COMMENTARY

Prophylactic HPV vaccination and anal cancer

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ABSTRACT

The incidence of anal cancer is increasing. High risk populations include HIV-positive men who have sex with men (MSM), HIV-negative MSM, HIV-positive women and heterosexual men and women with a history of cervical cancer. HPV has been detected in over 90% of anal cancers. HPV16 is the most common genotype detected in about 70% of anal cancers. The quadrivalent HPV (qHPV) vaccine has been demonstrated to prevent vaccine associated persistent anal HPV infections as well as anal intraepithelial neoplasia grades 2–3 (AIN2+) in young MSM not previously infected. A retrospective analysis also suggests that qHPV vaccination of older MSM treated for AIN2+ may significantly decrease the risk of recurrence of the AIN2+. The HPV types detected in anal cancer are included in the 9-valent vaccine. Thus, the 9-valent HPV vaccine, when administered to boys and girls prior to the onset of sexual activity, should effectively prevent anal cancer.

ARTICLE HISTORY

Received 14 January 2016
Accepted 27 January 2016

KEYWORDS

anal cancer; HPV; HPV vaccine

The incidence of squamous cell cancer of the anus (SCCA) in the US has more than doubled over the past 4 decades among both men and women. Although anal cancer is still more common among women than men, the incidence of SCCA in all ages and races have increased from .95 and .66 per 100,000 in 1975 to 2.12 and 1.52 per 100,000 in 2012 in women and men respectively.¹ HIV+ men who have sex with men (MSM) have the highest incidence of SCCA, 67 per 100,000 person years and this incidence appears to be independent of widespread use of combination antiretroviral therapy (cART).² Others at increased risk of anal cancer women with history of cervical cancer, HIV+ men and women (regardless of sexual orientations), immunosuppressed individuals (e.g., transplant patients), as well as HIV- men who have sex with men.^{2,3}

Recent publications report that HPV is detected in over 90% of SCCA, (see Table 1) whereas a meta-analysis of older publications had detected HPV in 80–84% of anal cancers.⁴ HPV 16 is the most common genotype detected, accounting for 70–88% of anal cancers. Interestingly, in 2–3% of specimens, only low risk HPV-types (primarily 6) were detected, and low risk HPV types were also detected in co-infections (primarily with HPV 16). Table 1 summarizes the major recent publications of HPV detection in SCCA with special attention to the HPV types included in the nonavalent HPV vaccine (9v-HPV vaccine).

SCCA shares biological similarities with cervical cancer, including detectable precancerous lesions and high-risk (HR) HPV infection. HPV has been detected in 99% of cervical cancers and 80–90% of anal cancers, with HRHPV types 16 or 18 detected in about 70% of cervical and 80–90% of anal cancers. It appears that anal HPV infection, in conjunction with other yet-to-be determined factors, leads to the development of high-grade squamous anal intraepithelial lesion (anal

intraepithelial neoplasia [AIN] 2 or greater), a likely precursor to anal cancer.

In light of the similarities between anal cancer and cervical cancer, anal cancer prevention strategies have mirrored those of cervical cancer prevention (i.e., secondary prevention; note that administration of the prophylactic HPV vaccine prior to the onset of sexual activity is primary prevention tactic for cervical cancer prevention). Rates of cervical cancer incidence and mortality have dramatically decreased in countries with programmatic screening for cervical cancer with cytology. Women with abnormal cervical cytology are referred for colposcopic evaluation where precancerous cervical lesions (cervical intraepithelial neoplasia (CIN) grades 2 and 3) are identified and then treated (by excision or ablation). In the cervix, the entire squamocolumnar (SCJ) junction (between endocervical and ectocervical cells) is treated regardless of the size of the detected lesion. The detection and treatment of CIN2/3 is very effective at preventing the progression to cervical cancer.¹²

Anal cytology (from a Dacron swab inserted into the anal canal) has been utilized as a screening method for anal intraepithelial neoplasia (AIN). Individuals with abnormal anal screening cytology are referred for a colposcopic evaluation of the anus called high-resolution anoscopy (HRA) in which the anal canal is examined with a colposcope after the application of 5% acetic acid and/or lugol solution and detected lesions are biopsied for histological diagnosis. Patients with histologic results of anal intraepithelial neoplasia (AIN) 2 or 3 are recommended for treatment presumably to prevent the transformation from AIN2+ to invasive cancer. However, unlike the treatment of CIN2+ where the entire SCJ of the cervix is either ablated or excised, the entire SCJ of the anal canal cannot be surgically treated for concerns of stricture or other complications. Currently, the most commonly used treatment is directed ablation

Table 1. HPV types in invasive anal cancer.

