ORIGINAL ARTICLE

HPV Vaccination and the Risk of Invasive Cervical Cancer

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ABSTRACT

BACKGROUND

The efficacy and effectiveness of the quadrivalent human papillomavirus (HPV) vaccine in preventing high-grade cervical lesions have been shown. However, data to inform the relationship between quadrivalent HPV vaccination and the subsequent risk of invasive cervical cancer are lacking.

METHODS

We used nationwide Swedish demographic and health registers to follow an open population of 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017. We assessed the association between HPV vaccination and the risk of invasive cervical cancer, controlling for age at follow-up, calendar year, county of residence, and parental characteristics, including education, household income, mother's country of birth, and maternal disease history.

RESULTS

During the study period, we evaluated girls and women for cervical cancer until their 31st birthday. Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32 to 0.82). After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21 to 0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00 to 0.34) among women who had been vaccinated before the age of 17 years and 0.47 (95% CI, 0.27 to 0.75) among women who had been vaccinated at the age of 17 to 30 years.

CONCLUSIONS

Among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level. (Funded by the Swedish Foundation for Strategic Research and others.)

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The ultimate goal of human papillomavirus (HPV) vaccination is to prevent invasive cervical cancer by preventing infection with major oncogenic types of HPV.[1] As of December 2019, a total of 124 countries and territories had implemented national immunization programs for HPV vaccination.[2] In Sweden, HPV vaccination was approved in 2006, and the quadrivalent HPV vaccine, which covers HPV types 6, 11, 16, and 18, has been used almost exclusively.[3]

Previous studies of HPV vaccines, including randomized trials that assessed efficacy[4-6] or effectiveness,[7-13] have shown that these vaccines protect against HPV infection, genital warts, and high-grade precancerous cervical lesions (i.e., cervical intraepithelial neoplasia of grade 2 or higher [CIN2+] and grade 3 or higher [CIN3+]). One study — which used pooled data from passive follow-up of two randomized, controlled trials and from one community-randomized, phase 4 trial — showed efficacy of HPV vaccination against HPV-related cancers, although the number of cancers was small (10 cases), and the cancer types were not limited to cervical cancers.[14] Randomized, controlled trials cannot readily evaluate vaccine effectiveness against invasive cervical cancer because of the long lead time (the time from HPV infection to the clinical detection of cervical cancer) and the low risk of cervical lesions after vaccination. We used nationwide registry data from Sweden to examine the association between HPV vaccination and the risk of invasive cervical cancer.

Methods

Study Population

Beginning in May 2007, HPV vaccination was subsidized for girls in Sweden who were 13 to 17 years of age. In 2012, Sweden introduced a free catch-up HPV vaccination program for girls and women 13 to 18 years of age and a school-based HPV vaccination program for girls 10 to 12 years of age.[3] Currently, women 23 to 64 years of age are invited to participate in the population-based, organized cervical cancer screening program, which issues invitations every 3 to 7 years to women depending on their age.[15]

We used the Swedish Total Population Register to perform a registry-based cohort study from 2006 through 2017 that included an open population of girls and women 10 to 30 years of age who were living in Sweden (Fig. 1).[16] Information regarding the registries used in this study is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Girls and women were followed starting either on their 10th birthday or on January 1, 2006, whichever came later. Girls and women were included if they had no previous HPV vaccination, had no previous invasive cervical cancer, and had not immigrated to Sweden after January 1, 2006 (because the HPV vaccination status before immigration would have been unknown). All eligible girls and women were followed until they received a diagnosis of invasive cervical cancer, emigrated from Sweden, died, were lost from the registry, received bivalent HPV vaccination, or had their 31st birthday or until December 31, 2017, whichever came first. This study was approved by the regional ethical review board in Stockholm, which determined that informed consent from the persons included in the study was not required.

