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Article

Women with Inflammatory Bowel Disease Are Not at Risk of Abnormal Cervical Cytology: Results of a Retrospective Study

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Abstract

Introduction: Existing data on cervical intraepithelial neoplasia (CIN) in individuals with inflammatory bowel disease (IBD) are inconsistent. The aim of this study was to evaluate the prevalence of abnormal cervical cytology among patients with IBD. **Methods:** A retrospective analysis was conducted using digital records from patients with IBD, including those receiving immunosuppressive therapy, small molecules, or biological treatments, to assess the influence of these therapies on cervical cytology results. **Results:** Data were collected from 301 patients with IBD (150 with Crohn's disease [50.3%] and 151 with ulcerative colitis [49.8%]) and 40 control patients. The mean age in the IBD group was 36.96 ± 11.92 years for Crohn's disease and 43.19 ± 14.42 years for ulcerative colitis (mean difference = -6.23 , 95% CI [-9.23 ; -3.23]), while the control group had a mean age of 36.55 ± 12.70 years. Deviations from normal findings in the most recent cytology were observed in 6 IBD patients (2.3%) compared to 8 control patients (20.0%), OR = 0.10, 95% CI [0.03; 0.34], $p < 0.001$. Deviations from normal findings in the most recent cytology or any previous cytology were identified in 25 IBD patients (9.0%) versus 9 controls patients (22.5%), OR = 0.34, 95% CI [0.14; 0.91], $p = 0.021$. No significant differences were found between the IBD subgroups regarding smoking status, current or past exposure to immunosuppressive drugs, or frequency of gynaecological examinations. The frequency of biological treatment was higher in Crohn's disease patients (88.0%) compared to those with ulcerative colitis (74.2%) (OR = 2.55, 95% CI [1.36; 5.01], $p = 0.003$). **Conclusions:** Women with IBD exhibited a lower risk of cervical dysplasia compared to healthy controls, independent of treatment type. However, rigorous malignancy surveillance, including regular cervical cytology, remains essential to facilitate early detection of dysplasia.

Keywords: IBD; cervical cytology; Crohn's disease; ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract, encompassing ulcerative colitis (UC) and Crohn's disease (CD). In recent years, the incidence of IBD has increased globally, including in Asian countries, and new medications have been introduced and implemented [1]. Evidence regarding the association between IBD and cervical intraepithelial neoplasia (CIN) remains inconclusive; however, women with IBD may be at increased risk for CIN, particularly those who are immunocompromised or who smoke [2–5]. Therefore, regular screening and preventive measures are recommended for this population [6]. Additionally,

some studies indicate that immunocompromised patients, such as those with lupus, may be more susceptible to abnormal Pap smears and HPV infection [7]. The primary aim of this study was to retrospectively assess the prevalence and risk factors for abnormal cervical cytology in patients with IBD, considering variables such as disease type and both past and current medications. The secondary objective was to evaluate the risk of abnormal cytology in IBD patients compared to healthy controls.

2. Materials and Methods

2.1. Study Population

This study is a retrospective analysis of electronic medical records evaluating cytology results in women with IBD from the Department of Gastroenterology and Internal Medicine at the National Medical Institute of the Ministry of the Interior and Administration, Warsaw. Gynaecological history and medication use, including current and past immunosuppressive agents, small molecules, and biological treatments, were assessed. Data were compared with those of healthy controls who underwent cervical screening at the Department of Obstetrics and Gynaecology, Institute of Mother and Child, Warsaw, Poland.

2.2. Statistical Analysis

Statistical analyses were conducted using R version 4.2.1 (R Core Team (2022). R: Language and environment for statistical computing by R Foundation for Statistical Computing, Vienna, Austria). Nominal variables are presented as the number of observations and the percentage of the group, while continuous variables are reported as mean \pm standard deviation (SD) or median with interquartile range (Q_1 - Q_3), depending on the distribution. Normality was assessed using the Shapiro-Wilk test and visual inspection of histograms. Group comparisons were performed using the chi-square test or Fisher exact test for nominal variables, and the t-test or Mann-Whitney U test for continuous variables, as appropriate. Mean or median differences (MD) and odds ratios (OR) with 95% confidence interval (CI) were calculated. All statistical tests were two-tailed with $\alpha = 0.05$.

