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Article

Real-World Effectiveness of Human Papillomavirus Vaccination Against Vulvovaginal High-Grade Precancerous Lesions and Cancers

Christian Dehlendorff, PhD,[1] Louise Baandrup, PhD,[2] Susanne K. Kjaer, DMSc[2,3,*]

[1]Statistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark; [2]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; and [3]Department of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

*Correspondence to: Susanne K. Kjaer, DMSc, Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark (e-mail: susanne@cancer.dk).

Abstract

Background: Vaccination against human papillomavirus (HPV) has proven to be effective against severe cervical lesions and genital warts, whereas no previous study has provided real-world data on the HPV vaccine effectiveness against high-grade vulvovaginal lesions. **Methods:** A cohort of all women age 17-26 years living in Denmark during 2006-2019 was followed in nationwide registers for individual-level information about HPV vaccination and first diagnoses of vulvar and vaginal high-grade squamous intraepithelial lesions (HSIL+) or worse. The cumulative incidence of vulvar and vaginal HSIL+, respectively, was estimated with the Aalen-Johansen estimator, and Cox proportional hazards regression was used to estimate hazard ratios (HRs) for vulvar and vaginal lesions separately, comparing women vaccinated at age 16 years or younger and at age 17-26 years with unvaccinated women. **Results:** The cohort consisted of 514 537 women, of which 50.6% were vaccinated at baseline (<16 years), 31.8% were vaccinated during follow-up (17-26 years), and 17.6% remained unvaccinated. The cumulative incidence was less than 0.6‰ for vulvar HSIL+ and less than 0.2‰ for vaginal HSIL+. Adjusted analyses showed reduced HRs for both vulvar (HR = 0.22, 95% confidence interval = 0.13 to 0.38) and vaginal HSIL+ (HR = 0.16, 95% confidence interval = 0.04 to 0.55) for women vaccinated at age 16 years or younger compared with unvaccinated women. For women vaccinated at 17-26 years of age, the reductions in HRs were smaller for vaginal HSIL+ and close to 0 for vulvar HSIL+. **Conclusions:** HPV vaccination before 17 years of age reduces the risk of vulvar and vaginal HSIL+ based on real-world data.

Vulvar and vaginal cancer and their immediate precursor lesions known as high-grade squamous intraepithelial lesions (HSIL) are rare human papillomavirus (HPV) infection–related outcomes (1). The SIL terminology has replaced the former terminology of vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN), although differentiated VIN is still used for the HPV-independent precursor lesions (2). Two meta-analyses recently reported that 76% of VIN and 40% of vulvar cancers tested HPV positive (3) and that the HPV prevalence was 85% in VaIN and 67% in vaginal squamous cell carcinomas (4). Among the HPV-positive lesions, HPV16 is the predominant HPV type, indicating that the currently available HPV vaccines may prevent a substantial proportion of high-grade vulvovaginal disease (3-6).

There are currently 3 prophylactic HPV vaccines on the market. The quadrivalent HPV vaccine (HPV 6, 11, 16, and 18) has been available since 2006 and has been followed by license of the bivalent vaccine (HPV 16 and 18) and, most recently, the nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). Randomized clinical trials have shown high efficacy of the HPV vaccines against genital warts and high-grade cervical, vulvar, and vaginal disease (1,7-12). Now, after 14 years with the HPV vaccines on the market, several studies have documented the real-world vaccine effectiveness against genital warts (13,14) and severe cervical lesions (14-16). However, due to the rare occurrence of high-grade vulvar and vaginal disease and the lack of registration of these outcomes, the real-world effectiveness of HPV vaccination on these lesions has not yet been evaluated.