Data Collection

The nationwide Swedish registers that we used in this study were linked at the individual level with the use of the unique personal identity number that is assigned to all Swedish residents, which resulted in virtually complete coverage of the population.[17] The Swedish Total Population Register[16] was used to identify the population at risk and to retrieve information on immigration, emigration, and death. Exposure to quadrivalent HPV vaccination was determined with the use of HPV vaccination records retrieved from the Swedish HPV Vaccination Register,[18] the Prescribed Drug Register,[19] and the National Vaccination Register[20] (Fig. S2 in the Supplementary Appendix). A vaccination recorded in any of these registries was considered to be vaccine exposure. The Swedish HPV Vaccination Register is a voluntary registry that has been in operation since 2006 and has recorded all HPV vaccinations that were administered from 2006 through 2015.[18] The Prescribed Drug Register[19] has been in operation since 2005 and is a mandatory registry of dispensed pharmaceuticals; all quadrivalent HPV vaccinations administered within a governmentally subsidized program from 2007 through

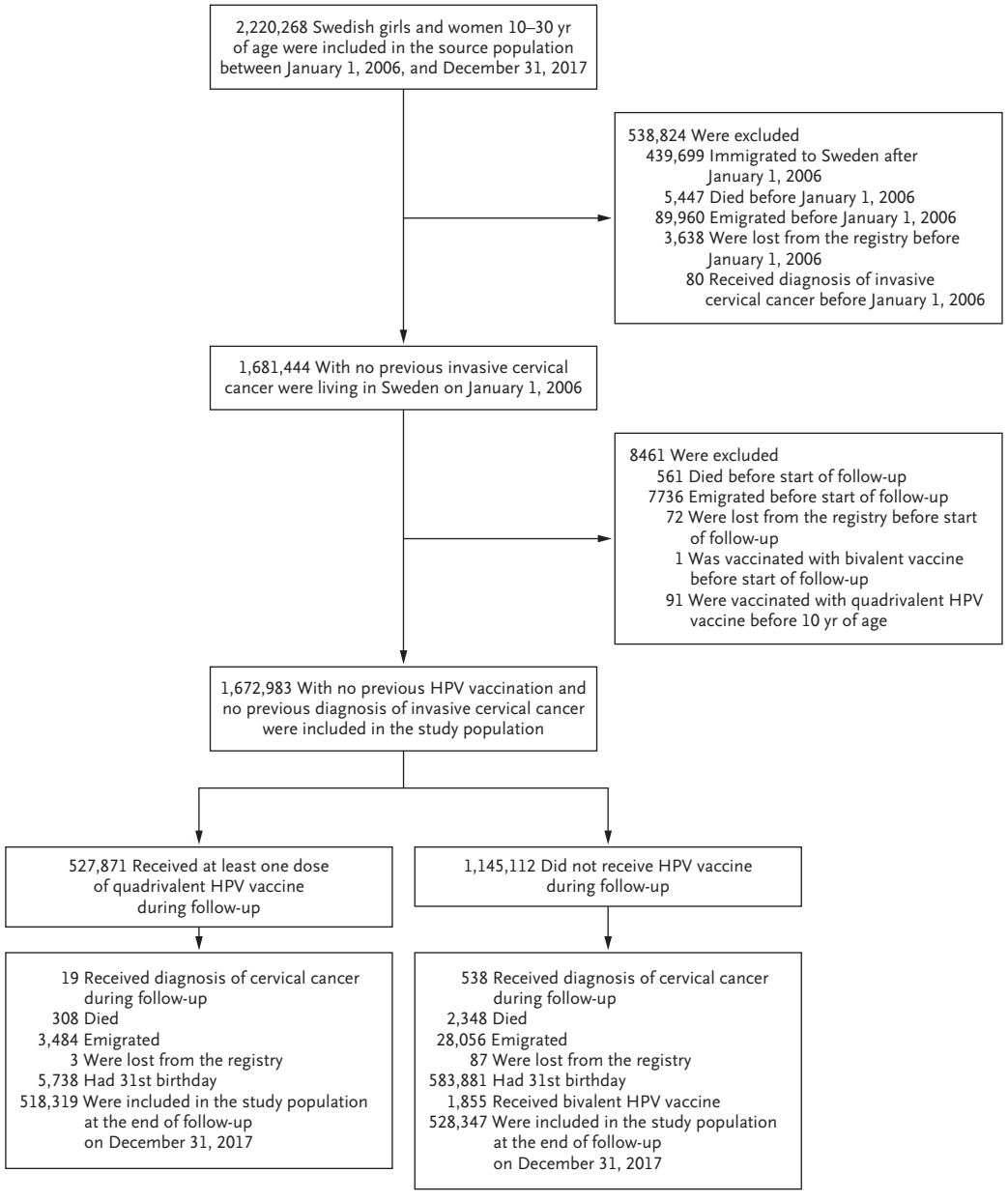

Figure 1. Study Population.
HPV denotes human papillomavirus.

2012 were identified in this registry with the use of Anatomical Therapeutic Chemical code J07BM01. The National Vaccination Register[20] is a mandatory registry of childhood vaccinations that began in 2013 and has virtually complete coverage for the school-based HPV vaccination program. Administered doses of vaccine included in the Swedish HPV Vaccination Register for which consent was not obtained were recorded without the personal identity number. Although most vaccinations were also recorded in the Prescribed Drug Register, approximately 8% of administered quadrivalent HPV vaccine doses in the Swedish HPV Vaccination Register could not

be confirmed in another database (Table S1). The occurrence of invasive cervical cancer and the date of diagnosis were identified in the Swedish Cancer Register (a compulsory reporting registry founded in 1958 that covers the entire population)[21] with the use of code C53 in the *International Classification of Diseases, 10th Revision*.

