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Vaccine-preventable anal human papillomavirus in Australian gay and bisexual men

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ABSTRACT

Objective: HPV causes ~90% of anal cancer and HPV16 is the type most commonly associated with anal cancer. Gay and bisexual men (GBM) are at greatly increased risk. We investigated patterns of vaccine-preventable anal HPV in older GBM.

Methods: The Study of the Prevention of Anal Cancer (SPANC) is an ongoing, prospective cohort study of HIV-positive and HIV-negative Australian GBM. Participants completed questionnaires and underwent an anal swab for HPV genotyping using Roche Linear Array. We analysed baseline data from SPANC by HPV type, mean number of types, stratified by age and HIV status.

Results: Anal HPV results from 606 (98.2%) of 617 participants (median age 49 years, 35.7% HIV-positive) showed 525 (86.7%) had ≥1 HPV type and 178 (29.4%) had HPV16. Over one third of participants (214, 35.3%) had no nonavalent vaccine-preventable types detected. Two (0.3%) participants had all quadrivalent types and none had all nonavalent vaccine types. HIV-positive participants ($p < 0.001$) and younger participants ($p=0.059$) were more likely to have more vaccine-preventable HPV types detected.

Conclusion: Anal HPV was highly prevalent in this largely community-based GBM cohort. Vaccine-preventable HPV16 was detected in approximately one third of participants. These findings suggest that the potential efficacy of HPV vaccination of older GBM should be explored.

1. Introduction

Squamous cell carcinoma of the anal canal ("anal cancer") is rare, but its incidence has been increasing worldwide for decades [1–4]. A key feature of anal cancer epidemiology is that its occurrence is heavily concentrated in certain population subgroups. Anal cancer is caused by anal exposure to human papillomavirus (HPV) and for this reason gay and bisexual men (GBM) are at particularly high risk, experiencing rates of anal cancer that are at least 20-fold higher than the general population [5]. The overall rates of anal cancer in people living with HIV are 30-fold higher than in the general population [6], but HIV positive GBM are the most affected population due to their combination of impaired immune function and increased anal HPV exposure, with up to a 100-fold higher incidence of anal cancer reported [7].

Anal cancer is believed to be preceded by persistent infection with high-risk types of HPV (HrHPV), with HPV16 comprising a large

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majority (75–80%) [8]. The strong association between anal HPV infection and cancer indicates that anal cancer is potentially preventable by HPV vaccination [9], with either the quadrivalent HPV vaccine (4vHPV) or the nonavalent HPV vaccine (9vHPV). There is evidence of HPV vaccine efficacy in prevention of cervical infection and disease in sexually active women aged up to 45 years [10–12] and in anal infection and disease in GBM aged up to 26 years [13]. Despite HPV-related anal cancer being one of the most pressing health issues in GBM, very few data exist to inform the potential efficacy of HPV vaccination in those aged older than 26 ("older GBM"). There is a concern that many older GBM may be currently HPV infected, and there is evidence that the vaccine does have an impact on current infections [14]. We explored patterns of vaccine-preventable anal HPV in a community-based cohort of older HIV-positive and HIV-negative Australian GBM.

2. Methods

2.1. Study design

The Study of Prevention of Anal Cancer (SPANC) is a prospective cohort study of the epidemiology of anal HPV infection and related cytological and histological anal abnormalities in GBM aged 35 years and older in Sydney, Australia. The methods of the study have been described in detail elsewhere [15]. Briefly, men aged ≥35 years who reported having sex with another man in their lifetime were eligible. Participants were recruited mainly from community-based settings in Sydney, including gay community social events and organizations, as well as referrals from other participants. At the baseline visit, participants completed a detailed risk factor questionnaire and had an anal swab for cytology and HPV DNA testing.

Signed, informed consent was provided by all participants. Ethics approval was granted by the Human Research Ethics Committees of St. Vincent's Hospital, Sydney, the Royal Prince Alfred Hospital, Sydney and the University of New South Wales.

2.2. Anal HPV genotyping

The PreservCyt anal swab specimens were tested for HPV DNA using the Roche Linear Array (LA) HPV genotyping test (Roche Molecular Systems, Alameda, CA, United States). DNA was extracted with the automated MagNA Pure isolation and purification system (Roche) by a modified protocol using 1 ml aliquots of PreservCyt specimens as described previously [16]. The LA HPV genotyping test involves PCR amplification of a 450 bp region of the HPV L1 gene and allows for the identification of 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 (HPV 82v subtype), and CP6108 (HPV 89) as well as amplification of a 265 bp region of the human ß-globin gene, serving as an internal control. As an in-house modification, samples that produced a negative internal control were retested with half the volume of eluted DNA, in order to reduce inhibition due to bacterial DNA in those samples. In addition, due to possible cross-reactivity of the HPV-52 probe with types 33, 35, and 58 amplicons, samples positive for one or more of HPV-33, 35, and 58 probes were further tested using a real-time PCR assay with an HPV52 specific hydrolysis probe to confirm the presence or absence of HPV52 in addition to those types [17].

2.3. Statistical analyses

The exact binomial method was used to calculate 95% confidence intervals (CIs) for anal HPV prevalence values for each HPV type and vaccine-targeted HPV types, (4vHPV: HPV6, HPV11, HPV16 and HPV18 and 9vHPV: HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52 and HPV58). Generalised linear regression was used for univariate analyses to identify the association of number of vaccine-preventable anal HPV types with age and/or HIV status. A *t*-test was used to test for trend for means. A rank sum test was then performed as a sensitivity analysis, to test the robustness of the results. Among HIV-positive men, nadir and current $CD4^+$ T-cell counts were also assessed. STATA Version 14 (StataCorp, College Station, Texas USA) was used for the analysis.

Table 1
SPANC participant baseline characteristics by HIV status (n=617).

	Overall n=617	**HIV negative** n=397	**HIV positive** n=220
Age (year groups)			
35–44	198	134	64
45–54	236	141	95
55–64	124	76	48
≥65	59	46	13
Cigarette smoking status			
Never	334	232	102
Past smoker	196	121	75
Current smoker	87	44	43
Sexual identity			
Heterosexual or straight	4	3	1
Bisexual	17	11	6
Gay	390	256	134
Queer	8	4	4
Homosexual	190	120	70
Other	8	3	5
Lifetime number of male sexual partners			
< 10	11	10	1
11–50	102	81	21
51–200	173	116	57
201–500	122	76	46
> 500	196	105	91
Lifetime number of R-CLAI[a] partners			
0–1	84	74	10
2–5	165	146	19
6–10	125	84	41
> 10	243	93	150
Number of male sexual partners in past 6 months			
None	49	15	34
1	123	90	33
2–5	164	114	50
6–10	106	65	41
> 10	175	113	62
Number of R-CLAI[a] partners in past 6 months			
None	289	194	95
1	184	142	42
≥2	144	61	83

[a] R-CLAI – participant reports receptive anal intercourse without a condom.

3. Results

A total of 617 men were enrolled in SPANC, with a median age of 49 years (range 35–79 years). Nearly all men (588, 95.3%) identified as gay or homosexual. Greater than one-third (220, 35.7%) were HIV-positive (Table 1). The great majority of these men (206, 93.6%) were currently receiving antiretroviral therapy, reported an undetectable viral load (197, 89.5%) and had a CD4 T-cell count of more than 350 cells/μL (194, 88.0%). Of the 582 men (94.3%) who completed a