In Denmark, HPV vaccination has been part of the free-of-charge childhood vaccination program offered to 12-year-old girls since January 2009, with free-of-charge catch-up vaccination of older birth cohorts offered in 2 rounds. In the first catch-up starting in October 2008, vaccination was offered to girls age 13-15 years. This was followed by a second catch-up in August 2012 offering vaccination to girls and women up to age 27 years. Although Denmark experienced a short decrease in vaccine

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uptake during 2015-2016 (17), it is a country with a high vaccine coverage. We also have the advantage of complete nationwide registration of HPV vaccination and pathology diagnoses. To our knowledge, this is the first real-world study to examine the effectiveness of HPV vaccination against vulvar and vaginal high-grade precancerous lesions and cancers.

Methods

Study Population and Follow-Up

This cohort study consists of all women in Denmark born 1985-2002 and living in Denmark between October 2006 and December 2019. All these birth cohorts were covered by the childhood vaccination program or the catch-up program. Individual-level information on exposure, outcomes, and covariates was retrieved from nationwide registries (18-22). Unambiguous linkage between registries was ensured by the unique personal identification number assigned to all Danish residents since 1968 (22). The personal identification number contains information on sex and date of birth, and it is used universally in society, including all health registries, as a unique identifier.

The women were followed from October 2006 or from their 17th birthday, whichever came last, and until first occurrence of either death, emigration, their 27th birthday, or end of follow-up (December 2019). For each outcome (vulvar or vaginal HSIL+), we excluded women with the particular outcome before start of follow-up (vulvar HSIL+: $n = 10$; vaginal HSIL+: $n < 5$). This meant that cohort sizes differed slightly by outcome of interest.

Exposure

The exposure of interest was HPV vaccination with any of the 3 commercially available HPV vaccines. Information about free-of-charge HPV vaccination was obtained from the National Health Service Registry (18), which holds information on activities of primary health professionals since 1990. Vaccines bought at own cost were identified in the Danish National Prescription Registry holding information on all redeemed prescriptions since 1995 (21). The free-of-charge Danish vaccination program offered the quadrivalent HPV vaccine from the beginning in January 2009 and up until January 2016. Hereafter, the bivalent HPV vaccine was offered up until October 2017 and followed by the nonavalent vaccine. Women were considered vaccinated after the first dose of HPV vaccine and further classified according to age at vaccination (≤16 years and 17-26 years). The reason for this grouping is based on data showing that the median age for sexual debut among Danish girls is 16 years (23) and on previous findings of a high HPV vaccine effectiveness against cervical lesions in girls vaccinated at age 16 years and younger (15).

Outcomes

Study outcomes were identified in the nationwide Danish Pathology Registry (19), which holds information on all diagnoses performed at pathology departments in Denmark since 1997. We considered 2 separate outcomes; respectively, vulvar HSIL or worse (vulvar HSIL+) and vaginal HSIL or worse (vaginal HSIL+). In the Pathology Registry, codes for topography and morphology are based on the Systematized Nomenclature of Medicine (SNOMED). Cases were identified by the SNOMED topography codes starting with T80 (vulva) and T81 (vagina) and the SNOMED morphology codes corresponding to moderate or severe dysplasia, adenocarcinoma in situ, or cancer.

Covariates

We selected a priori attained age and socioeconomic position as potential confounders. Because the girls and women in our study cohort may not all have finished their education, we used the highest obtained level of either their own, their mothers', or their fathers' education as a proxy for socioeconomic position, classified into basic, vocational, higher, and missing. The parents of the girls and women in the cohort were identified in the Civil Registration System (22), and educational information was retrieved from Statistics Denmark (20).

Statistical Analysis

The exposure of interest, HPV vaccination, was treated as a time-varying covariate. Thus, each woman could contribute both unvaccinated and vaccinated person-time during follow-up. In all analyses, vulvar and vaginal HSIL+ were analyzed separately.

The cumulative incidence of vulvar and vaginal HSIL+, respectively, was estimated with the Aalen-Johansen estimator (24) using death as a competing event with 95% confidence intervals (CIs) and attained age as underlying timescale. We used Cox proportional hazard regression to estimate hazard ratios (HRs) and 95% CIs comparing vaccinated women according to age at vaccination with unvaccinated women using attained age as underlying timescale. The hazard ratios were presented unadjusted and adjusted for maximum educational level. The proportional hazards assumption was checked by looking for trends in the scaled Schoenfeld residuals.