We identified the biologic and adoptive parents for each study participant through the Multi-Generation Register,[22] which contains information on familial links for persons born in Sweden from 1932 onward. We used the Longitudinal Integration Database for Health Insurance and Labor Market Studies,[23] the Swedish Cancer Register, and the Total Population Register to retrieve data regarding parental characteristics, including mother's country of birth, highest parental education level, annual household income level, maternal history of CIN3+, and maternal history of cancers other than cervical cancer (a history of these cancers might affect both vaccine uptake and the risk of cervical cancer). All covariates were measured as fixed values before the start of follow-up.

HPV VACCINATION

Since 2006, the quadrivalent HPV vaccine has been administered according to a three-dose vaccination schedule; from 2015 onward, a two-dose schedule has been used for school-based vaccination programs. We considered HPV vaccination as a time-varying exposure, and girls and women were considered to have been vaccinated if they received at least one dose of quadrivalent HPV vaccine (Table S2). The index date of vaccination was defined as the date the first dose of vaccine was administered. Girls and women who were vaccinated during follow-up were moved to the vaccinated population beginning on the index date of vaccination. If no vaccine was received during the study period, participants continued to contribute to person-time in the unvaccinated population (Fig. S3). Because no HPV vaccination was available before 2006, our design ensured that the comparison was between persons who received the vaccine for the first time and those who had never been vaccinated. The age at initiation of vaccination was assessed with the use of two age cutoffs (vaccination before 17 years of age and vaccination before 20 years of age) on the basis of previous work that showed that initiation of vaccine at a younger age was associated with greater effectiveness in preventing genital warts and high-grade precancerous cervical lesions.[10-13]

SENSITIVITY ANALYSES

We included an interaction term between the variables of HPV vaccination and birth cohort to test whether the risk reduction with vaccination varied among birth cohorts because of different degrees of vaccination coverage. The purpose of this analysis was to examine whether herd effects (in addition to individual-level, vaccination-derived effects) might be present in our data. Further, to exclude possible prevalent cervical cancers at the date of HPV vaccination, we used a buffer period of 1 to 5 years at 1-year intervals after the index date of HPV vaccination (Figs. S4 and S5). Finally, we used multiple imputation to address the missing covariate data.

