Prevention of Recurrent High-Grade Anal Neoplasia With Quadrivalent Human Papillomavirus Vaccination of Men Who Have Sex With Men: A Nonconcurrent Cohort Study

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Background. Most squamous cell anal cancers and precancerous lesions are attributed to human papillomavirus (HPV) infection. By preventing HPV infection, quadrivalent HPV vaccine (qHPV) reduces risk of anal cancer/precancerous lesions in young men who have sex with men (MSM) without history of anal cancer/precancerous lesions. In our practice, many persons with history of precancerous anal lesions or high-grade anal intraepithelial neoplasia (HGAIN) have been vaccinated electively. We determined whether qHPV is effective at preventing recurrence of HGAIN.

Methods. This nonconcurrent cohort study evaluated 202 patients with a history of previously treated HGAIN. Eighty-eight patients were vaccinated, and 114 patients were unvaccinated. We determined the recurrence rate of histologic HGAIN in vaccinated versus unvaccinated patients.

Results. During 340.4 person-years follow-up, 12 (13.6%) vaccinated patients and 35 (30.7%) unvaccinated patients developed recurrent HGAIN. Multivariable hazards ratio (HR) analysis showed testing positive for oncogenic HPV genotypes within 8 months before study entry was associated with increased risk of recurrent HGAIN at 2 years after study entry (HR 4.06; 95% confidence interval [CI], 1.58–10.40; $P = .004$), and qHPV was associated with decreased risk of recurrent HGAIN (HR .50; 95% CI, .26–.98; $P = .04$). Among patients infected with oncogenic HPV, qHPV was associated with decreased risk of recurrent HGAIN at 2 years after study entry (HR .47; 95% CI, .22–1.00; $P = .05$).

Conclusions. qHPV significantly reduces HGAIN recurrence among MSM and may be an effective posttreatment adjuvant form of therapy. A randomized controlled trial is needed to confirm these results.

BACKGROUND

Human papillomavirus (HPV) is found in 75%–94% of precancerous high-grade anal intraepithelial neoplasia (HGAIN) and 80% or more of anal squamous cell carcinomas [1]. The quadrivalent HPV vaccine (qHPV) (Gardasil, Merck & Co., Inc, Whitehouse Station, NJ) is effective in preventing HPV infection and HPV-related cancers, including cervical, vulvar, vaginal, and anal cancers and their associated precancerous dysplastic lesions [2–4], but it has only been studied in persons without a history of HPV-related disease.

Men who have sex with men (MSM) have high rates of HPV infection, anal cancer, and HGAIN, as well as recurrent neoplasia after treatment. The prevalence of anal HPV infection in human immunodeficiency virus (HIV)–negative MSM ranges from 33% to 57% [5–8]. Unlike women who tend to have a bimodal distribution of cervical HPV infection, the prevalence of anal HPV infection remains constant as MSM age [7, 8]. The rate of anal cancer among HIV-negative MSM is approximately 35 per 100 000 person-years [9], and recurrence in those treated for HGAIN with ablation was 50% within 1 year [10].

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In one private practice (SEG), all HIV-negative MSM were offered qHPV off-label regardless of age, history of abnormal anal cytology, HGAIN, or prior HPV infection. The following is a nonconcurrent observational cohort study evaluating the effectiveness of qHPV in preventing recurrent HGAIN among HIV-negative MSM patients in this practice.

METHODS

Study Site

Study participants were recruited from a single anorectal surgery practice (SEG) in New York City that specializes in screening, diagnosis, and treatment of anorectal diseases, including condyloma and HGAIN. The majority of patients are MSM and approximately one third are HIV-positive.

