

Human papillomavirus bowel colonization in inflammatory bowel disease: A comparative case control study

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ABSTRACT

Background and Aims: Although much of the research on the plausible environmental triggers for inflammatory bowel disease (IBD) has focused on bacterial pathogens, the relationship between bowel colonization with human papillomavirus (HPV) and IBD has not been previously explored. In this study, we aimed to investigate the association between HPV ileocolonic colonization and IBD. **Patients and Methods:** We performed a cross-sectional study involving consecutive patients with established IBD who were referred for endoscopic evaluation. During endoscopy, mucosal biopsies were obtained from the most inflamed colonic or ileal segments in cases and from the rectosigmoid region for controls. A hybrid capture assay was used to detect tissue HPV. The prevalence of HPV colonization was determined for cases and controls and was compared using Fisher's exact test. **Results:** A total of 201 patients, including 104 patients with IBD and 97 non-IBD controls, were prospectively included. Females comprised 55.5% of the study participants (58% vs. 55.2% for controls, $P = 0.94$). Fifty-seven (54.8%) patients had ulcerative colitis, and 45 (43.2%) had Crohn's disease. The mean age was 43.2 ± 18.2 years. Endoscopically active disease was documented in 56 cases (56%). HPV colonization was detected in four (4.1%) subjects in controls vs. none in the cases, ($P = 0.05$). **Conclusions:** There was no evidence of HPV ileocolonic colonization in this cohort of patients with IBD, regardless of disease activity. HPV colonization does not appear to be linked to IBD diagnosis or disease severity.

Keywords: Colonization, disease activity, human papillomavirus, inflammatory bowel disease, Saudi Arabia

Introduction

Inflammatory bowel diseases (IBD), ulcerative colitis (UC), and Crohn's disease (CD) are chronic autoimmune diseases that result in inflammation of the bowel in a relapsing-remitting pattern.^[1] The incidence of IBD has markedly increased worldwide over

recent decades, especially in developing parts of the world, such as in Asia and South America.^[2] The reasons behind the emergence of IBD remain obscure, but urbanization and changes in dietary habits have been speculated to be contributing factors.^[3] Infectious agents such as *Salmonella* and *Campylobacter* have also been considered as potential etiological factors.^[4,5]

In the past few years, research interest in the potential association between viral agents and IBD has increased.^[6] Some eukaryotic viruses have been shown to interact with IBD risk genes, potentially altering the natural course of the disease in mouse models.^[7,8] Human papillomavirus (HPV) is thought to be related

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to genital,^[9] rectal, and colonic lesions in Western countries.^[10] A recent report by Gazzaz *et al.*^[11] showed that there is no association between HPV colonization and the development of colon cancer, at least in Kingdom Saudi Arabia (KSA). Conversely, it is unclear whether HPV plays a role in the pathogenesis of IBD. A previous study by Kane *et al.*^[12] demonstrated a higher incidence of abnormal pap smears in women with IBD. As such, this observation merits further study.

In this study, we aimed to investigate the association between HPV ileocolonic colonization and IBD diagnosis and disease activity.

Materials and Methods

Following approval by the unit of biomedical ethics, we performed a cross-sectional case-control comparative study. We included all consecutive adult patients with IBD who were referred to the endoscopy unit at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, to assess endoscopic disease activity through flexible sigmoidoscopy or ileo-colonoscopy between January 2017 and December 2019. Inclusion criteria included age between 18 and 85 years, symptoms, endoscopic findings, and histological findings consistent with a diagnosis of IBD. Written informed consent for participation was obtained from all the study participants. Patients who declined to consent for enrollment in the study were excluded. Clinical and demographic data were collected prior to the procedure.

Biopsies (at least two) were collected using 8 mm forceps from the colonic mucosa of each patient recruited at the time of endoscopic evaluation. Samples were taken from the most inflamed colonic or ileal segments. Biopsies were taken from areas that were documented in previous assessments to be the most severely active segment if the entire examination was normal (inactive disease). Biopsies were sent to the laboratory for the analysis and detection of HPV.