STATISTICAL ANALYSIS

We estimated the statistical power for the comparison of incidence rates among unvaccinated and vaccinated girls and women before performing the analysis (Table S3). The median power for this comparison in all assumed scenarios was 0.94 (range, 0.43 to 1.00), which corresponds to an assumed vaccine coverage of 30%, an assumed risk reduction of 70% in the vaccinated population, an incidence rate in the unvaccinated population of 4 per 100,000 person-years, and no herd effect for 1 year of follow-up of 1.5 million persons, without censoring of data.

The cumulative incidence of cervical cancer according to HPV vaccination status was plotted according to age at follow-up. Incidence rates of cervical cancer were estimated for girls and women until their 31st birthday. We used Poisson regression models to estimate incidence rate ratios, comparing the incidence rate among vaccinated women with that among unvaccinated women. We report 95% bootstrap confidence intervals of the incidence rate ratios based on bias-corrected percentiles from 2000 bootstrap replications. We used age at follow-up as the underlying timescale, controlling for age during follow-up (as a spline term with 3 degrees of freedom), calendar year, county of residence, and parental characteristics. Missing values were included as separate strata in the corresponding covariate. Separate Poisson models were fitted to estimate the overall incidence rate ratio for quad-

Table 1. Characteristics of the Study Population at Baseline.*

Variable	Unvaccinated	Vaccinated	Vaccinated before Age 17 Yr	Vaccinated before Age 20 Yr
Total population — no.	1,145,112	527,871	438,939	498,524
Birth cohort — no. (%)				
1975–1979	258,244 (22.6)	190 (<0.1)	0	0
1980–1984	243,776 (21.3)	2,602 (0.5)	0	0
1985–1989	246,446 (21.5)	21,763 (4.1)	4 (<0.1)	4,604 (0.9)
1990–1994	174,458 (15.2)	117,758 (22.3)	61,683 (14.1)	108,409 (21.7)
1995–1999	100,162 (8.7)	129,796 (24.6)	121,585 (27.7)	129,749 (26.0)
2000–2007	122,026 (10.7)	255,762 (48.5)	255,667 (58.2)	255,762 (51.3)
Mother's country of birth — no. (%)†				
Sweden	882,560 (77.1)	448,652 (85.0)	373,292 (85.1)	424,223 (85.1)
Other country	195,601 (17.1)	77,810 (14.7)	64,673 (14.7)	73,094 (14.7)
Missing data‡	66,951 (5.8)	1,409 (0.3)	974 (0.2)	1,207 (0.2)
Highest parental education level — no. (%)†§				
Low	84,301 (7.4)	14,107 (2.7)	11,087 (2.5)	12,997 (2.6)
Middle	528,999 (46.2)	206,050 (39.0)	169,608 (38.6)	195,522 (39.2)
High	467,543 (40.8)	307,002 (58.2)	257,808 (58.8)	289,407 (58.1)
Missing data‡	64,269 (5.6)	712 (0.1)	436 (<0.1)	598 (0.1)
Highest annual household income level — no. (%)†¶				
Low	204,079 (17.8)	69,323 (13.1)	57,651 (13.1)	65,871 (13.2)
Middle	429,852 (37.5)	204,812 (38.8)	173,234 (39.5)	195,639 (39.2)
High	446,765 (39.1)	253,337 (48.0)	207,812 (47.3)	236,718 (47.5)
Missing data‡	64,416 (5.6)	399 (0.1)	242 (0.1)	296 (0.1)
Maternal history of CIN3+ — no. (%)‖				
Yes	50,217 (4.4)	21,085 (4.0)	17,227 (3.9)	19,681 (3.9)
No	1,094,895 (95.6)	506,786 (96.0)	421,712 (96.1)	478,843 (96.1)
Maternal history of noncervical cancer — no. (%)‖				
Yes	47,293 (4.1)	13,570 (2.6)	10,730 (2.4)	12,404 (2.5)
No	1,097,819 (95.9)	514,301 (97.4)	428,209 (97.6)	486,120 (97.5)