Within the practice, routine screening for anal cancer began in the mid-1990s and is recommended for all MSM regardless of reason for visit. Screening consists of anal cytology sampling using a Dacron swab, as described previously [11]. When insurance allows, patients are tested for the 13 oncogenic HPV genotypes (16/18/31/33/35/39/45/51/52/56/58/59/68) most commonly associated with anal cancer using Hybrid-Capture 2 High-Risk HPV DNA Test (QIAGEN, Gaithersburg, MD). Patients with abnormal cytology results or who test positive for oncogenic HPV are evaluated further with high-resolution anoscopy (HRA; essentially colposcopy of the anal canal). During HRA, acetic acid and/or Lugol's iodine is applied to the mucosa, allowing areas suspicious for HGAIN to be identified by abnormal vascular patterns (including punctuation and mosaic pattern) and/or lack of uptake of iodine stain, then targeted for biopsy [12]. Histology is reported as normal, reactive or inflammation, low-grade anal intraepithelial neoplasia (LGAIN), HGAIN, or invasive squamous cell carcinoma. It is the practice of the authors (SEG) to monitor flat LGAIN lesions, but HGAIN is treated with local excision or targeted ablation to prevent progression to carcinoma. Patients are monitored for recurrence with cytology and HRA.

Starting in June 2006, the 3-dose qHPV series (0 months, 2 months, 6 months) was offered off-label to all HIV-negative MSM patients at each clinical visit. Medical insurance paid for vaccine in sporadic cases, but most paid up to $200 out-of-pocket per injection.

Study Population and Data Collection

For the current study, eligible patients were 18 years of age or older, HIV-negative, self-identified MSM, and had a history of biopsy-proven and treated HGAIN. Medical charts of all eligible patients seen during 2007–2010 were screened for inclusion.

Study patients were identified as exposed to vaccination when review of billing records found payment for 3 qHPV doses and the medical record noted vaccination. Study patients were identified as unvaccinated when review of billing records found payments lacking for qHPV and medical records did not note vaccination. Patients who did not receive all 3 doses of vaccine and those vaccinated at other sites were excluded.

Vaccinated patients "entered" the study 1 month after receiving their third qHPV dose (usually 7 months after receiving their first dose), similar to other qHPV studies [2–4, 13]. Because vaccination began in June 2006, the first vaccinated patients were eligible to enter the study in January 2007. To choose a similar start time for unvaccinated study patients, they entered the study at least 7 months after their first practice visit, with April 1, 2007 being the earliest possible day.

Clinical charts were reviewed for demographics (age, race/ethnicity, insurance type [none, public, commercial]), sexually transmitted infections ([STIs] gonorrhea, chlamydia, syphilis), history of anogenital condyloma, and HGAIN. HPV status was based on results from oncogenic HPV testing performed at time of anal cytology collection within 8 months before the first vaccine dose for vaccinated patients and within 8 months before study entrance for unvaccinated patients. Study patients whose insurance allowed testing for oncogenic HPV genotypes were either identified as "infected" or "uninfected" with oncogenic HPV based on test results. Study patients who had not had an oncogenic HPV test within 8 months before were defined as "unknown."

Recurrent HGAIN was defined as biopsy proven HGAIN subsequent to prior treatment. The date of biopsy was used as the date of recurrence. Patients with HGAIN at study start were excluded.

This study was approved by the Mount Sinai School of Medicine Institutional Review Board. Informed consent was waived.

Statistical Methods

The vaccinated and unvaccinated groups were compared on baseline demographics, smoking status, oncogenic HPV status, and history of STIs. Comparisons were done using χ^2 tests for categorical variables; Fisher's exact test for categorical variables, as appropriate; and Student's t tests for normally distributed, continuous variables.

To determine effect of vaccine on recurrence, Kaplan–Meier and Cox proportional hazards analysis compared time to HGAIN in vaccinated and unvaccinated study patients. For Kaplan–Meier, the log-rank test determined significance. For Cox proportional hazards, vaccination status, demographic characteristics, smoking status, history of anogenital condyloma, oncogenic HPV infection, and STIs were evaluated individually to identify variables associated with time to recurrence. STIs diagnosed after study entry were treated as time-dependent variables. Variables with $P < .20$ in individual analysis were evaluated in multivariable Cox proportional hazards analysis

to identify those variables significantly associated with time to recurrence. The best multivariable model was the one with maximal likelihood based on the Wald Statistic and the −2 log likelihood ratio.

