithKline) are available in Israel since 2007. In 2013, the HPV vaccine was introduced as a part of the national immunization program in schools for 8th grade girls and since 2015, it is administered to boys as well. Before its inclusion to the national immunization program, the HPV vaccines were available only through the private market and through supplementary health insurances provided by one of four independent healthcare providers in Israel, including Maccabi Healthcare Services (MHS) that covers 25% of the Israeli population. It is recommended by the Israeli Ministry of Heath for females ages 9–26 years, and in 2012, indication was expanded to age 45 years. During the opportunistic vaccination period, the vaccines were administered to candidate individuals upon request.

The HPV vaccine can reduce vaccine-type HPV infections and abnormal Papanicolaou (Pap) test results (3–9), but showed little protection against nonvaccine oncogenic types in postmarket surveillance (10, 11). Moreover, it has no efficacy against prior infections (4, 12). As such, cervical cancer screening is still essential for cancer prevention. National guidelines in Israel currently recommend that women undergo Pap testing (free of charge) at 3-year intervals starting at 25 years of age, regardless of HPV vaccination status.

Findings from a recently published analysis of multi-year responses from the U.S. Behavioral Risk Factor Surveillance System showed declines in the proportion of women receiving and adhering to Pap testing guidelines, while the uptake of the HPV vaccine series is increasing (13). In addition, a previous study from Australia has reported that vaccinated women are being screened at lower rates than unvaccinated women (14), while a more recent research has indicated that young women who initiated HPV vaccination were more likely than unvaccinated women to report having a Pap test in the previous 3 years (9). The objective of this study was,

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therefore, to evaluate the association of HPV vaccination and uptake of initial Pap testing among women who were not previously vaccinated through the national immunization program in Israeli schools (catch-up immunization).

Materials and Methods

Setting

This retrospective cohort analysis was carried out at MHS, a 2.3 million enrollee state-mandated health provider in Israel. According to the Israeli 1994 National Health Insurance Act, MHS may not bar applicants on any grounds, including age or state of health. Therefore, all Israeli subpopulations are represented in MHS. The MHS central database retains complete historical records of patient demographic data, physician data, laboratory results, and filled prescription information, using the patient's unique national identification number.

Study population

Using MHS' database, we identified a total of 47,690 women immunized with at least one dose of catch-up HPV vaccine from the date of its introduction in Israel (June 2007) until December 31, 2018. Women ages 18–45 years can purchase HPV vaccine at full cost (declining from a total of $800 in early years to ~$200 today). Members with supplementary insurance (owned by 85% of MHS members) benefit from a 50% discount. These data do not include adolescents vaccinated as part of the national immunization program.

Women who had a Pap test prior to vaccination ($n = 24,642$), as well as women who were no longer members of MHS on December 2018 ($n = 2,121$) were excluded from the study. All eligible vaccinated women ($n = 20,904$) were individually matched with nonvaccinated MHS members on one to one ratio by year of birth, residential enumeration area socioeconomic level, and district of residence.

Pap smear data and other study variables

MHS offers free cervical screening test every 3 years to women ages of 25 and 54 years. Women out of age range can be tested at a copay of approximately $25. Data on the uptake of Pap smears were extracted from MHS central datasets, and the number of Pap smears for each woman during the study period was counted. We collected information on demographic factors (date of birth, district of residence, and enumeration area), body mass index (BMI), and cigarette smoking status. Socioeconomic status was categorized according to the poverty index of the member's enumeration area (small geographic areas used for census data collection) based on several parameters, including household income, educational qualifications, crowding, material conditions, and car ownership.

Statistical analysis

We started follow-up at the date of receipt of first HPV vaccination dose and then followed them forward until Pap test or December 2018, whichever occurred first. Pearson χ^2 test was used to compare Pap uptake rates. Survival analysis was performed using the Kaplan–Meier method. Cox proportional hazards regression, with days of follow-up as the time scale, was performed to estimate HRs and 95% confidence intervals (CI) of Pap test among women exposed to HPV vaccine compared with those unexposed. Assumption for Cox models was verified by Schoenfeld residuals. *P* values for all comparisons were two-sided, and an alpha of 0.05. Analyses were conducted using IBM SPSS version 25.0 (IBM Corp) and figures were produced using the R package, ggplot2 (15). The research was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the MHS Institutional Review Board with waiver of informed consent.