* Percentages may not total 100 because of rounding.
† When data were available for both biologic and adoptive parents, data from the adoptive parents were used.
‡ Missing data for mother's country of birth, highest parental education level, and highest annual household income level were classified as a separate stratum and were included in the regression model.
§ The highest parental education level was assessed in the year before the start of follow-up and was classified as "low" if the parent had 9 years or less of primary education, "middle" if the parent had 2 to 3 years of secondary schooling (similar to senior high school), and "high" if the parent had postsecondary education and above (equivalent to university studies).
¶ The highest annual household income level was assessed in the year before the start of follow-up and was categorized as "low" if it was below the 33rd percentile, "middle" if was from the 33rd to the 67th percentile, and "high" if it was above the 67th percentile, determined on the basis of three levels of annual household income derived from data for all Swedish persons 35 to 65 years of age in the year that income was assessed.
‖ Maternal history of CIN3+ (cervical intraepithelial neoplasia of grade 3 or worse) and noncervical cancer were considered to be a diagnosis of the disease at any time before the start of follow-up. When data were available for both a biologic and an adoptive mother, a maternal diagnosis of CIN3+ or a diagnosis of noncervical cancer was recorded if both the biologic mother and the adoptive mother had the corresponding disease.

Table 2. HPV Vaccination and Invasive Cervical Cancer.

HPV Vaccination Status	No. of Cases of Cervical Cancer	Crude Incidence Rate per 100,000 Person-Yr (95% CI)	Age-Adjusted Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)*
Unvaccinated	538	5.27 (4.84–5.73)	Reference	Reference
Vaccinated	19	0.73 (0.47–1.14)	0.51 (0.32–0.82)	0.37 (0.21–0.57)
Status according to age cutoff of 17 yr				
Vaccinated before age 17 yr	2	0.10 (0.02–0.39)	0.19 (0.05–0.75)	0.12 (0.00–0.34)
Vaccinated at age 17–30 yr	17	3.02 (1.88–4.86)	0.64 (0.39–1.04)	0.47 (0.27–0.75)
Status according to age cutoff of 20 yr				
Vaccinated before age 20 yr	12	0.49 (0.28–5.73)	0.52 (0.29–0.94)	0.36 (0.18–0.61)
Vaccinated at age 20–30 yr	7	5.16 (2.46–10.83)	0.50 (0.24–1.06)	0.38 (0.12–0.72)

* The adjusted incidence rate ratios were adjusted for age as a spline term with 3 degrees of freedom, county of residence, calendar year, mother's country of birth, highest parental education level, highest annual household income level, previous diagnosis in mother of CIN3+, and previous diagnosis in mother of cancers other than cervical cancer. The 95% confidence intervals were bias-corrected percentile confidence intervals that were estimated with the use of bootstrapping with a resampling frequency of 2000 times.

rivalent HPV vaccination as well as separate incidence rate ratios for age at initiation of vaccination. We used SAS software, version 9.4 (SAS Institute), for data management and power calculation and Stata software, version 15.0 (StataCorp), and R software, version 3.6.3 (R Foundation for Statistical Computing), for all other statistical analyses. All statistical tests were two-sided. Additional details regarding statistical methods are provided in the Supplementary Appendix.

RESULTS

STUDY POPULATION

Our study population included 1,672,983 girls and women 10 to 30 years of age, 527,871 of whom received at least one dose of HPV vaccine during the study period (Table 1). Among all vaccinated girls and women included in the study population, 438,939 (83.2%) initiated vaccination before the age of 17 years. During the study period, cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine (Table 2).

HPV VACCINATION AND CERVICAL CANCER

The cumulative incidence of cervical cancer increased rapidly at 23 years of age among both vaccinated and unvaccinated women; this is the age when Swedish women are first invited to participate in the cervical cancer screening program. The cumulative incidence among unvaccinated women rose sharply to 94 cases per 100,000 persons by 30 years of age, whereas the cumulative incidence among vaccinated women was 47 cases per 100,000 persons by 30 years of age. Among women who had initiated vaccination at the age of 17 to 30 years, the cumulative incidence was 54 cases per 100,000 persons by the age of 30 years. Among women who had initiated vaccination before the age of 17 years, the cumulative incidence was 4 cases per 100,000 persons by the age of 28 years (Fig. 2).