To determine the effect of vaccine on recurrent HGAIN among MSM known to be infected with oncogenic HPV genotypes, we again used Kaplan–Meier and Cox proportional hazards analysis to compare the time to HGAIN in vaccinated and unvaccinated study patients.

SAS Version 9.1 (SAS Institute Inc, Cary, NC), SPSS Version 19 (IBM Corporation, Somers, NY), and EPI Info Version 3.5.3 (Centers for Disease Control and Prevention, Atlanta, GA) were used for the analysis. A P value of $\leq .05$ was considered significant.

RESULTS

There were 694 HIV-negative MSM seen in the practice from 2007 to 2010. Based on chart review, 202 had prior biopsy-confirmed and treated HGAIN. Their mean age was 40.4 years with standard deviation (SD) 10.2, range 20.2–72.3 years. Data on race/ethnicity were missing for 30% (60 of 202) of study patients. Of those whose race/ethnicity was identified, 89% (127 of 142) were white.

Of 202 eligible participants, 88 (44%) were vaccinated and 114 (56%) were unvaccinated. Vaccinated patients were younger than unvaccinated patients (vaccinated mean age 37.5 years with SD 8.2, unvaccinated mean age 42.6 with SD 11.1, $P < .001$). Vaccinated patients were more likely to have unknown race/ethnicity and a history of anogenital condyloma ($P = .05$). Unvaccinated patients were more likely to have unknown HPV status and a history of gonorrhea ($P = .05$) (Table 1). Unvaccinated study patients had a longer duration between initial HGAIN treatment and study time zero (median 315 days compared with 211 days) and longer follow-up time (median 722 days compared with 489 days). Rates of gonorrhea, chlamydia, and syphilis after study entry were comparable between groups (0%–4%).

Vaccinated patients entered the study from June 23, 2007 through December 3, 2010, with median date March 14, 2009. Unvaccinated patients entered the study from April 1, 2007 through December 15, 2009, with 73 of 114 (64%) entering on April 1, 2007.

Among vaccinated patients, 12 developed recurrent HGAIN during 117.6 person-years of follow-up giving an incidence rate of 10.2 per 100 person-years (95% confidence interval [CI], 5.3–17.8/100 person-years). Among unvaccinated patients, 35 developed recurrent HGAIN during 222.8 person-years of follow-up giving an incidence rate of 15.7 per 100 person-years (95% CI, 10.9–21.9/100 person-years).

Table 1. Baseline Characteristics of Vaccinated and Unvaccinated Men Who Have Sex With Men With a History of Treated High-Grade Anal Neoplasia, New York City, April 2007–December 2010 (n = 202; No. [%])

Characteristic	Vaccinated (n = 88)	Unvaccinated (n = 114)	*P* Value
Demographics			
Age			.02
20–29 years	17 (19)	16 (14)	
30–39 years	39 (44)	33 (29)	
40–49 years	26 (30)	37 (33)	
50–59 years	5 (6)	20 (18)	
60–69 years	1 (1)	6 (5)	
70–79 years	0	2 (2)	
Race/Ethnicity			.26
White	49 (56)	78 (68)	
Black	1 (1)	3 (3)	
Asian	1 (1)	2 (2)	
Hispanic	4 (5)	4 (4)	
Unknown	33 (38)	27 (24)	
Insurance status			.07
None	5 (6)	11 (10)	
Public	0	5 (4)	
Commercial	83 (94)	98 (86)	
Cigarette smoking			.24
Smokers	16 (18)	14 (12)	
Nonsmokers	72 (82)	100 (88)	
Medical History			
Oncogenic HPV status[a]			.09
Infected	47 (53)	58 (51)	
Not infected	26 (30)	23 (20)	
Unknown	15 (17)	33 (29)	
History of anogenital condyloma within previous 5 years			.05
Yes	67 (76)	72 (63)	
No	21 (24)	42 (37)	
History of Gonorrhea			.05
Yes	15 (17)	33 (29)	
No	73 (83)	81 (71)	
History of Chlamydia			.71
Yes	14 (16)	16 (14)	
No	74 (84)	98 (86)	
History of syphilis			
Yes	3 (3)	8 (7)	.36
No	85 (97)	106 (93)	

Abbreviation: HPV, human papillomavirus.