Results

The baseline characteristics of the 20,904 vaccinated study patients and their matched controls are given in **Table 1**. The

Table 1. Characteristics of study population and baseline.

		HPV vaccination			
		No ($n = 20,904$)		Yes ($n = 20,904$)	
		N	%	*N*	%
Age, years M (SD)		19.68	(3.88)	19.23	(4.58)
BMI (kg/m^2)		23.56	(4.98)	23.08	(4.41)
Smoking[a]	Current	1,655	8.31%	1,507	7.28%
	Past smoker	208	1.05%	197	0.95%
	Never smoked	18,041	90.64%	18,999	91.77%
SES, median (interquartile range)		7	(6–9)	7	(6–9)
District	North	3,338	16.0%	3,338	16.0%
	Sharon	5,428	26.0%	5,428	26.0%
	South	2,467	11.8%	2,467	11.8%
	Center	5,316	25.4%	5,316	25.4%
	Jerusalem and Shfela	4,355	20.8%	4,355	20.8%
Pap test	No	16,222	77.6%	15,298	73.2%
	Yes	4,682	22.4%	5,606	26.8%

Abbreviations: M, mean; SES, socioeconomic status.
[a]Data were missing for 1,021 participants.

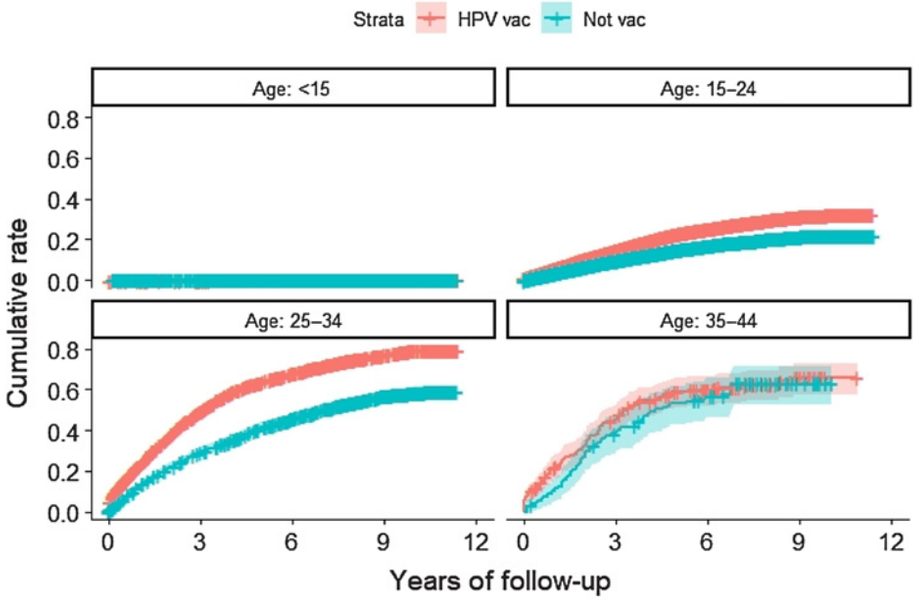

Figure 1.
Time to first Pap test since day of HPV vaccination (same date for nonvaccinated), by age at date of vaccination (vac).

mean (± SD) age at first HPV vaccine dose was 19.23 (± 4.58) and 19.68 (± 3.88) years among vaccinated and unvaccinated participants, respectively. In both groups, less than 10% were ever smokers at baseline.

During the observed follow-up period (mean, 6.6 years; interquartile range, 3.9–8.7 years), the cumulative uptake rate of Pap testing (26.8%) in vaccinated women (mean ± SD age at first test = 26.04 ± 4.13 years) was significantly ($P < 0.001$) greater than the uptake (22.4%) among unvaccinated women (26.14 ± 3.82 years). Kaplan–Meier curves for Pap testing by age at HPV vaccination are given in **Fig. 1**. In women ages 25–34 years, the cumulative testing rate over 10 years of follow-up reached 79.3% (SE = 1.2%) in vaccinated and 68.8% (SE = 1.4%) in unvaccinated women.