After adjustment for age at follow-up, the incidence rate ratio for the comparison of vaccinated women with unvaccinated women was 0.51 (95% confidence interval [CI], 0.32 to 0.82). After additional adjustment for calendar year and residential and parental characteristics, the incidence rate ratio was 0.37 (95% CI, 0.21 to 0.57) (Table 2). With stratification according to age at initiation of vaccination, the fully adjusted incidence rate ratios for cervical cancer among women who had been vaccinated before the age of 17 years and women who had been vaccinated between the ages of 17 and 30 years were 0.12 (95% CI, 0.00 to 0.34) and 0.47 (95% CI, 0.27 to 0.75), respectively. The fully adjusted incidence

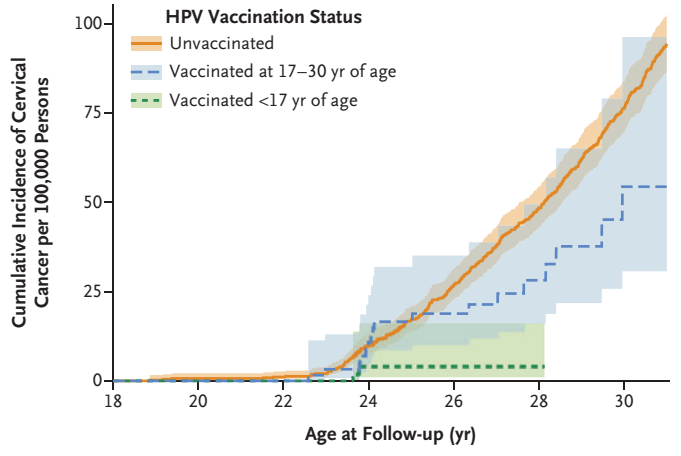

Figure 2. Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.

Age at follow-up is truncated in the graph because no cases of cervical cancer were observed in girls younger than 18 years of age.

rate ratio was 0.36 (95% CI, 0.18 to 0.61) among women who had been vaccinated before the age of 20 years and 0.38 (95% CI, 0.12 to 0.72) among women who had been vaccinated between the ages of 20 and 30 years.

SENSITIVITY ANALYSIS

We did not find a significant difference in risk reductions associated with HPV vaccination among birth cohorts (Table S4). With the introduction of a buffer period, the risk of cervical cancer among HPV-vaccinated women remained consistently lower than that among unvaccinated women (Table S5). With the use of a 5-year buffer period, the risk reduction among HPV-vaccinated women appeared more pronounced than that among unvaccinated women: 8 cases of cervical cancer were diagnosed in vaccinated women, and 549 cases were diagnosed in unvaccinated women. After multiple imputation, the estimated incidence rate ratios were almost identical to those in the main analysis (Table S6).

DISCUSSION

In this population-based cohort study, we found that quadrivalent HPV vaccination was associated with a substantially lower risk of invasive cervical cancer. When the analysis was stratified according to age at vaccination, the reduction in the incidence of invasive cervical cancer was more pronounced among women who were vaccinated at a younger age.

Although the efficacy[4-6] and effectiveness[7-13] of the HPV vaccination against HPV infection, genital warts, and high-grade cervical lesions (CIN2+ and CIN3+) have been established, our results extend this knowledge base by showing that quadrivalent HPV vaccination is also associated with a substantially reduced risk of invasive cervical cancer, which is the ultimate intent of HPV vaccination programs. The greater risk reduction associated with younger age at initiation of vaccination is consistent with previous findings that showed a lower risk of genital warts and high-grade cervical lesions with HPV vaccination.[10-13] Our results also support the recommendation to administer quadrivalent HPV vaccine before exposure to HPV infection to achieve the most substantial benefit, since vaccination has no therapeutic effect against preexisting HPV infection.[24,25]