All gastroenterologists performing the endoscopic evaluations for study participants were blinded to the results of HPV detection at the time of reporting the endoscopic procedure. Similarly, the laboratory personnel who received and processed the biopsies were blinded to the endoscopic reports.

Control selection

Consecutive patients without IBD diagnosis who underwent ileocolonoscopy for lower gastrointestinal symptoms and were found to have a normal examination were consecutively recruited if they consented to participate, as controls in a 1:1 ratio. Biopsies for HPV were obtained from the rectosigmoid colon.

HPV colonization assessment

The Digene procedure was performed to extract DNA and detect HPV in colonic or ileal tissue. The hybrid capture assay was performed according to the manufacturer's

instructions (Digene Corporation, Gaithersburg, MD, USA). Digene (HC2) technology, which detects RNA: DNA hybrids using a signal-amplified, chemiluminescent signal was used to detect HPV DNA in biopsies. Hybrid capture 2 delivers the accuracy and flexibility necessary for routine detection of HPV DNA in biopsies, which can differentiate between two HPV DNA groups, the low-risk HPV types (6, 11, 42, 43, 44), and the high/intermediate risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Accordingly, reports were either positive or negative for HPV.

Endoscopic assessment

For UC, the Mayo endoscopic scoring system was used to assess endoscopic disease activity. The presence or absence of ulcerations was used for CD.

Outcomes

The primary endpoint of this study was to estimate the prevalence of HPV bowel colonization in patients with IBD compared to controls. The main secondary outcome was the association between HPV colonization and endoscopic disease activity where possible.

Statistical analysis

The data were collected using a standard data extraction sheet and then entered into an Excel spreadsheet for further statistical analysis. Descriptive statistics were calculated for continuous variables using the means and standard deviations (SD). Frequencies and percentages were reported for categorical variables. The prevalence ratio of HPV in patients with IBD compared to controls was calculated using a standard formula. Where appropriate, we used Fisher's exact or Chi-square to compare frequencies and standard Students t-test or Mann-Whitney U test to compare means and medians, respectively. When possible, simple and multiple logistic regression analyses were used to examine the association between endoscopic disease activity and HPV colonization. STATA 11.2 (StataCorp, Texas, USA) was used for the analysis. A *P* value of <0.05, with two tails, was considered statistically significant.

Ethical considerations

The King Abdulaziz University Hospital Research Ethical Committee approved the study protocol prior to commencement (#337-16). All patients provided written informed consent at the time of recruitment, and the data were anonymized.

Results

Baseline characteristics

A total of 201 patients, including 104 IBD patients and 97 non-IBD controls were recruited and examined. Females comprised 55.5% of the cohort (55.8% vs. 55.2% for controls, *P* = 0.94). Fifty-seven (54.8%) patients had UC and 45 (43.2%)

had CD. Endoscopically active disease was documented in 56 patients (56%). Average age was 43.2 ± 18.2 years (33.1 ± 13.4 for cases vs. 54.1 ± 16.3 for controls, $P < 0.001$) [Table 1].

Study outcome

Among all included study participants, only four subjects in the control group had HPV colonization, resulting in an overall prevalence of 1.9%. HPV colonization was detected in of 4/97 (4.1%) of the controls vs. IBD cases, $P = 0.05$ [Table 2].

Discussion

The environmental trigger for the pathogenesis of IBD is speculated to be, at least in part, due to dysregulation of the gut microbiome. While much of the research has focused on bacterial pathogens, we thought that exploring the relationship between a common viral pathogen and IBD is equally important. In this case-control study, we found no relationship between the HPV ileocolonic colonization rate of 4.1% in the control group, and no cases were detected in the IBD group.

HPV is a small, circular, double-stranded, nonenveloped DNA virus. The HPV DNA genome integrates into host DNA after infection. Transmission requires the presence of microtrauma in the epithelial layer.^[13] It is one of the most common sexually transmitted viruses, with an estimated 14 million new infections

in the United States every year.^[14] HPV-associated diseases are thought to occur due to persistent infection. The median age of patients with precancerous cervical lesions in the United States is approximately 10 years older than the median age of starting sexual activity.^[15]

Although intercourse remains the most important mode of transmission, nonpenetrating sexual interactions are plausible routes for infection. Age at the first sexual encounter, number of partners, and smoking are important risk factors.^[16] Most infections are cleared after 12 months due to host immunity.^[17] Although our IBD cohort tested negative for the virus, some may have been exposed and cleared the virus. However, the effect of such exposure requires further research.