[a] Oncogenic HPV status: within 8 months before first vaccine dose (vaccinated patients) or within 8 months before start time (unvaccinated patients).

Kaplan–Meier survival analysis demonstrated improved recurrence-free survival of vaccinated persons compared with unvaccinated persons (log-rank at 1 year $P = .01$, log-rank at

2 years $P = .05$, log-rank at 3 years $P = .06$). (Figure 1) In univariate Cox proportional hazards analysis at 2 years, age ($P = .02$) and positive oncogenic HPV test ($P = .003$) were associated with increased risk of recurrent HGAIN and qHPV was associated with a decreased risk of recurrent HGAIN ($P = .05$) (Table 2). The best multivariate model at 1 year, including oncogenic HPV and vaccination statuses, showed that a positive oncogenic HPV test was associated with an increased risk of recurrent HGAIN (HR 3.78; 95% CI, 1.48–9.66; $P = .006$) and qHPV was associated with a decreased risk of recurrent HGAIN (HR 0.42; 95% CI, .22–.82; $P = .01$). The best multivariate model at 2 years, including oncogenic HPV and vaccination statuses, showed that a positive oncogenic HPV test was associated with an increased risk of recurrent HGAIN (HR 4.06; 95% CI, 1.58–10.40; $P = .004$) and qHPV was associated with a decreased risk of recurrent HGAIN (HR 0.50; 95% CI, .26–.98; $P = .05$). The best multivariate model at 3 years, including oncogenic HPV and vaccination statuses, showed that a positive oncogenic HPV test was associated with an increased risk of recurrent HGAIN (HR 4.19; 95% CI, 1.63–10.77; $P = .003$) and qHPV was associated with a decreased risk of recurrent HGAIN (HR 0.52; 95% CI, .27–1.02; $P = .06$) (Table 3).

One hundred fifty-four participants were tested for oncogenic HPV in the 8 months before first vaccine dose (vaccinated patients) or study entry (unvaccinated patients); 105 (68.2%) tested positive. Forty-seven persons in this group were vaccinated (45%). Among MSM with prior history of HGAIN and oncogenic HPV infection, the incidence of recurrent HGAIN in the vaccinated group was 15.4 per 100 person-years (95% CI, 7.0–29.2/100 person-years) compared with 28.3 per 100 persons-years (95% CI, 18.3–41.8/100 person-years) in the unvaccinated group.

Among the 105 study patients with a prior history of treated HGAIN and a positive oncogenic HPV test, Kaplan–Meier survival analysis demonstrated improved recurrence-free survival among vaccinated persons compared with unvaccinated persons (log-rank at 1 year $P = .02$, log-rank at 2 years $P = .05$, log-rank at 3 years $P = .06$) (Figure 2). In univariate and multivariate Cox proportional hazards analysis, only qHPV was significantly associated with recurrent HGAIN (Table 4). qHPV was associated with decreased risk of HGAIN at 1 year (HR 0.40; 95% CI, .19–.86; $P = .02$), 2 years (HR 0.47; 95% CI, .22–1.00; $P = .05$), and 3 years (HR 0.48; 95% CI, .22–1.04; $P = .06$) (Table 5).

