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Alcohol consumption and prevalence of human papillomavirus (HPV) infection among US men in the HIM (HPV in Men) Study

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Abstract

Objectives—Moderate alcohol consumption can impair host defense against viral infections. The objective of this cross-sectional analysis was to assess the association between alcohol intake and prevalent HPV infection among U.S. men enrolled in the *HIM* (HPV in Men) *Study* utilizing quantitative alcohol intake measured from a food frequency questionnaire.

Methods—*The HIM study* is a prospective, multinational study of the natural history of HPV infection. For this report we restricted our analyses to men from the US cohort (No. = 1,313). Samples from the corona of glans penis, penile shaft, and scrotum were combined for HPV DNA testing. Self-reported alcohol intake was quantified by grams of alcohol intake per day. Multivariable prevalence ratios (mPR) were used to assess the association between alcohol intake and HPV infections.

Results—Prevalent infections were significantly higher among men in the highest quartile of alcohol intake and multivariable models revealed that the highest quartile of alcohol intake was associated with significantly increased risks for any- (mPR=1.13; 95% CI 1.00–1.27) and oncogenic (mPR=1.35; 95% CI 1.08–1.68) HPV types. The fourth quartile of alcohol intake was

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associated with elevated risks for prevalent HPV infection across all strata of number of sexual partners and among never- and current smokers, but not among former smokers.

Conclusions—These results demonstrate that high intake of alcohol is associated with an increased risk for prevalent HPV infections among men. The biological role that alcohol plays in genital HPV infection remains understudied and limited epidemiologic data exist especially among men.

Keywords

HPV; alcohol; drinking; smoking; sexual behavior; men

Introduction

With more than 6 million new infections occurring annually in the United States (1, 2), human papillomavirus (HPV) is one the most common sexually transmitted infections. There are more than 120 different HPV types of which 40 or more types are transmitted through sexual contact (3). In addition to the clinical endpoints HPV causes in men, including genital warts and various cancers, HPV is readily transmitted from person to person and is strongly associated with cancer risk in women (4-6). Although the majority of HPV infections are transient and do not result in disease, failure to develop an immune response to control an infection results in viral persistence and, in the case of the oncogenic HPV types, an increased risk of progression to cancer (7).

Alcohol consumption is a potent modulator of immune function which can lead to immune deficiency and increased susceptibility to various chronic and infectious diseases (8-11). Not only chronic alcohol abuse but also acute and moderate alcohol consumption can adversely affect the immune system (9, 11-13). Pathogen response is divided into two phases: the first phase is an inflammatory reaction, which provides protection against the immediate effects of the infection, and the second phase involves the development of immunity to the pathogen. Alcohol consumption can interfere with both phases of the immune response (9). The consequences of alcohol-induced immunodysfunction include increased susceptibility to numerous infectious endpoints including bacterial pneumonia, septicemia, tuberculosis, and hepatitis (10, 12, 13). Currently, there are few published data on the association between alcohol consumption and genital HPV infection among men. Revealing the association between a potential risk factor and prevalent HPV infections is the obligatory step prior to initiating longitudinal analyses of HPV infection endpoints. Thus, the objective of this analysis was to utilize alcohol consumption data from a food frequency questionnaire (FFQ) to assess the association between alcohol intake and prevalent HPV infection among U.S. men in the HIM study. To evaluate potential effect modification, we also stratified the data by smoking status and lifetime number of sexual partners. To date, this is one of the largest analyses exploring the association between alcohol intake and HPV infection.

Materials and Methods

Study population and risk factor questionnaire

The human-subjects' committees from The University of South Florida (USF) approved all study procedures before study initiation (USF IRB# 102660). The HIM study is a prospective, multinational study of the natural history of HPV infection in men; a full description of cohort procedures, HPV prevalence, and factors associated with prevalent infections has been published (14, 15). For this report, we restricted our analysis to men from the US cohort because of potential regional and cultural differences in alcohol consumption (i.e., types of alcohol, frequency of use, age of initiation, etc.) and behavior. Men who provided informed consent had a clinical examination two weeks prior to the enrollment visit (No. = 1,427) and every 6 months thereafter. Only men who returned for the enrollment visit (No. = 1,313) from 2005 through 2006 were included in this report.