In a multivariable model, HPV vaccination was associated with an HR of 1.34 (95% CI, 1.29–1.41) to perform Pap testing. Other variables associated with higher likelihood of Pap testing were past smoking (as compared with never smokers) and BMI (**Table 2**).

Discussion

Our findings suggest that uptake of catch-up HPV vaccine is positively correlated to increased adherence of Pap testing.

Table 2. Baseline variable and Cox model for Pap smear test.

		HR (95% CI)	*P*
Smoking	Never	1 (ref)	
	Current	0.93 (0.86–1.01)	0.087
	Past	1.20 (1.01–1.43)	0.038
BMI	Per 1 kg/m^2	1.01 (1.01–1.02)	<0.001
Birth year	Per year	0.85 (0.84–0.86)	<0.001
HPV vaccinated	Yes vs. no	1.34 (1.29–1.41)	<0.001

We found no evidence to support previous concerns of negative impact of HPV immunization on cervical screening attending rates. This is in line with previous studies suggesting that voluntary vaccination against HPV is associated with higher participation in cervical cancer screening. This has been demonstrated across studies on various populations and study designs, including self-reported data from nationally representative samples (16–18), retrospective cohort among high-risk underserved young females (19), members of health maintenance organization (20), data from the Scottish cervical screening program (21), a registry linkage study among young (22) and adult (20) women in Sweden, a prospective cohort of adult women who had been offered the HPV vaccine and cervical screening in Wales (23), and a nested case–control in Alberta, Canada (24). The finding of a 10% lowered attendance among HPV-vaccinated individuals in Australia (14) has been explained, in part, by data mismatching that resulted in an inaccurate estimation of nonattendance.

According to one model (25), both cervical cancer screening uptake and HPV vaccination uptake are affected by socio-structural determinants, such as age, education, residential size and setting, and distance to the gynecologist office. These factors were widely accounted for in this study by matching. Thus, differences in Pap uptake rates could be explained by more subjective characteristics. These may include fear of cancer, attitudes toward health and toward cancer prevention, health literacy, and personal risk perception. The positive association between HPV vaccination and Pap test performance can, therefore, be explained by a stronger perception of cervical cancer risk in vaccinated women, and more importantly, a higher perception of the vaccine effectiveness in reducing the risk (17). It has been suggested that this relationship can be explained by the

classic theory of cognitive dissonance, according to which women who are unvaccinated might unconsciously weigh cancer prevention less favorably to resolve any dissonance between their perception of the vaccine and their own vaccination decisions. Women with a more positive attitude toward preventive services may be more likely to obtain both vaccination and screening (25). Because failure-to-screen behavior has been shown as an important predictor of cervical cancer, this emphasizes on the importance of providing complete information about cervical screening among unvaccinated women.

Strengths of this study include the relatively long follow-up period of up to 13 years and the large sample size from an unselected population-based cohort utilizing electronic record linkage of real-world data on HPV vaccinations and cervical screening. The main limitation of this real-world data analysis is that we investigated voluntary vaccination, rather immunization given as part of a childhood immunization program. This self-selected immunization may introduce bias and, therefore, findings may not be extrapolated to other contexts. Our analysis accounted for important confounders both by matching for year of birth, socioeconomic level, and district of residence, as well as adjusting for BMI and smoking status in a multivariable model. However, we did not account for gynecologic histories, healthcare utilization, and use of other preventive services. Nonetheless, these factors were not shown to explain differences in cervical cancer screening practices (20). 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.

Conclusions

This population-based study found that voluntary HPV vaccination is associated with increased attention to cervical screening attendance over a follow-up period of up to 13 years. Whereas, those who are not vaccinated and unprotected from HPV in terms of primary prevention, are those who are more likely to abstain from secondary prevention screening tests too and further increase their cervical cancer risk. These findings should further inform investigation into effective interventions to address undervaccination and underscreening among women at risk for cervical cancer.

Authors' Disclosures

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