Our findings are consistent with limited trial data[14] and with data from a previous ecologic study.[26] A study involving passive follow-up of participants in HPV vaccine trials that used the Finnish Cancer Registry showed no HPV-related cancers in vaccinated women, but there were 10 cases of HPV-related invasive carcinomas in unvaccinated women (including 8 cases of cervical cancer), which corresponds to 100% (95% CI, 16 to 100) vaccine efficacy.[14] A study from the United States showed a significantly lower incidence of cervical cancer among girls and women 15 to 34 years of age during the postvaccination period than during the prevaccination period.[26]

We found that the risk of cervical cancer among participants who had initiated vaccination before the age of 17 years was 88% lower than among those who had never been vaccinated; the 95% confidence interval around the relative risk indicated that the plausible risk was 66 to 100% lower with vaccination. The overall percentage of cases of cervical cancer caused by HPV types 16 and 18 is approximately 70% globally,[27] but the distribution of HPV types may be different among younger women than among older women. We conducted an unpublished reanalysis of our previously published results in which we used HPV genotyping of 2850 cervical cancer tumors; the analysis showed that 84.4%

of invasive cervical cancers diagnosed in persons 30 years of age or younger were associated with HPV types 16 or 18 (Table S7).[28] It is also possible that the vaccine results in cross-protection against other HPV types.[29]

Unvaccinated persons would indirectly benefit from HPV vaccination if vaccination coverage of girls and women in a population exceeds 50%.[7] A herd effect of HPV vaccination against genital warts has been observed previously in the Swedish population.[30] A vaccination coverage of at least 50% was recorded among women born in 1993 or later in our study, but our sensitivity analysis did not suggest herd effects with respect to the risk of cervical cancer. This is understandable, since there is usually a span of 5 to 20 years between acquisition of persistent HPV infection and development of cervical cancer,[31] and we observed very few cases of invasive cervical cancer among the relevant birth cohorts during follow-up.

Our study has some limitations. A small proportion of vaccinated women were misclassified as unvaccinated in the analysis. However, such misclassification would be expected to produce a bias toward the null. A potentially greater concern is the possibility that the relationship of HPV vaccination and the risk of cervical cancer is confounded by other factors — in particular, HPV-vaccinated women could have been generally healthier than unvaccinated women (i.e., healthy volunteer bias). We adjusted for several parental characteristics that might be associated with both vaccination uptake and underlying risk of cervical cancer. However, confounding by lifestyle and health factors in the women (such as smoking status, sexual activity, oral contraceptive use, and obesity) cannot be excluded; these factors are known to be associated with a risk of cervical cancer,[32-34] although their independent association with HPV vaccine uptake is not conclusive.[35,36] The adjustment for parental education level and annual household income level in our analysis may serve to some extent as proxies for lifestyle factors such as smoking status.[37] Whereas healthy volunteer bias would be expected to be more prominent among women who had paid for opportunistic vaccinations (a population that almost exclusively received vaccination after the age of 17 years), we found greater risk reductions among women who were vaccinated before the age of 17 years. Moreover, the higher rate of screening for cervical cancer among HPV-vaccinated women[38,39] would be expected to increase the likelihood that asymptomatic cervical cancer would be detected on screening, and this could potentially cause an underestimation of the risk reduction. Because the risk of CIN2+ among HPV-vaccinated women is substantially lower than that among unvaccinated women, it is unlikely that differential rates or types of treatment of premalignant cervical lesions between vaccinated and unvaccinated women could account for the lower risk of invasive cervical cancer in the vaccinated population.[6,11,12] Owing to the small number of cases of cervical cancer observed among the vaccinated women, we could not reliably estimate the association of vaccination with the risk of cervical cancer according to the number of doses of vaccine.

In this large, nationwide study of girls and young women 10 to 30 years of age who had been vaccinated through HPV vaccination programs, we found that HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer.

This study was approved by the regional ethical review board in Stockholm (Dnr. 02-556, 2011/921-32, 2012/216-32, and 2014/246-32), which determined that written informed consent was not required from the persons included in the study.

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