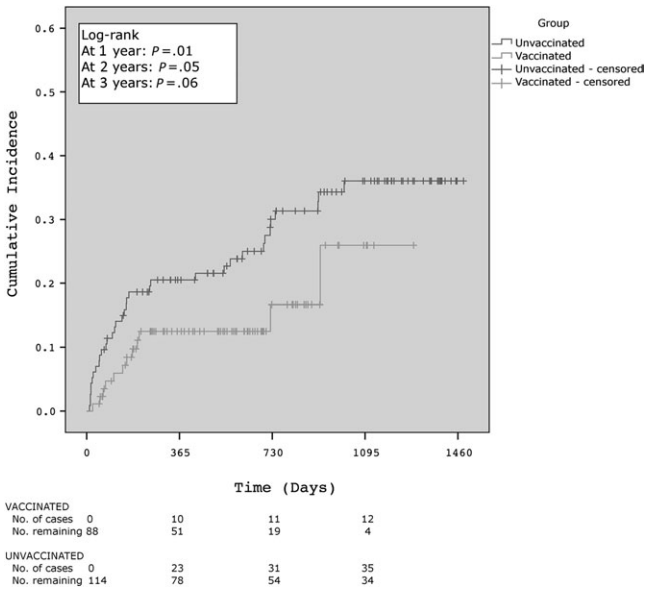

Figure 1. Time to recurrence of high-grade anal neoplasia among vaccinated and unvaccinated men who have sex with men with a history of high-grade anal neoplasia, New York City, April 2007–April 2011 (n = 202).

DISCUSSION

MSM with a history of treated HGAIN who received qHPV had a decreased risk of recurrent HGAIN compared with those who did not receive the vaccine. The decreased risk appears to endure for at least 2 years. MSM with a history of treated HGAIN and known oncogenic HPV infection who received qHPV were similarly at decreased risk of recurrent disease for at least 2 years. Unlike previous studies that have looked at primary disease in young MSM, this study evaluated secondary disease in older MSM.

This is the first study to demonstrate an association between qHPV after primary disease and decreased risk of recurrent HGAIN. Previous analysis of clinical trial data demonstrated an association between qHPV followed by treated primary disease and a subsequent decreased risk of recurrent HPV-related disease of the cervix, vulva, and vagina [14]. Although women in the clinical trial developed primary disease after vaccination while men in this study had primary disease before vaccination, a similar biological mechanism may be responsible. HPV gains access to the basement membrane through a traumatic epithelial tear during sex. Once attached to the basement membrane, the virus changes configuration and binds to a basal epithelial cell before entering the cell's nucleus where it can reproduce. As the cell matures, viral particles move to the epithelial surface and are released, free to infect other adjacent basal cells in the host or a sexual partner. Sometimes viral DNA integrates into the host's genome. Although the integrated viral DNA can no longer reproduce or infect other cells, it can promote mutations that sometimes lead to neoplasia and cancer. Antibody levels, much higher after vaccination than natural infection, prevent viral binding to the basement membrane and entry into basal cells [15]. We

Table 2. Characteristics Associated With a Recurrent Case of High-Grade Anal Neoplasia Among 202 Men Who Have Sex With Men With a History of High-Grade Anal Neoplasia Using Cox Proportional Hazards Univariate Analysis at 2 Years After Study Entry, New York City, April 2007–April 2011

Predictor Variable	HGAIN Recurrence (n = 47)	No HGAIN Recurrence (n = 155)	*P* Value	Univariate HR (95% CI)	*P* Value
qHPV vaccine status					
Vaccinated	12 (26)	76 (49)	.004	.52 (0.27, 1.00)	.05
Not vaccinated	35 (74)	79 (51)			
Age (mean [SD])	43.7 (11.5)	39.4 (9.7)	.01	1.03 (1.01, 1.06)	.02
Race					
White	32 (68)	95 (61)	.57	1.00	
Black	1 (2)	3 (2)		1.29 (0.18, 9.41)	.81
Asian	0	3 (2)		.00 (ND)	.99
Hispanic	3 (6)	5 (3)		1.59 (0.49, 5.20)	.44
Unknown	11 (23)	49 (32)		1.08 (0.54, 2.19)	.82
Insurance					
None	4 (9)	12 (8)	.65	1.06 (0.38, 2.96)	.91
Public	2 (4)	3 (2)		2.58 (0.47, 14.12)	.27
Private	41 (87)	140 (90)		1.00	
Cigarette smoking					
Yes	10 (21)	20 (13)	.16	1.51 (0.75, 3.03)	.25
No	37 (79)	135 (87)		1.00	
Oncogenic HPV infection before time zero					
Infected	34 (72)	71 (46)	.005	4.19 (1.63, 10.73)	.003
Unknown	8 (17)	40 (26)		1.80 (0.59, 5.50)	.30
Uninfected	5 (11)	44 (28)		1.00	
Anogenital condyloma within prior 5 years before time zero					
Yes	33 (70)	106 (68)	.81	1.23 (0.65, 2.29)	.53
No	14 (30)	49 (32)			
Gonorrhea infection after study entry					
Yes	4 (9)	3 (2)	.05	.00 (ND)	.99
No	43 (91)	152 (98)			
Chlamydia infection after study entry					
Yes	1 (2)	5 (3)	1.00	.00 (ND)	.99
No	47 (98)	150 (97)			
Syphilis infection after study entry					
Yes	1 (2)	1 (1)	.41	.00 (ND)	.99
No	47 (98)	154 (99)			