An extensive sexual history and health questionnaire, which required approximately 15 minutes to complete, was administered at the enrollment visit to assess sociodemographic information and risk factors. Using the U.S. Centers for Disease Control (CDC) definition (16), never smokers were defined as men who had smoked less than 100 cigarettes in their lifetime. Likewise, (17) former smokers were defined as men who had smoked at least 100 cigarettes in their lifetime but quit smoking at least 1 year before the enrollment interview. Current smokers were defined as men who smoked at least 100 cigarettes in their lifetime and were currently smoking (or quit within the previous 12 months) at the time of the enrollment visit.

Arizona Food Frequency Questionnaire (AFFQ)

The AFFQ is a modification of the NCI Health Habits and History FFQ (18) that consists of a semi-quantitative 159-item questionnaire which asks respondents to report how often they usually consumed each particular item over the prior 12-month period. The AFFQ was completed by the men at the enrollment visit and required about 30 minutes to complete. The AFFQ contained questions on alcohol consumption including serving size and frequency of light beer, beer, wine, and liquor. Serving size was subjectively defined as the average serving size compared to other men of the same age and classified as small, medium, or large. Frequency of consumption was collected as 6+ times per day, 3 to 5 times per day, twice a day, once a day, 5 to 6 times a week, 2 to 4 times a week, once a week, 1 to 3 times a month, and rarely/never. The FFQ analysis program quantified alcohol intake by grams of alcohol intake per day and percent calories from alcohol per day. All findings were consistent when alcohol intake was evaluated according to percent calories from alcohol per day. In this report, we present results for grams of alcohol intake per day.

Sample Collection, DNA Extraction, and HPV Genotyping

Details of sample collection, DNA extraction and HPV genotyping have been published elsewhere (14, 15). Briefly, three separate specimens were obtained from the corona of glans penis, penile shaft, and scrotum, placed into 450 μL of Specimen Transport Medium, and then combined into one sample before DNA extraction. The extracted DNA samples were tested for the presence of HPV types by amplification with the PGMY09/11 L1 consensus

primer system (19, 20) and HPV genotyping was performed with the Linear Array method on all samples irrespective of the HPV PCR result (Roche Molecular Diagnostics, Alameda, CA, USA). Only samples that tested positive for β-globin (99% at enrollment) were judged to be adequate and included in the analysis.

Statistical Analysis

Four HPV categories were assessed in this analysis (i.e., “any HPV”, “oncogenic HPV”, “non-oncogenic HPV”, and “quadrivalent vaccine types”). A participant was considered positive for “any HPV” if he tested HPV-positive by PCR or tested positive for at least one genotype. The “oncogenic HPV” category included men who were positive for at least one of the 13 oncogenic types tested (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) and included men infected with both oncogenic and non-oncogenic types. “Non-oncogenic HPV” infections included single or multiple infections with only non-oncogenic HPV types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67, 68–73, 81–84, IS39, and CP6108). The “quadrivalent vaccine types” included men with one or more prevalent infections of HPV 6, 11, 16, or 18.

All statistical analyses were performed using R version 2.14 (R Project for Statistical Computing, http://www.r-project.org) and SAS version 9.3 (Cary, NC). Alcohol intake was categorized by the quartile intake values among HPV negative men. Sociodemographic and sexual behavioral cohort characteristics across quartiles of alcohol intake were compared by use of Fisher's exact test. The Wilcoxon signed-rank test was used to test for differences in the median alcohol intake and the Pearson's chi-square test was used to test for differences in the distribution of HPV positivity across quartiles of alcohol intake. Multivariable Poisson regression (PROC GENMOD) was used to generate prevalence ratios (PRs) and 95% Confidence Intervals (CIs).