Author	Year	Country	Sample Size	Sex of Subjects (m/f)	HR HPV (number (%))										LR HPV	
					HPV+	HPV16	HPV18	HPV31	HPV33	HPV45	HPV52	HPV58	HPV6	HPV11		
Barcicic	2015 ⁵	United Kingdom	151	m: 67 (44%) f: 84 (54%)	144 (95.4%)	134 (88.7%)	5%	3%	7%	0%	1%	5%	12%	3%		
Serrano	2015 ⁶	Worldwide	329	females only: 329	296 (90%)	274 (83.4%)	12 (3.6%)	6 (1.8%)	16 (3.1%)	23 (0.7%)	10 (0.3%)	7 (2%)	23 (0.7%)	10 (0.3%)		
Ouhoumane	2014 ⁷	Canada	96	m: 33 (34%) f: 63 (66%)	88 (92%)	79 (82%)	2 (2%)	NR	3 (3%)	NR	1 (1%)	2 (2%)	3 (3%)	1 (1%)		
Hillman	2014 ⁸	Australia	112	m: 92 (82%) f: 20 (18%)	108 (96.4%)	81 (75%)	4 (3.6%)	5 (4.5%)	5 (4.5%)	1 (0.9%)	14 (12.5%)	NR	11 (9.8%)	6 (5.4%)		
Aleman	2014 ⁹	Worldwide	496	m: 157 (31.7%) f: 329 (66.3%) missing info: 10 (2%)	438 (88.3%)	354 (80.7%)	16 (3.6%)	8 (1.9%)	12 (2.7%)	4 (0.9%)	3 (0.7%)	8 (1.8%)	16 (3.6%)	5 (1.1%)		
Stein	2013 ¹⁰	USA	146	m: 53 (36.3%) f: 93 (63.7%)	133 (91.1%)	113 (77.4%)	5 (3.4%)	2 (1.4%)	9 (6.2%)	NR	NR	2 (1.4%)	6 (4.1%)	5 (3.4%)		
Abramowitz	2011 ¹¹	France	366	m: 137 (37.4%) f: 225 (61.5%) NA: 4 (1.1%)	354 (96.7%)	274 (75.7%)	21 (5.8%)	<5%	<5%	<5%	5.20%	<5%	6%	7.4%		
DuVuyt	2009 ⁴	Worldwide	955	meta-analysis	805 (84.3%)	73.4%	5.2%	<2%	2.8%	<2%	0%	0%	<2%	0%		

Notes. NR: Not reported in article

*estimated percentage based on graphs

of apparent AIN2+ lesions. Unfortunately, recurrence rates are very high and frequently additional treatments are needed.

Given the similarities between cervical and anal HPV-associated diseases, the sentinel study to evaluate the efficacy of the HPV vaccine used AIN2+ as a surrogate endpoint for anal cancer. The efficacy of the qHPV vaccine in preventing persistent vaccine related anal HPV infections and AIN2+ was evaluated by a double blind study of young MSM.¹³ 602 sexually active MSM, age 16 to 26, were randomized to receive 3 doses of the qHPV vaccine or placebo and evaluated every 6 months by HRA and HPV testing over 3 y. The rate of AIN2/3 related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI, 18.0 to 75.3) in the intention-to-treat (ITT) population and by 74.9% (95% CI, 8.8 to 95.4) in the per-protocol efficacy (PPE) population.¹³ The corresponding risks of persistent anal infection with HPV-6, 11, 16, or 18 were reduced by 59.4% (95% CI, 43.0 to 71.4) and 94.9% (95% CI, 80.4 to 99.4), respectively.¹³ In the ITT population, there was also a significant reduction of anal intraepithelial neoplasia associated with any type of HPV in those who received the qHPV compared to those who received the placebo.¹³ This study suggests that the qHPV vaccination can be efficacious in preventing anal HPV infections and associated AIN.¹³

It is important to note the baseline findings in the study by Palefsky et al. 165 (27.4%) men were seropositive or HPV DNA-positive for HPV-6 or 11, 99 (16.4%) for HPV-16, and 68 (11.3%) for HPV-18.¹³ The high rates of prevalent HPV infection at the time of vaccination of young MSM suggests that the qHPV vaccine would be most effective when administered before the onset of sexual activity to all boys.¹⁴