The relatively low prevalence of HPV in our study may be explained by several factors. The study was conducted in Saudi Arabia where male circumcision is a common practice. This has been shown to reduce the transmission of HPV and other sexually transmitted diseases.^[18] The socially conservative attitudes towards sex in Saudi Arabia may also have contributed to the lower prevalence of infection.^[19] This has also been shown in studies examining the prevalence of HPV among Saudi women. A prevalence of 9.8% was previously estimated in a study on cervical samples.^[20]

Although we did not find an association between HPV ileocolonic colonization and IBD, the potential association between the gut virome and IBD remains an important question. In the recent years, several studies have examined the interactions between IBD and the gut viral community. In a study examining stool samples from 60 IBD patients and 12 household controls, metagenomic sequencing of stool infiltrates was performed. Marked expansion of *Caudovirales* bacteriophages was observed in IBD samples. Furthermore, there was a significant difference in richness and the type of bacteriophage taxa identified between CD and UC patients.^[21,22] As the authors of that study suggested, advances in this field may provide a rationale for considering manipulation of the enteric virome as a novel therapeutic strategy in managing IBD.^[22]

To our knowledge, this is the first study to explore the potential role of HPV in IBD pathogenesis. The strength of our study stems from the prospective nature of the recruitment. The controls used in this study were recruited from the same hospital. Therefore, a similar socioeconomic background is expected for both cases and controls. Nonetheless, our study results should be interpreted with caution. Although the IBD and control groups had similar sex distributions, the average age was higher in the control group. This may have affected our results. In an epidemiological study examining cervical HPV in Costa Rica, older women had a second peak in prevalence.^[23] The older average age of our control group reflects the population seeking care at our endoscopy unit. Many of these patients present with age-specific conditions, such as screening for colon cancer or iron deficiency anemia.

Table 1: Baseline demographics of the study cohort

	Cases (n=104)	Control (n=97)	P
Mean age in years +- SD	33.1±13.4	54.1±16.3	<0.001
Female gender (%)	58 (55.8)	53 (55.2)	0.94
IBD subtype (%)			
UC	57 (54.8)	-	-
CD	45 (43.3)	-	-
IBDU	2 (1.9)	-	-
Family history of IBD	9 (9)	-	-
Active disease on endoscopy	56 (56)	0 (0)	<0.001
Site of biopsy			
Anal canal	1 (1)	-	-
Recto-sigmoid	33 (31.7)	97 (100)	<0.001
Descending colon	4 (3.9)	-	-
Splenic flexure	3 (2.9)	-	-
Transverse colon	2 (1.9)	-	-
Hepatic flexure	5 (4.8)	-	-
Ascending colon	13 (12.5)	-	-
Cecum	7 (6.7)	-	-
Ileocecal valve	16 (15.4)	-	-
Terminal ileum	20 (19.2)	-	-

IBD: Inflammatory bowel disease, CD: Crohn's disease, UC: Ulcerative colitis, IBDU: Inflammatory bowel disease unclassified

Table 2: Study outcomes

	Controls	Cases	Total
HPV negative	93 (95.6)	104 (100)	197 (98)
HPV positive	4 (4.1)	0 (0)	4 (2.0)
Total	97 (100)	104 (100)	201 (100)

*Fisher's exact=0.05

Another limitation is the recruitment process. Patients with IBD and controls were recruited from a single tertiary care center. Therefore, the sample in our study may not be representative of a wider population with IBD. One of the challenges in examining the association of a particular virus and an illness is controlling for other factors, such as changes in geographical regions, diet, and medication exposure. These effects could be minimized in future studies by recruiting household controls for patients with IBD.^[7]

In conclusion, this case-control study revealed no evidence of HPV colonization in the active or inactive bowel segments in our cohort of patients with IBD. HPV colonization likely does not play a role in IBD activity.

Data availability

The study data is available.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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