Results

Alcohol consumption was categorized according to quartiles of grams (g) of alcohol intake per day among HPV negative men: Q1 < 0.10 g/day; Q2 ≥ 0.10 to < 3.13 g/day; Q3 ≥ 3.13 to < 9.91 g/day; and Q4 ≥ 9.91 g/day (Table 1). The mean (standard deviation [SD]) of grams of alcohol intake per day was: 0.02 g/day (0.02), 1.69 g/day (0.84), 5.88 g/day (2.02), and 35.9 g/day (39.8), in quartiles 1 to 4, respectively. Statistically significant differences were observed for the distribution of study population characteristics by quartiles of alcohol intake. Men that consumed higher levels of alcohol (quartiles 3 and 4) were younger, current smokers, White, reported more female sexual partners, and were more likely to be circumcised (Table 1).

Compared to HPV negative men, the median intake of alcohol was significantly higher among HPV positive men (Table 2). The median alcohol intake per day among HPV negative men was 3.13 g (Interquartile [IQ] 0.1 – 9.9) compared to men who were positive for any HPV (median = 4.52 g; IQ 0.6 – 15.5; P < 0.001), the oncogenic HPV types (median = 5.23 g; IQ 1.1 – 18.3; P < 0.001), the non-oncogenic HPV types (median = 5.29 g; IQ 0.6 – 17.5; P = 0.006), and the quadrivalent vaccine HPV types (median 6.31 g; IQ 1.2 – 19.4; P < 0.001). When HPV prevalence was analyzed by quartiles of alcohol intake (Table 2), we

noted a significantly higher prevalence of HPV among men in the highest quartile of alcohol consumption. Across the four quartiles of alcohol intake, the prevalence was 56.7%, 56.2%, 57.9%, and 68.9% for any HPV ($P < 0.001$), 22.8%, 24.7%, 27.0%, and 35.2% for oncogenic HPV types ($P < 0.001$), 16.1%, 12.0%, 15.5%, and 19.5% for non-oncogenic HPV types ($P = 0.002$), and 11.7%, 12.0%, 15.1%, and 19.5% for the quadrivalent vaccine HPV types ($P < 0.001$).

In Table 3 we present the mPRs for the association between alcohol intake and HPV infection, adjusting for potential confounders including age, race, smoking status, ethnicity, circumcision, total number of female partners in the last 3 months, and total number of female sex partners. Overall, the highest quartile (Q4) of alcohol intake compared to the lowest quartile (Q1) was significantly associated with an increased risk for any- (mPR = 1.12; 95% CI 1.03 – 1.27) and oncogenic HPV types (mPR = 1.35; 95% CI 1.08 – 1.68), and a borderline significant increased risk for the quadrivalent vaccine HPV types (mPR = 1.47; 95% CI 0.98 – 2.23). To increase statistical power we also assessed alcohol intake by combining the first three quartiles of intake into a new referent group. As evident in Table 2, HPV prevalence was similar for the first three quartiles (Table 2) and the overall point estimates (Table 3) for the first three quartiles clustered around 1.00. Generally, the point estimates for Q4 were similar, but the confidence intervals were narrower. We did not adjust for sex with male partners since over 94% of the men in this analysis reported having zero male partners and there was no difference ($P = 0.739$) across quartiles of alcohol intake as noted in Table 1. We performed an exploratory analysis that included number of male sex partners in the model and also restricted to men who reported zero male sex partners; however, there was no appreciable difference in the point estimates (*data not shown*).

We also stratified the analyses by smoking status. Significant associations were observed for high intake (Q4) and HPV prevalence among never smokers for any HPV (PR = 1.22; 95% CI 1.03 – 1.44) and the oncogenic types (PR = 1.48; 95% CI 1.09 – 2.02), and borderline significant associations for the non-oncogenic- and quadrivalent vaccine HPV types. There were no statistically significant associations among former smokers. We noted borderline significant associations among current smokers for high alcohol intake (Q4) compared to the grouped referent (Q1 to Q3) for any- (mPR = 1.14; 95% CI 0.95 – 1.37) and oncogenic HPV infections (HR = 1.26; 95% CI 0.98 – 1.70).