Abbreviations: CI, confidence interval; HGAIN, high-grade anal intraepithelial neoplasia; HPV, human papillomavirus; HR, hazards ratio; ND, not defined; qHPV, quadrivalent HPV vaccine; SD, standard deviation.

hypothesize that in both studies, the mutated epithelial cells with integrated virus in the primary disease were removed at treatment, but cells with free nuclear HPV were left behind. Whereas replicating virus could infect a sexual partner, qHPV antibodies prevent host reinfection. Reinfection would increase risk of integration and neoplasia, but antibody response stops the cascade, reducing the risk of recurrent high-grade cervical and anal neoplasia.

Whereas qHPV appears effective in preventing recurrent disease, it was not effective at preventing all recurrence. Of the 88 vaccinated patients, 12 (13.6%) developed recurrent HGAIN. It is possible that these patients developed disease related to non-qHPV genotypes or that some HGAIN had not been identified and treated before vaccination. It is also possible that viral integration into the host genome had already occurred and the vaccine is not effective after integration.

Our results imply that qHPV was most effective in preventing recurrence in the first year after vaccination, with slightly declining effectiveness over the next 2 years. The biology of antibody development suggests that responses can be time-limited, with antibody response likely to decrease over time. Although previous research in women demonstrated

Table 3. Characteristics Associated With a Recurrent Case of High-Grade Anal Neoplasia Among 202 Men Who Have Sex With Men With a History of High-Grade Anal Neoplasia Using Cumulative Cox Proportional Hazards Multivariate Analysis at 1, 2, and 3 Years After Study Entry, New York City, April 2007–April 2011

Predictor Variable	1 Year (n = 202)		2 Years (n = 129)		3 Years (n = 73)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
qHPV vaccine status						
Vaccinated	.42 (.22, .82)	.01	.50 (.26, .98)	.05	.52 (.27, 1.02)	.06
Not vaccinated	1.00		1.00		1.00	
Oncogenic HPV infection before time zero						
Infected	3.78 (1.48, 9.66)	.006	4.06 (1.58, 10.40)	.004	4.19 (1.63, 10.77)	.003
Unknown	1.51 (.49, 4.63)	.47	1.58 (.52, 4.86)	.42	1.58 (.52, 4.87)	.42
Uninfected	1.00		1.00		1.00	

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, hazards ratio; qHPV, quadrivalent HPV vaccine.

that qHPV was effective through 5 years and monovalent HPV 16 vaccine was effective through 8.5 years for prevention of infection and primary disease caused by qHPV genotypes [16, 17], it is possible that duration of protection against secondary HPV-related disease is shorter. However, in this study, the difference in effectiveness seen after 2 years remains nearly significant and is more likely related to the small sample size than a true decrease in vaccine effectiveness. Further research with greater numbers of patients with HPV-related disease is necessary to elucidate the qHPV duration of protection against recurrent HPV-related disease.