Given that the highest risk population for anal cancer is HIV+ MSM, studies of the qHPV vaccine in this population are of great importance. Wilkin et al. evaluated 112 HIV+ men (ages 27+ with no evidence of AIN2+) with the 3 dose course of qHPV vaccine and found that all of these HIV+ men seroconverted.¹⁵ Thus, it appears that the qHPV vaccine is both immunogenic and safe in HIV+ men. The efficacy of primary prevention of AIN in HIV+ MSM is being evaluated in an ongoing trial, Protective Effect of Quadrivalent Vaccine in Young HIV-Positive Males Who Have Sex With Males.¹⁶

The effectiveness of the qHPV vaccine in preventing recurrent AIN2+ in older HIV- negative MSM was demonstrated by a retrospective non-concurrent cohort study by Swedish et al.¹⁷ 202 patients over the age of 18 y with a history of previously treated AIN2+, were divided into 2 groups: "vaccinated" (88 patients; 44%), identified by 3 qHPV doses on their medical and billing records after treatment of AIN2+ and "unvaccinated" (114; 56%), identified by a lack of qHPV vaccination in their medical and billing records.¹⁷ Among vaccinated patients, during 117.6 person-years of follow up, 12 developed recurrent AIN2+ (95% CI, 5.3-17.8/100 person years), and among the unvaccinated patients during a 222.8 person-years of follow up, 35 developed recurrent AIN2+ (95% CI, 10.9-21.0/100 person years).¹⁷ According to a multivariate hazards model, qHPV vaccination was associated with a statistically significant decreased risk of recurrent AIN2+ regardless of oncogenic

HPV status (HR 0.47; 95% CI, 22-1.00; P = 0.5) for at least 3 y following vaccination.¹⁷

These striking findings by Swedish et al. that qHPV vaccine may significantly decrease the rate of recurrent AIN2+ in HIV-negative MSM inspired several cost effectiveness analyses.¹⁷ Deshmukh et al. found that qHPV vaccination of HIV-negative MSM age 27+ treated for AIN2+ reduced the lifetime risk of anal cancer by 60.77% at an incremental increase of cost effectiveness ratios (ICER) of US\$87,240 per quality-adjusted life-year.¹⁸ The results were highly sensitive to vaccine efficacy, transition of AIN2+ to anal cancer, cost of treatment for AIN2+, vaccine degree of protection over time, and the vaccine duration of protection and less sensitive to HPV clearance, cost of qHPV vaccine, and the transitions from normal to AIN1 and normal to AIN2+. Deshmukh's modeling suggests that qHPV vaccination in HIV-positive MSM aged ≥ 27 years who have been diagnosed and treated for AIN2+ decreases the lifetime risk of anal cancer and is a cost-saving strategy because it decreases lifetime costs and increases quality-adjusted life expectancy. The results were robust irrespective of reasonable changes in vaccine effectiveness and age at vaccination.¹⁸

Note that studies for AIN/anal cancer prevention were conducted with the qHPV vaccine (as the 9-valent (9v)HPV vaccine was not available). Joura et al. evaluated the safety and efficacy of the 9v HPV vaccine through a double-blind international multicenter trial of 14215 young women randomized to 9vHPV vaccine or qHPV vaccine.¹⁹ The investigators found that the 9vHPV vaccine prevented infection and disease related to HPV-31, 33, 45, 52, and 58 in a susceptible population and generated an antibody response to HPV-6, 11, 16, and 18 that was non-inferior to that generated by the qHPV vaccine.¹⁹ From this data, it is assumed that the 9v HPV vaccine will provide the same degree of protection from persistent HPV infections and development of AIN2+ in patients without evidence of prior vaccine type HPV infection.¹⁹

In summary, administering the 9-valent HPV vaccine to girls and boys prior to the onset of sexual activity could effectively prevent almost all anal cancers (primary prevention of SCCA). In addition, the 9v HPV vaccine may be helpful in preventing recurrent AIN2+ and possibly the progression to SCCA, especially in individuals at increased risk for SCCA including all HIV-positive men and women, HIV-negative MSM, and women with history of CIN3 or cervical cancer. The role of the 9v HPV vaccine in improving secondary prevention of SCCA is currently being evaluated in prospective randomized trials.

Abbreviations

AIN	Anal intraepithelial neoplasia
Cart	combination antiretroviral therapy
HIV	Human immunodeficiency Virus
HPV	Human Papillomavirus
HIV+	HIV-positive
HR	High risk
LR	Low risk
MSM	Men who have sex with men
SCCA	Squamous cell cancer of the anus
9v-HPV	vaccine nonavalent HPV vaccine

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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