The main analysis was a complete case analysis corresponding to approximately 97% of the total cohort. Education level was the only covariate with missing information, and as a sensitivity analysis we applied multiple imputations of covariates by the smcfcs package. We also evaluated the effect of potential misclassification between vaginal and cervical high-grade disease by censoring women at time of diagnosis of cervical intraepithelial neoplasia (CIN) grade 2 or worse.

All analyses were performed using the statistical software R version 3.4.2 (25) with the survival, smcfcs, and prodlim packages. Use of registry data for this study was approved by the Danish National Board of Health Data (FSEID-0045 and FSEID-4711).

Results

The cohort consisted of 514 537 women. At baseline, 260 571 women (50.6%) were vaccinated before the age of 17 years and 253 966 (49.4%) were unvaccinated (Table 1). During follow-up, an additional 163 491 (31.8%) women were vaccinated at 17-26 years of age and 90 475 (17.6%) remained unvaccinated. Nearly all women vaccinated at age 16 years and younger were born in 1993 or later. Women vaccinated at 17-26 years and women unvaccinated at baseline were more often from the older birth cohorts (1985-1992) (Table 1). At baseline, the educational level of girls vaccinated at 16 years and younger was slightly higher than that among women vaccinated between 17 and 26 years and unvaccinated girls and women.

Table 1. Characteristics of unvaccinated and vaccinated (≤16 years) girls at baseline and girls vaccinated (17-26 years) during follow-up

Characteristic	Unvaccinated at baseline No. (%)	Vaccinated, age at first dose	
		≤16 y (at baseline) No. (%)	17-26 y (during follow-up) No. (%)
Total	253 966[a]	260 571	163 491[a]
Birth year[b]			
1985-1992	236 182 (93.0)	13 950 (5.4)	161 853 (99.0)
1993-1995	8299 (3.3)	94 500 (36.3)	1082 (0.7)
1996-2002	9485 (3.7)	152 121 (58.4)	556 (0.3)
Educational level[c]			
Higher	94 576 (37.2)	115 453 (44.3)	61 988 (37.9)
Vocational	116 622 (45.9)	118 901 (45.6)	79 001 (48.3)
Basic	35 270 (13.9)	24 020 (9.2)	21 288 (13.0)
Missing	7498 (3.0)	2197 (0.8)	1214 (0.7)

[a]Women can contribute person-time to both unvaccinated and vaccinated after the age of 17 years.
[b]Stratification according to birth year reflects that girls and women born 1993-1995 and 1985-1992 were offered human papillomavirus vaccination in the first and second catch-up programs and girls and women born 1996-2002 were covered by the routine vaccination program.
[c]Maximum educational level of own, mother, or father.

The average length of follow-up was 6.4 years (median = 6.9, interquartile range = 4.0 to 9.2), during which 16 cases of vulvar HSIL+ and less than 5 cases of vaginal HSIL+ were diagnosed among women vaccinated before 17 years. The corresponding numbers for women vaccinated at 17-26 years were 39 and 6, respectively, and among unvaccinated women, the numbers were 72 and 18, respectively. Both outcomes were rare, with cumulative incidence of less than 0.6‰ for vulvar HSIL+ and less than 0.2‰ for vaginal HSIL+ but with a clear separation in the cumulative incidence among women vaccinated age 16 years and younger of age compared with unvaccinated women (Figure 1). The difference in cumulative incidence between unvaccinated women and women vaccinated at 17-26 years of age was less pronounced.