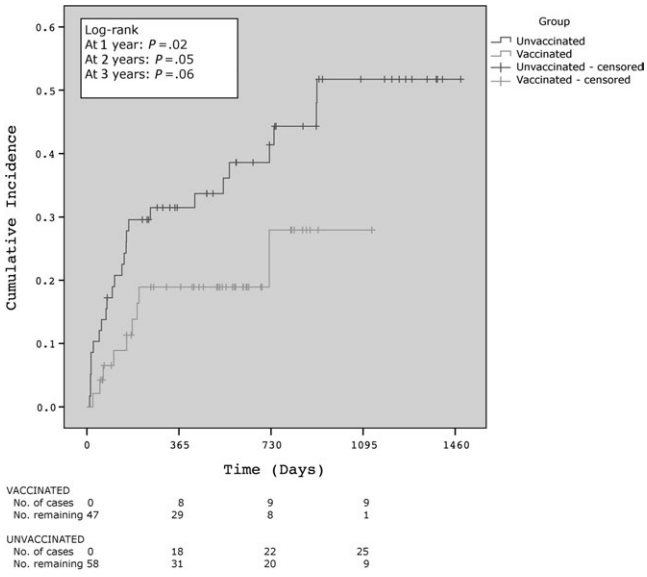

Figure 2. Time to recurrence of high-grade anal neoplasia among vaccinated and unvaccinated oncogenic human papillomavirus–infected men who have sex with men with a history of high-grade anal neoplasia, New York City, April 2007–April 2011 (n = 105).

The vaccinated and unvaccinated groups were not comparable at baseline in several aspects. However, multivariable analysis determined that these differences did not significantly affect the outcome enough to be included in the multivariable models.

We do not believe that the decreased risk of HGAIN recurrence in vaccinated patients was due to a decrease in risky sexual behavior. STIs acquired after study entry acted as surrogate markers for risky sexual behavior. There was no association between STIs and risk of HGAIN recurrence, suggesting that there was no difference in sexual risk taking between vaccinated and unvaccinated patients after study entry. These findings are consistent with a previous study of vaccinated patients in this practice that found no significant differences in number of recent sexual partners, engagement in receptive anal intercourse, and rates of unprotected anal intercourse after vaccination [18].

There are several limitations to our study. This nonconcurrent cohort study relied on medical records, limiting available data to information contained in the medical chart. Although sexual practice was often noted in the chart, it was not systematic enough for inclusion in statistical modeling. The missing data on race/ethnicity and oncogenic HPV infection status prevented studying their effect on recurrent HGAIN and prevented adequate adjustment in the analysis. This cohort was a population of mostly white, urban, nonsmoking MSM with private insurance, and findings may not be generalizable to other populations. Finally, because we relied on medical records, it was difficult to determine the date of ''study entry'' for unvaccinated patients. The method we used ensured that unvaccinated patients entered the study in a time period comparable with that of vaccinated patients to limit bias related to changes in diagnostic techniques. Whereas it would have been more appropriate to correlate study entry to the initial offer and refusal of qHPV, that information was not available in the medical records.

Table 4. Characteristics Associated With a Recurrent Case of High-Grade Anal Neoplasia Among 105 Oncogenic Human Papillomavirus–Infected Men Who Have Sex With Men With a History of High-Grade Anal Neoplasia Using Cox Proportional Hazards Univariate Analysis at 2 Years After Study Entry, April 2007–April 2011

