

## No Association between Antibodies to Sexually Transmitted Infections and Colorectal Hyperplastic Polyps in Men: Minnesota Cancer Prevention Research Unit Polyp Study

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### Abstract

**Background:** Oncogenic human papillomaviruses (HPV) are sexually transmitted and linked to several epithelial malignancies, but an association between HPV and colorectal neoplasia is not established. Previously, we reported a three-fold increase in the odds of colorectal hyperplastic polyps associated with oncogenic HPV seropositivity in men but detected no HPV DNA in colorectal tissues from these same men.

**Methods:** To test the reproducibility of our prior HPV antibody results and to explore the hypothesis that colorectal hyperplastic polyps may be associated with sexual behavior in men, we conducted a case-control study of hyperplastic polyps and antibodies to eight oncogenic HPV types (including 16 and 18), Herpes simplex virus-2 (HSV-2), and hepatitis C virus (HCV). Study participants were men, ages 30–74 years, enrolled in the Minnesota Cancer Prevention Research Unit Polyp Study who had an index colonoscopy from 1991 to 1994, and received a diagnosis of hyperplastic polyps ( $n = 97$ ) or were polyp-free ( $n = 184$ ). Plasma was assessed for antibodies to the eight oncogenic HPV types, HSV-2, and HCV using a bead-based multiplex assay.

**Results:** The adjusted ORs for the association between hyperplastic polyps and seropositivity to oncogenic HPV (all eight types combined) was 0.84 [95% confidence interval (CI), 0.44–1.58; for HSV-2, OR, 0.98, 95% CI, 0.48–1.99; and for HCV, OR, 0.61; 95% CI, 0.11–3.26].

**Conclusions:** Our study suggested no association between colorectal hyperplastic polyps and antibodies to specific sexually transmitted infections (STI) in men.

**Impact:** Factors associated with STIs are unlikely to play a role in the etiology of colorectal hyperplastic polyps in men. *Cancer Epidemiol Biomarkers Prev*; 21(9); 1599–601. ©2012 AACR.

### Introduction

Oncogenic human papillomavirus (HPV) genus alpha types, 16, 18, and others, are sexually transmitted and causally associated with cervical cancer and other epithelial malignancies including anal carcinomas (1). Because the anal canal is contiguous with the rectum and colon and colorectal cancer is an epithelial malignancy, the association between colorectal cancer or polyps and oncogenic HPV has been investigated in more than 20 studies (2). Some studies reported a positive association between

HPV and colorectal neoplasia whereas others reported no association (2).

Previously, we evaluated the association between oncogenic HPV and colorectal polyps, including adenomas and hyperplastic polyps (3). We detected no oncogenic HPV DNA in more than 600 polyp and normal colorectal tissue samples. However, among men without previous polyps, we observed a 3-fold increase [95% confidence interval (CI), 1.1–7.9] in the odds of hyperplastic polyps associated with oncogenic HPV seropositivity (3), suggesting a possible sexually transmitted etiology for these lesions. To follow-up our prior results, we conducted a case-control study of hyperplastic polyps among men enrolled in the Minnesota Cancer Prevention Research Unit Polyp Prevention Study.

### Materials and Methods

#### Study population

Details of this study population were previously described (4). Briefly, participants were recruited before an elective colonoscopy for any indication at a gastroenterology practice in Minneapolis, MN, from 1991 to 1994. Eligible participants were 30 to 74 years old and residents of the Minneapolis/St. Paul metropolitan area with no

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history of colorectal polyps. Before colonoscopy, written informed consent and study questionnaires were completed and a blood sample collected. Among men with blood samples and questionnaire data available, we selected all participants diagnosed with hyperplastic polyps but no other polyps ( $n = 97$ ) and all participants who were polyp-free at the colonoscopy ( $n = 184$ ).

### Antibody assay

Plasma samples were tested for antibodies to HPV types 16, 18, 31, 33, 35, 45, 52, and 58, Herpes simplex virus-2 (HSV-2), and hepatitis C virus (HCV) using a multiplex, bead-based Luminex assay (5–7). For each HPV type, we used a bead set carrying the type-specific HPV L1 antigen. For HSV-2, the bead set included the protein domain of the membrane glycoprotein G (mgG) not shared with HSV-1, and for HCV, we used 2 bead sets, one with the HCV core antigen and one with the NS3 antigen. For quality control, we used a bead set with the viral capsid (VP1) antigen of BK virus, a ubiquitous polyomavirus with almost universal positive antibody status (8) and a bead set without antigens. Beads were differentiated, and antibodies bound to each bead were quantified as median fluorescence intensity (MFI).

### Statistical analyses

Seropositivity was determined using prespecified, antigen-specific cutoff points ( $>400$  MFI for HPV L1 antigens and  $>500$  MFI for HSV-2 and HCV antigens). For HCV, a positive value for either the core or NS3 antigens was used as a marker of HCV seropositivity. We also included a variable for seropositivity to types 16 or 18 and a variable for seropositivity to any oncogenic HPV tested. We conducted multivariable logistic regression to estimate the ORs and 95% CIs for hyperplastic polyps by comparing seropositivity to each antigen in cases to polyp-free controls. Regression models included age, race, smoking status (never, former, current), education, body mass index (BMI), and usual alcohol consumption (drinks/wk).