Table 2 shows HRs comparing vaccinated women according to age at vaccination with unvaccinated women for the 2 outcomes. For both vulvar and vaginal HSIL+, Cox proportional hazards regression showed reduced HRs for women vaccinated at age 16 years or younger (vulvar HSIL+ HR = 0.22, 95% CI = 0.13 to 0.38; vaginal HSIL+ HR = 0.16, 95% CI = 0.04 to 0.55) compared with unvaccinated women. For women vaccinated at 17 years or older, the HRs were either neutral (vulvar HSIL+ HR = 0.97, 95% CI = 0.64 to 1.48) or decreased (vaginal HSIL+ HR = 0.56, 95% CI = 0.20 to 1.54). The 2 sensitivity analyses applying multiple imputation and censoring at time of CIN2+ yielded results similar to the main analysis (data not shown in table).

Discussion

As the first observational study, to our knowledge, we present real-world data on HPV vaccine effectiveness against vulvar and vaginal high-grade precancerous lesions and cancer, and our results for the youngest girls vaccinated confirm the excellent efficacy demonstrated in the clinical trials of the HPV vaccines (1,8-12). A recent systematic review of all published phase II and III trials on the efficacy of HPV vaccination against vulvar and vaginal cancer and precursor lesions reported that vaccine efficacy in the intention-to-treat population was 71% (95% CI = 40% to 86%) (1). The mixture of HPV-exposed and -unexposed women in the intention-to-treat analysis is most comparable with our real-world data. Because the likelihood of HPV exposure increases with age, we stratified the analysis according to age at vaccination (≤16 years or 17-26 years), assuming that the majority of the girls vaccinated at a younger age were HPV naive at their first dose. Among these girls, the risk of vulvar HSIL+ was reduced by 78% compared with unvaccinated girls and women. For vaginal HSIL+, the reduction was 84%. In comparison, quadrivalent HPV vaccine effectiveness was 63% against CIN3 or worse among Danish girls vaccinated before 17 years of age (15).

Out of the total burden of HPV-associated disease, vulvovaginal high-grade disease constitutes only a limited fraction, and cervical lesions are by far the largest contributor (6). The greater burden of cervical disease compared with noncervical anogenital malignancies is most likely because the transformation zone of the cervix is more vulnerable to HPV infection and cancer development (26). Differences in the cellular origin of anogenital cancers are also reflected in the different proportions of these cancers being attributable to HPV. Whereas virtually all cervical cancers are caused by HPV (6), in theory making it possible to eliminate by the vaccine (and screening) (27), a considerable fraction of the vulvovaginal malignancies develops independently of HPV. Approximately 60%-70% and 25%-35% of vulvar and vaginal cancers, respectively, are HPV negative (3,4,6), whereas the HPV-negative proportions of the high-grade precancerous lesions are low (5%-15%) (6).

Vulvovaginal malignancies also differ from cervical cancer because they are not covered by national screening programs. Vaginal cancer incidence may have benefited from the cervical cancer screening program because the incidence in Denmark has decreased since 1978 (28), but during the same period Denmark has experienced an increasing incidence of vulvar squamous cell carcinomas (29,30). The observed vaccine effectiveness against high-grade vulvar and vaginal disease supports that HPV vaccination is also an effective preventive measure against noncervical HPV–associated female genital malignancies.

There are several strengths of this study. They include a nationwide, population-based cohort design with individual-level information on vaccination status and information on outcome from high-quality nationwide registries and with virtually no loss to follow-up. HPV vaccine coverage in our study was high, because the Danish decline in HPV vaccine uptake did not affect the included birth cohorts markedly (17). Moreover, we were able to adjust the analyses for highest educational level, which is important because there is some degree of socioeconomic