Predictor Variable	HGAIN Recurrence (n = 34)	No HGAIN Recurrence (n = 71)	*P* Value	Univariate HR (95% CI)	*P* Value
qHPV vaccine status					
Vaccinated	9 (27)	38 (54)	.009	.47 (0.22, 1.00)	.05
Not vaccinated	25 (74)	33 (47)			
Age (mean [SD])	44.0 (11.5)	41.6 (9.9)	.26	1.02 (0.98, 1.05)	.33
Race					
White	23 (68)	41 (58)	.66	1.00	
Black	1 (3)	2 (3)		1.45 (0.20, 10.77)	.72
Asian	0	1 (1)		.00 (ND)	.99
Hispanic	0	3 (4)		.00 (ND)	.99
Unknown	10 (29)	24 (34)		1.12 (0.52, 2.39)	.78
Insurance					
None	3 (9)	4 (6)	.71	1.18 (0.36, 3.08)	.78
Public	1 (3)	1 (1)		1.89 (0.26, 14.00)	.53
Private	30 (88)	66 (93)		Referent	
Cigarette smoking					
Yes	6 (18)	4 (6)	.07	1.94 (0.80, 4.68)	.14
No	28 (82)	67 (94)			
Anogenital condyloma within prior 5 years before time zero					
Yes	23 (68)	49 (69)	.89	1.12 (0.55, 2.32)	.75
No	11 (32)	22 (31)			
Gonorrhea infection after study entry					
Yes	4 (12)	2 (3)	.09	.00 (ND)	.99
No	30 (88)	69 (97)			
Chlamydia infection after study entry					
Yes	1 (3)	3 (4)	1.00	.00 (ND)	.99
No	33 (97)	68 (96)			
Syphilis infection after study entry					
Yes	1 (3)	1 (1)	.55	.00 (ND)	.99
No	33 (97)	70 (99)			

Abbreviations: CI, confidence interval; HGAIN, high-grade anal intraepithelial neoplasia; HR, hazards ratio; ND, not defined; qHPV, quadrivalent human papillomavirus vaccine; SD, standard deviation.

There was a longer duration between initial HGAIN treatment and study time zero in unvaccinated patients compare with vaccinated patients. The median difference was 104 days. Based on our Kaplan–Meier curves, this would bias the results in favor of the unvaccinated: in both curves, the incidence slope is steep in both groups at the start of follow-up time and levels off over time. This result suggests that by starting follow-up in the unvaccinated group later in their posttreatment course, the

Table 5. Characteristics Associated With a Recurrent Case of High-Grade Anal Neoplasia Among 105 Oncogenic Human Papillomavirus–Infected Men Who Have Sex With Men With a History of High-Grade Anal Neoplasia Using Cumulative Cox Proportional Hazards Multivariate Analysis at 1, 2, and 3 Years After Study Entry, April 2007–April 2011

Predictor Variable	1 Year (n = 105) HR (95% CI)	*P* Value	2 Years (n = 60) HR (95% CI)	*P* Value	3 Years (n = 28) HR (95% CI)	*P* Value
qHPV vaccine status						
Vaccinated	.40 (.19, 0.86)	.02	.47 (.22, 1.00)	.05	.48 (.22, 1.04)	.06
Not vaccinated	1.00		1.00		1.00	

Abbreviations: CI, confidence interval; HR, hazards ratio; qHPV, quadrivalent human papillomavirus vaccine.

study was not covering unvaccinated persons during their period of highest risk. It is possible that longer duration of follow-up among the unvaccinated overestimated or underestimated our crude incidence rates of disease recurrence (10.2 per 100 person-years in the vaccinated and 15.7 per 100 person-years in the unvaccinated). However, because Cox proportional hazards analysis adjusts for time, it is unlikely that a longer follow-up period among unvaccinated patients had an effect on findings from the multivariable models.

This is the first study to show that qHPV decreases HGAIN recurrence, and it suggests that further research be done on the ability of the vaccine to prevent secondary HPV-related disease. The reduction in recurrence of HGAIN after prior treatment has public health implications. We and others have previously demonstrated high recurrence rates after treatment with surgery, topical, and pharmacologic therapy [10, 19, 20]. Given the results of this study, qHPV may be an effective posttreatment adjuvant to prevent recurrent HGAIN. Although the vaccine is currently licensed and recommended for primary prevention of HPV infection in young persons ages 9–26 years, if our results are confirmed by a randomized, placebo-controlled trial, then indications for vaccination and the age of the target population should be expanded.

Notes

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Potential conflicts of interest. S. E. G. has been paid by Merck & Co to participate in the Gardasil vaccine trial in men, received a grant from QIAGEN to participate in a trial for HPV testing in the anal canal, and is a speaker for Merck & Co, QIAGEN, and ASHA. K. A. S. and S. H. F. certify no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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