We also stratified the association between alcohol intake and HPV infection by lifetime number of sexual partners (0 to 1, 2 to 9, and ≥ 10). For these analyses, we utilized the grouped referent (Q1 to Q3) and found that high alcohol intake (Q4) was associated with relatively modest elevated point estimates across all strata of number of sexual partners (Table 4).

Discussion

Assessing the impact of a potential risk factor and prevalent HPV infections is an important step prior to initiating longitudinal analyses. Thus, this study sought to assess the association between self-reported alcohol intake and prevalent HPV infections among U.S. men. Our analyses revealed that prevalent infections were significantly higher among men in the

highest quartile of alcohol intake and multivariable analyses, adjusting for potential confounding including sexual behavior and smoking, revealed that the highest quartile of alcohol intake was associated with an increased risk of prevalent genital HPV infection. Furthermore, we found no evidence of confounding by sexual behavior and smoking following stratification by these risk factors.

The association between alcohol consumption and HPV-related endpoints has been reported in other study populations. A cross-sectional study of men in the Danish Army reported that alcohol intake was associated with having multiple HPV types (21). A prospective study of the natural history of cervicovaginal papillomavirus infection in women (22) found an elevated risk (RR = 2.0; 95% CI 1.2–3.1) of incident HPV infection associated with high alcohol consumption. A cross-sectional study that assessed sexual practices and cervical HPV infection among college women (23) reported alcohol use was significantly more frequent among women who were HPV DNA positive. A case-control study of both sexes from four clinics in Washington state (24) reported that four alcoholic drinks/week was associated with nearly a two-fold increased risk of genital warts (95% CI 1.0-3.6) and five or more alcoholic drinks/week revealed a 2.4-fold increased risk (95% CI 1.2-5.1). Conversely, two studies found no relationship between alcohol intake and HPV endpoints. A cross-sectional analysis of women seeking contraceptive advice in three Swedish clinics reported that recent use of alcohol was not associated with cervical HPV infection after adjustment for sexual/behavioral factors (25). In a separate study among high-risk HPV-positive women, alcohol intake was not associated with risk of high-grade squamous intraepithelial lesions (26). In spite of some inconsistency in the literature, evidence suggests a modest association between alcohol consumption and prevalent HPV infection.

Previous studies in both men and women have shown that cigarette smoking is associated with HPV prevalence (27, 28), incidence (29), and persistence (30). We found significant point estimates for the association between alcohol consumption and HPV infection among never smokers and borderline significant associations among current smokers. The observed effects among never smokers are novel and of potential public health importance as there are few risk factors for HPV infection among never smokers.

It is plausible that the association between higher alcohol intake and HPV infection could be due to increased sexual disinhibition and promiscuous sexual behavior. To account for potential confounding, we adjusted for sexual activity in the multivariable models and we stratified by lifetime number of sexual partners to reveal potential effect modification by sexual activity. Interestingly, the stratified analyses demonstrated that high alcohol intake was generally associated with a modest increased risk of HPV risk infection regardless of the number of sexual partners. If increased sexual behavior is solely responsible for our findings, we would have expected to see no association between high alcohol intake and HPV after adjustment and elevated effects only in the highest sexual activity strata. Because differences in sexual behavior by alcohol intake do not appear to explain our findings, the observed associations could be due other factors such as the systemic effects of alcohol on immune function. The immune system serves as defense against infections and alcohol consumption is a potent modulator of immune function (8-11). Studies in laboratory animals and in humans have demonstrated that acute and moderate alcohol consumption can

transiently impair host defense against viral infections (9). Although the clinical implications of such a transient immuno-depression are not completely understood, the epidemiologic evidence adds insight into the putative consequences of alcohol consumption on HPV susceptibility.