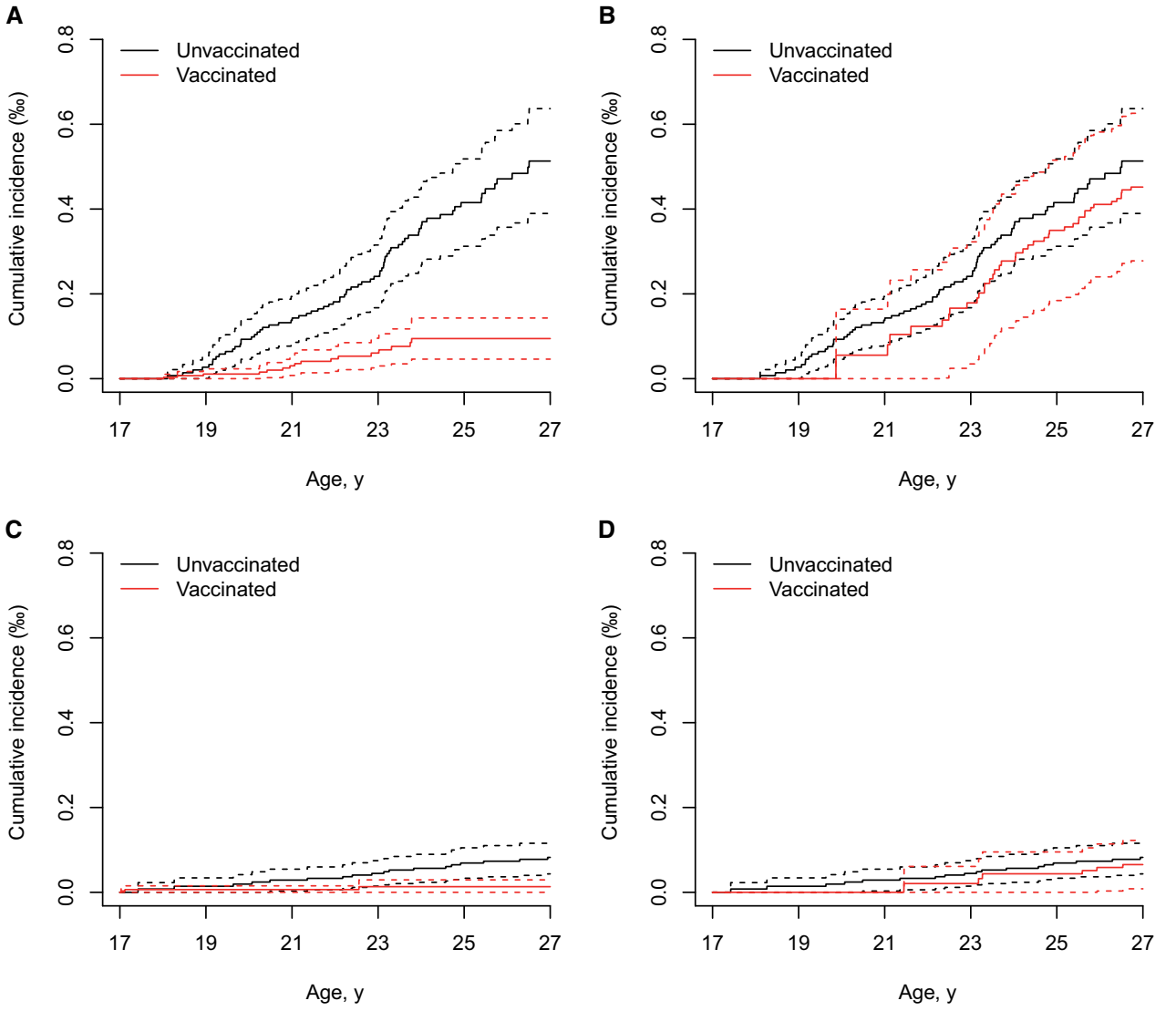

Figure 1. Cumulative incidence of vulvar high-grade squamous intraepithelial lesion (HSIL+) and vaginal HSIL+ by vaccination status and age at first dose. (A) Vulva HSIL+ in women vaccinated age 16 years or younger. (B) Vulva HSIL+ in women vaccinated 17-26 years. (C) Vaginal HSIL+ in women vaccinated age 16 years or younger. (D) Vaginal HSIL+ in women vaccinated 17-26 years. The shaded areas represent 95% confidence intervals.