### Power calculation

Using Power (version 3.0, 1999, National Cancer Institute, Bethesda, MD), we calculated that given our sample size and  $\alpha = 0.05$ , our study had 99% power to detect an OR  $\geq 3$ , the point estimate from our prior study (3).

### Results

Hyperplastic polyp cases were more likely than controls to be former/current smokers and have a BMI  $\geq 25$  kg/m<sup>2</sup> (Table 1). There was no association between hyperplastic polyp and antibodies to any of the viruses evaluated (Table 2). For HPV, the adjusted OR for the association between seropositivity to any of the oncogenic HPV types evaluated and hyperplastic polyp was 0.84 (CI, 0.44–1.58); for HSV-2, OR = 0.98 (CI, 0.48–1.99); and for HCV, OR = 0.61 (CI, 0.11–3.26).

**Table 1.** Characteristics of controls and hyperplastic polyp cases among men undergoing colonoscopy, 1991–1994: Minnesota Cancer Prevention Research Unit Polyp Study

Characteristic	Controls	Hyperplastic
	(N = 184)	polyps (N = 97)
	n (%)	n (%)
Age, y		
30–44	38 (21)	18 (19)
45–54	66 (36)	34 (35)
55–64	46 (25)	35 (36)
65–74	34 (18)	10 (10)
Caucasian	179 (97)	96 (99)
Cigarette smoking status		
Never	75 (41)	18 (19)
Former	76 (41)	49 (50)
Current	33 (18)	30 (31)
Education		
Less than high school graduate	16 (9)	6 (6)
High school graduate	34 (18)	17 (18)
Some college/vocational school	68 (37)	41 (42)
College graduate/post-graduate studies	66 (36)	33 (34)
BMI, kg/m <sup>2</sup>		
<25	67 (37)	22 (23)
25–29.9	72 (39)	50 (53)
$\geq 30$	43 (24)	22 (23)
Alcohol consumption, drinks/wk		
0	47 (26)	18 (19)
1–7	88 (48)	43 (44)
8–14	32 (17)	21 (22)
>14	17 (9)	15 (15)

### Discussion

In contrast to our prior study (3), antibodies to HPV were not associated with hyperplastic polyp in men without a history of polyps. Furthermore, there was no association between hyperplastic polyp in men and antibodies to 2 other infections that are transmitted sexually. These results suggest that specific sexually transmitted infections (and possibly sexual risk factors more generally) are not associated with hyperplastic polyp in men.

Our prior study of HPV and colorectal polyps included both sexes, hyperplastic polyp and adenomas, and participants with and without a history of colorectal polyps. Therefore, we previously included analyses for both adenomas and hyperplastic polyp, stratified by sex, and restricted to participants without a history of colorectal polyps. These multiple analyses increased the chance of a

**Table 2.** ORs and 95% CIs for hyperplastic polyps in relation to HPV, HSV-2, and HCV seropositivity among men undergoing colonoscopy, 1991–1994: Minnesota Cancer Prevention Research Unit Polyp Study

	Controls (N = 184)		Hyperplastic polyps (N = 97)	
	n pos (%)	n pos (%)	Crude OR	Adjusted <sup>a</sup> OR
Any HPV type <sup>b</sup>	43 (23)	21 (22)	0.91 (0.50–1.64)	0.84 (0.44–1.58)
HPV-16 or -18	18 (10)	5 (5)	0.50 (0.18–1.39)	0.46 (0.16–1.34)
HPV-16	9 (5)	3 (3)	0.62 (0.16–2.35)	0.66 (0.17–2.58)
HPV-18	11 (6)	2 (2)	0.33 (0.07–1.52)	0.25 (0.05–1.22)
HPV-31	17 (9)	8 (8)	0.88 (0.37–2.13)	0.94 (0.36–2.50)
HPV-33	4 (2)	3 (3)	1.44 (0.31–6.55)	1.39 (0.28–6.83)
HPV-35	14 (8)	8 (8)	1.09 (0.44–2.70)	0.97 (0.38–2.48)
HPV-45	4 (2)	1 (1)	0.47 (0.05–4.25)	0.38 (0.03–3.71)
HPV-52	5 (3)	2 (2)	0.75 (0.14–3.96)	0.83 (0.14–4.84)
HPV-58	8 (4)	2 (2)	0.46 (0.10–2.23)	0.51 (0.10–2.69)
HSV-2	30 (16)	16 (16)	1.01 (0.52–1.97)	0.98 (0.48–1.99)
HCV <sup>c</sup>	6 (3)	2 (2)	0.62 (0.12–3.15)	0.61 (0.11–3.26)

<sup>a</sup>Adjusted for age, race, education, smoking status, alcohol consumption, and BMI.

<sup>b</sup>Seropositive to 1 or more oncogenic types analyzed, including 16, 18, 31, 33, 35, 45, 52, and 58.

<sup>c</sup>Seropositive to hepatitis C core or NS3 antigens.

type I error. In our replication study, we selected an independent study population that included only men without prior polyps, and we excluded those with adenomas, greatly decreasing the chance of a type I error and illustrating the importance of following up provocative findings based on subgroup analyses with a rigorous, directed replication study.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** A.N. Burnett-Hartman, S.M. Schwartz, M. Pawlita

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