There are both strengths and limitations in the present analyses. Because of the potential to report socially desirable responses, self-reported data have inherent biases that could lead to underreporting of alcohol consumption, tobacco use, and number of sex partners (31, 32). Additionally, FFQs are subject to random and systematic error (33) and differential misclassification of dietary intake is a concern if a study participant were aware of his disease status. However, differential misclassification would not impact the present findings as men were not aware of their HPV status during the administration of the risk factor questionnaire and FFQ. Also, FFQs cannot estimate intake from the remote past and have been shown to introduce biased associations (34), so we attempted to reduce potential measurement errors attributable to recall bias by assessing intake during the year prior to enrollment into the study. We acknowledge that we cannot account for bias due to unmeasured or unknown confounding. Although we accounted for potential confounding by adjusting for self-reported sexual behavior and stratifying by smoking status and lifetime number of sexual partners, residual confounding still may exist which could potentially inflate the observed point estimates. We also acknowledge that the US men in the *HIM* cohort may not be a representative of the general male population of the US which may limit the generalizability of our findings.

Overall, the results from these analyses demonstrated that high intake of alcohol is associated with an increased risk for prevalent HPV infections. Although these results cannot be considered causal and should be interpreted with caution, our findings do provide additional support to current public health messaging regarding the importance of moderate alcohol consumption, smoking cessation, and safe sex practices. The biological mechanisms underlying the association between alcohol consumption and genital HPV infection remains understudied and limited epidemiologic data exist especially among men. Additional research is needed to replicate the current findings before clinical interventions can be recommended. Nonetheless, these data are important since there is limited information on the association between alcohol consumption and genital HPV infection in men and future longitudinal analyses will be needed to assess whether alcohol consumption is associated with HPV acquisition and clearance.

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Key Messages

- This analysis revealed that the highest quartile of alcohol consumption is associated with an increased risk for prevalent HPV infections.
- We found no evidence of confounding by sexual behavior and smoking following multivariable adjustment and stratification by these covariates.
- High alcohol intake was also associated with increased risk of HPV infection among never smokers and current smokers.
- The observed effects among never smokers are novel and of potential public health importance as there are few risk factors for HPV infection among never smokers.

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Table 1

HIM study demographics among U.S. men overall and by quartiles of alcohol intake

		By grams of alcohol intake per day[2]			
Characteristic[1]	**Overall (N = 1309)**	**Q1 (N=298)**	**Q2 (N = 292)**	**Q3 (N= 304)**	**Q4 (N= 415)**
Alcohol intake per day, grams					
Interquartile range	0.56 to 13.4	< 0.10	≥ 0.10 to < 3.13	≥ 3.13 to < 9.91	≥ 9.91
Mean (SD) within each quartile	12.8 (27.1)	0.02 (0.02)	1.69 (0.84)	5.88 (2.02)	35.9 (39.8)
Age					
Mean (SD)	29.2 (12.6)	31.3 (13.7)	29.8 (12.6)	27.2 (10.9)	28.6 (12.6)
P-value			**< 0.001**		
Categorical, N (%)					
18-24	720 (55.0)	141 (47.3)	151 (51.7)	184 (60.5)	244 (58.8)
25-29	123 (9.4)	24 (8.1)	23 (7.9)	35 (11.5)	41 (9.9)
30-44	292 (22.3)	74 (24.8)	85 (29.1)	56 (18.4)	77 (18.6)
≥ 45	174 (13.3)	59 (19.8)	33 (11.3)	29 (9.5)	53 (12.8)
P-value			**< 0.001**		
Smoking Status, No. (%)					
Never	836 (63.7)	194 (65.1)	211 (72.3)	206 (67.8)	225 (54.2)
Former	206 (15.7)	51 (17.1)	29 (9.9)	44 (14.5)	82 (19.8)
Current	267 (20.3)	53 (17.8)	52 (17.8)	54 (17.8)	108 (26.0)
P-value			**< 0.001**		
Race, No. (%)					
White	873 (66.7)	182 (61.1)	174 (59.6)	208 (68.4)	309 (74.5)
Black	230 (17.6)	67 (22.5)	59 (20.2)	42 (13.8)	62 (14.9)
Asian/Pacific Islander	85 (6.5)	21 (7.0)	30 (10.3)	21 (6.9)	13 (3.1)
American Indian	2 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Mixed/Unknown/Refused	119 (9.1)	27 (9.1)	29 (9.9)	33 (10.9)	30 (7.2)
P-value			**< 0.001**		
Ethnicity, No. (%)					
Hispanic	199 (15.2)	37 (12.4)	55 (18.8)	46 (15.1)	61 (14.7)
Non-Hispanic	1100 (83.8)	257 (86.2)	236 (80.8)	255 (83.9)	352 (84.8)