Table 2. Hazard ratios comparing vaccinated with unvaccinated women for vulvar and vaginal HSIL+

Vaccination status	No.[a]	Person-years[a]	Events,[b]No.	Unadjusted HR (95% CI)	Adjusted[c] HR (95% CI)
Vulvar HSIL+					
Unvaccinated	260 494	1 379 035	72	Reference	Reference
Vaccinated, all ages	479 255	2 300 894	55	0.48 (0.34 to 0.68)	0.48 (0.34 to 0.69)
Age at vaccination <16 y	315 208	1 639 241	16	0.22 (0.13 to 0.38)	0.22 (0.13 to 0.38)
Age at vaccination 17-26 y	164 047	661 653	39	0.98 (0.65 to 1.49)	0.97 (0.64 to 1.48)
Vaginal HSIL+					
Unvaccinated	260 502	1 379 199	18	Reference	Reference
Vaccinated, all ages	479 294	2 301 172	<11	0.28 (0.13 to 0.64)	0.30 (0.13 to 0.68)
Age at vaccination <16 y	315 207	1 639 290	<5	0.15 (0.04 to 0.52)	0.16 (0.04 to 0.55)
Age at vaccination 17-26 y	164 087	661 882	6	0.52 (0.19 to 1.40)	0.56 (0.20 to 1.54)

[a]Number of women and person-years differ between outcomes types due to exclusion of the specific outcomes before start of follow-up. CI = confidence interval; HR = hazard ratio; HSIL = high-grade squamous intraepithelial lesion.
[b]Cell counts less than 5 are not permitted due to Danish legislation.
[c]Adjusted for maximum educational level of own, mother, or father, and attained age.

inequality in participation in the HPV vaccination program in Denmark (31), which may have caused some self-selection bias in our study.

There are also some limitations. In spite of the nationwide cohort, we recognize that the number of outcomes in our study was limited, resulting in low to moderate statistical power, especially in the analyses on vaginal HSIL+. There may be some misclassification because diagnoses were made in pathology departments all over Denmark, and we did not perform a central pathology review. Moreover, differentiated VIN was not a specific SNOMED morphology code in Denmark until 2018, and some of the included vulvar outcomes may therefore be unrelated to HPV. However, it seems appropriate to assume that this resulted in only minor misclassification because differentiated VIN predominantly occurs among postmenopausal women (2). Another potential limitation is selection bias because vaccinated women may be more likely to access health care or have different sexual behavior compared with unvaccinated women. However, we have previously shown similar cervical cancer screening rates in these 2 groups of women (15), indicating that differences between them may not be substantial and analyses were adjusted for socioeconomic position because low educational level among Danish girls has been shown to be associated with young age at first sexual intercourse and never-use of condoms (23). Our study was also limited by the lack of information on HPV exposure before vaccination. It has previously been reported that the mean time from incident HPV infection to the development of vulvar lesions is approximately 18 months (5). To accommodate this limitation, we stratified the analysis according to age at first dose. The majority of women vaccinated at a young age were birth cohorts covered by the routine vaccination program (12-year-old girls) and were thus vaccinated much earlier than 16 years, which is the median age of sexual debut among Danish girls (23). In addition, HPV status of the outcome was not available. However, virtually all outcomes were HSIL, for which the HPV prevalence is reported to be 85% or higher (6). Finally, the observed number of cancer cases was close to 0, which made it impossible to assess the effectiveness against cancer alone. Although HPV-positive vulvar and vaginal cancer occur at a younger age compared with the HPV-negative types (3,32), documentation of vaccine effectiveness on these cancers will require several more years of follow-up.

In conclusion, this is the first study to report the real-world HPV vaccine effectiveness against high-grade vulvar and vaginal lesions. Among girls vaccinated at age 16 years or younger, HPV vaccination is effective in reducing the risk of vulvar and vaginal HSIL+. The reduction was less pronounced for women vaccinated at age 17-26 years.

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Data Availability

The data underlying this article cannot be shared publicly due to ethical/privacy reasons.

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