Characteristic[1]	Overall (N = 1309)	By grams of alcohol intake per day[2] Q1 (N=298)	Q2 (N = 292)	Q3 (N= 304)	Q4 (N= 415)
Refused	10 (0.8)	4 (1.3)	1 (0.3)	3 (1.0)	2 (0.5)
P-value			0.294		
Lifetime number of female sex partners, No. (%)					
0	141 (10.8)	44 (14.8)	38 (13.0)	32 (10.5)	27 (6.5)
1	130 (9.9)	38 (12.8)	41 (14.0)	32 (10.5)	19 (4.6)
2 to 9	502 (38.3)	92 (30.9)	117 (40.1)	119 (39.1)	174 (41.9)
10 to 19	204 (15.6)	43 (14.4)	44 (15.1)	45 (14.8)	72 (17.3)
20 to 49	199 (15.2)	43 (14.4)	26 (8.9)	51 (16.8)	79 (19.0)
≥ 50	92 (7.0)	25 (8.4)	21 (7.2)	16 (5.3)	30 (7.2)
Refused	41 (3.1)	13 (4.4)	5 (1.7)	9 (3.0)	14 (3.4)
P-value			**< 0.001**		
Total number of female partners last 3 months to 6 months, No. (%)					
0	141 (10.8)	44 (14.8)	38 (13.0)	32 (10.5)	27 (6.5)
1	856 (65.4)	212 (71.1)	209 (71.6)	194 (63.8)	241 (58.1)
2	128 (9.8)	17 (5.7)	24 (8.2)	37 (12.2)	50 (12.0)
3	171 (13.1)	22 (7.4)	21 (7.2)	39 (12.8)	89 (21.4)
Refused	13 (1.0)	3 (1.0)	0 (0.0)	2 (0.7)	8 (1.9)
P-value			**< 0.001**		
Circumcision, No. (%)					
Yes	1029 (78.4)	224 (75.2)	224 (75.2)	212 (72.6)	240 (78.9)
No	247 18.8)	67 (22.5)	67 (22.5)	67 (22.9)	57 (18.8)
Partial	33 (2.5)	7 (2.3)	7 (2.3)	13 (4.5)	7 (2.3)
P-value			**0.002**		
Total number of male partners last 3 months to 6 months, No. (%)					
0	1269 (96.9)	**295 (99.0)**	**281 (96.2)**	**293 (96.4)**	**400 (96.4)**
≥ 1	40 (3.1)	**3 (1.0)**	**11 (3.8)**	**11 (3.6)**	**15 (3.6)**
P-value			0.140		
Lifetime number of male sex partners, No. (%)					
0	1233 (94.2)	**284 (95.3)**	**272 (93.2)**	**286 (94.1)**	**391 (94.2)**
1	23 (1.8)	**6 (2.0)**	**5 (1.7)**	**9 (3.0)**	**3 (0.7)**

Characteristic[1]	Overall (N = 1309)	By grams of alcohol intake per day[2] Q1 (N=298)	Q2 (N = 292)	Q3 (N= 304)	Q4 (N= 415)
2+	53 (4.1)	**8 (2.7)**	**15 (5.2)**	**9 (3.0)**	**21 (5.1)**
P-value			0.152		

Bold font indicates a statistically significant p-value.

Abbreviations: Quartile, Q*n*

[1] *P*-values were calculated from the Fisher's exact test for the categorical variables by quartiles of alcohol intake and analysis of variance (ANOVA) for the continuous variable (i.e., age) by quartiles of alcohol intake. All P-values are two-sided.

[2] Alcohol intake was categorized by the quartile intake values among HPV negative men

Table 2

Alcohol intake by HPV infection status and HPV prevalence by quartiles of alcohol intake

		Median grams of alcohol intake per day by HPV infection status			HPV prevalence by quartiles[3] of grams of alcohol intake per day				
	No.	Median	(IQ Range)	P-value[1]	Q1 No. (%)	Q2 No. (%)	Q3 No. (%)	Q4 No. (%)	P-value[2]
HPV Negative	514	3.13	(0.1 – 9.9)		129 (43.3)	128 (43.8)	128 (42.1)	129 (31.1)	
Positive for:									
Any HPV	795	4.52	(0.6 – 15.5)	< **0.001**	169 (56.7)	164 (56.2)	176 (57.9)	286 (68.9)	< **0.001**
Oncogenic HPV	368	5.23	(1.1 – 18.3)	< **0.001**	68 (22.8)	72 (24.7)	82 (27.0)	146 (35.2)	< **0.001**
Non-oncogenic HPV	211	5.29	(0.6 – 17.5)	**0.006**	48 (16.1)	35 (12.0)	47 (15.5)	81 (19.5)	**0.002**
HPV 6, 11, 16, or 18[4]	197	6.31	(1.2 – 19.4)	< **0.001**	35 (11.7)	35 (12.0)	46 (15.1)	81 (19.5)	< **0.001**

Bold font indicates a statistically significant p-value.

Abbreviations: Interquartile Range, IQ; Quartile, Q*n*

[1] P-values were calculated using the Wilcoxon rank sum test comparing the median value of alcohol consumption by HPV negativity versus HPV positivity

[2] P-values were calculated by the $\chi 2$ test for the distribution of HPV positivity compared to HPV negativity by quartiles of alcohol intake. The percentages presented are prevalence using the total number of subjects within each quartile of intake as the denominator.

[3] Alcohol intake was categorized by the quartile intake values among HPV negative men

[4] HPV 6, 11, 16, or 18 are the quadrivalent vaccine HPV types

Table 3

Risk of prevalent HPV infection by quartiles of alcohol intake stratified by smoking status[1]

		By smoking status		
HPV status	**Overall (No. = 1309) mPR[2,4]**	**Never Smokers (No. = 836) mPR[3,4]**	**Former Smokers (No. = 206) mPR[3,4]**	**Current Smokers (No. = 267) mPR[3,4]**
Any HPV				
Q1	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q2	1.01 (0.88 – 1.16)	1.16 (0.97 – 1.39)	0.72 (0.39 – 1.34)	0.81 (0.62 – 1.06)
Q3	1.00 (0.88 – 1.15)	1.11 (0.92 – 1.33)	0.83 (0.48 – 1.43)	0.80 (0.61 – 1.06)
Q4	**1.13 (1.00 – 1.27)**	**1.22 (1.03 – 1.44)**	0.90 (0.57 – 1.42)	0.99 (0.79 – 1.23)
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	**1.12 (1.03 – 1.23)**	**1.12 (0.99 – 1.26)**	1.03 (0.72 – 1.48)	1.14 (0.95 – 1.37)
Oncogenic				
Q1	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q2	1.09 (0.85 – 1.42)	1.38 (0.99 – 1.90)	0.54 (0.17 – 1.68)	0.77 (0.48 – 1.24)
Q3	1.11 (0.87 – 1.43)	1.25 (0.90 – 1.75)	1.01 (0.46 – 2.25)	0.75 (0.46 – 1.23)
Q4	**1.35 (1.08 – 1.68)**	**1.48 (1.09 – 2.02)**	1.10 (0.54 – 2.23)	1.04 (0.71 – 1.53)
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	**1.26 (1.07 – 1.47)**	1.23 (0.99 – 1.52)	1.20 (0.70 – 2.04)	1.26 (0.94 – 1.70)
Non-oncogenic				
Q1	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q2	0.78 (0.50 – 1.22)	1.01 (0.55 – 1.85)	0.69 (0.25 – 1.89)	0.58 (0.24 – 1.43)
Q3	0.98 (0.65 – 1.48)	1.31 (0.75 – 2.28)	0.66 (0.23 – 1.85)	0.73 (0.31 – 1.69)
Q4	1.20 (0.83 – 1.74)	1.56 (0.91 – 2.67)	0.89 (0.38 – 2.06)	0.90 (0.44 – 1.84)
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	1.30 (0.97 – 1.73)	1.39 (0.93 – 2.08)	1.15 (0.60 – 2.20)	1.18 (0.67 – 2.07)
HPV 6, 11, 16, or 18[5]				
Q1	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q2	1.01 (0.63 – 1.61)	1.41 (0.77 – 2.55)	0.26 (0.03 – 2.17)	0.69 (0.26 – 1.80)
Q3	1.15 (0.73 – 1.79)	1.33 (0.73 – 2.41)	0.96 (0.31 – 2.92)	0.65 (0.25 – 1.74)
Q4	1.47 (0.98 – 2.23)	**1.73 (0.99 – 3.03)**	0.75 (0.25 – 2.25)	1.14 (0.52 – 2.50)
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	**1.39 (1.04 – 1.88)**	1.40 (0.93 – 2.09)	0.86 (0.38 – 1.92)	1.50 (0.84 – 2.67)

Bold font indicates a statistically significant hazard ratio.; Abbreviations: Multivariable prevalence ratio, mPR; Quartile, Q*n*

[1] Alcohol intake was categorized by the quartile intake values among HPV negative men

[2] Adjusted for age, race, smoking status, ethnicity, circumcision, and total number of female partners in the last 3 months,.

[3] Adjusted for age, race, ethnicity, circumcision, and total number of female partners in the last 3 months

[4] We did not adjust for sex with male partners since over 94% of the men in this analysis reported having zero male partners and there was no difference (P = 0.739) across quartiles of alcohol intake as noted in Table 1.

[5] HPV 6, 11, 16, or 18 are the quadrivalent vaccine HPV types

Table 4

Risk of prevalent HPV infection by quartiles of alcohol intake stratified by lifetime number of sexual partners[1]

	By lifetime number of sex partners		
HPV status	**0 to 1 (No. = 719) mPR[2]**	**2 to 9 (No. = 302) mPR[2]**	**≥ 10 (No. = 288) mPR[2]**
Any HPV			
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	1.14 (1.00 – 1.29)	1.17 (0.96 – 1.44)	**1.16 (1.01 – 1.33)**
Oncogenic			
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	**1.36 (1.09 – 1.70)**	1.41 (0.93 – 2.12)	1.32 (0.90 – 1.96)
Non-oncogenic			
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	1.21 (0.87 – 1.69)	**1.96 (1.09 – 3.51)**	1.32 (0.79 – 2.20)
HPV 6, 11, 16, or 18[4]			
Q1 to Q3	*1.00 (referent)*	*1.00 (referent)*	*1.00 (referent)*
Q4	**1.58 (1.11 – 2.25)**	1.58 (0.93 – 2.67)	1.30 (0.76 – 2.26)[3]

Bold font indicates a statistically significant hazard ratio.

Abbreviations: Multivariable prevalence ratio, mPR; quartile, Q*n*

[1] Alcohol intake was categorized by the quartile intake values among HPV negative men and the first three quartiles were combined for the referent category. Lifetime number of sexual partners was defined as men who have sex with women and/or men.

[2] Adjusted for age, race, smoking status, ethnicity, and circumcision unless otherwise noted

[3] Because of small sample size, we could not adjust for race. Adjusted for age, smoking status, ethnicity, and circumcision.

[4] HPV 6, 11, 16, or 18 are the quadrivalent vaccine HPV types