3. Results

Data were collected from 301 patients with IBD (150 with Crohn's disease [50.3%] and 151 with ulcerative colitis [49.8%]) and 40 control patients. The mean age in the IBD group was 36.96 ± 11.92 years for Crohn's disease and 43.19 ± 14.42 years for ulcerative colitis (mean difference = -6.23 , 95% CI [-9.23 ; -3.23]), while the control group had a mean age of 36.55 ± 12.70 years. Significant differences were observed between the Crohn's disease and ulcerative colitis groups in both age ($p < 0.001$) and age at inflammatory bowel disease diagnosis ($p < 0.001$). The mean age was 36.96 ± 11.92 years for CD patients and 43.19 ± 14.42 years for UC patients (MD = -6.23 , 95% CI [-9.23 ; -3.23]). The mean age at IBD diagnosis was 26.32 ± 11.60 years for CD patients compared to 32.14 ± 14.24 years for UC patients (MD = -5.82 , 95% CI [-8.78 ; -2.87]). No significant difference in disease duration was identified between the groups. Additionally, no significant differences were found regarding smoking status, current or past exposure to immunosuppressive drugs, or frequency of gynaecological examinations. The current use of advanced therapies (biological agents or small molecules) was reported in 88.0% of CD patients and 74.2% of UC patients (OR = 2.55, 95% CI [1.36; 5.01], $p = 0.003$). In the past, 30.7% of CD patients and 31.1% of UC patients received advanced therapies ($p > 0.999$). Deviations from normal findings in the most recent cytology were observed in 5 CD patients (3.8%) and 1 UC patient (0.8%) (OR = 5.17, 95% CI [0.57; 247.51], $p = 0.120$). Deviations from normal findings in either the most recent or previous cytology were noted in 14 CD patients (10.3%) and 11 UC patients (7.7%) (OR = 1.34, 95% CI [0.54; 3.41], $p = 0.621$). Table 1 presents these data as well as the phenotype characteristics of CD patients according to the Montreal classification.

Table 1. Comparative Analysis of Ulcerative Colitis (UC) and Crohn's Disease (CD) Groups.

	UC		CD		MD / OR (95% CI)
	n	n=151	n	n=150	
Age [years], mean \pm SD	151	43.19 \pm 14.42	150	36.96 \pm 11.92	-6.23 (-9.23;-3.23)
Age at IBD diagnosis [years], mean \pm SD	150	32.14 \pm 14.24	149	26.32 \pm 11.60	-5.82 (-8.78;-2.87)
Disease duration [years], median (Q ₁ ; Q ₃)	150	10.00 (5.00;14.00)	149	9.00 (5.00;15.00)	-1.00 (-2.00;1.00)
Smoking status, n (%)					
Current smoker		7 (4.6)		11 (7.3)	
Former smoker	151	1 (0.7)	150	1 (0.7)	-
Never smoked		143 (94.7)		138 (92.0)	
Phenotype, n (%)					
Montreal A					
A				1 (0.7)	
A1			149	15 (10.1)	
A2				117 (78.5)	
A3				16 (10.7)	
Montreal L					
L1				5 (3.3)	
L2				31 (20.7)	
L3			150	107 (71.3)	
L4				1 (0.7)	
N/A				6 (4.0)	
Montreal B					
B1				73 (48.7)	
B2			150	30 (20.0)	
B3				34 (22.7)	
N/A				13 (8.7)	
Medication exposure, n (%)					
Current use of immunosuppressive therapy	151	43 (28.5)	150	45 (30.0)	1.08 (0.64;1.82)
AZA	151	37 (24.5)	150	40 (26.7)	1.12 (0.65;1.95)
MP / MTX	151	7 (4.6)	150	5 (3.3)	0.71 (0.17;2.67)
Previous use of immunosuppressive therapy	151	30 (19.9)	150	25 (16.7)	0.81 (0.43;1.51)
AZA	151	24 (15.9)	150	21 (14.0)	0.86 (0.43;1.71)
MP / MTX	151	1 (0.7)	150	1 (0.7)	1.01 (0.01;79.50)
Biologic agents or small molecule therapies					
Current use	151	112 (74.2)	150	132 (88.0)	2.55 (1.36;5.01)
Previous use	151	47 (31.1)	150	46 (30.7)	0.98 (0.58;1.64)
Gynaecological assessment, n (%)	146	141 (96.6)	138	137 (99.3)	4.84 (0.53;231.17)
Current cytological abnormalities, n (%)	131	1 (0.8)	130	5 (3.8)	5.17 (0.57;247.51)
Current or previous cytological abnormalities, n (%)	142	11 (7.7)	136	14 (10.3)	1.34 (0.54;3.41)

Groups were compared using the chi-square test or Fisher exact test¹ for nominal variables, and the t-test or Mann-Whitney U test² for continuous variables, as appropriate. CI – confidence interval, MD – mean / median difference for continuous variables, calculated as CD patients minus UC patients, OR – odds ratios for nominal variables, calculated as CD patients versus UC patients.

No significant association was observed between cytological deviations from the norm and the type of immunosuppressive therapy administered (AZA vs. MP/MPX). The frequency of deviations in the most recent cytology was 10.0% among AZA patients and 6.2% among MP/MPX patients (OR = 1.68, 95% CI [0.03; 19.77], p = 0.521). When considering deviations in either the most recent or any previous cytology, the respective frequencies were 10.0% and 9.9% (OR = 1.02, 95% CI [0.02; 9.62], p > 0.999; see Table 2).

Table 2. Deviation from normative values vs. the type of immunosuppressive administered.

	AZA	MP/MPX	OR (95% CI)	p
Current cytological deviation from normative values, n (%)	1 (10.0)	4 (6.2)	1.68 (0.03;19.77)	0.521
Current or historical cytological deviation from normative values, n (%)	1 (10.0)	7 (9.9)	1.02 (0.02;9.62)	>0.999

Data are presented as the number of patients (percentage of group in column). Groups were compared using the Fisher exact test. CI – confidence interval, OR – odds ratios calculated for AZA patients compared to MP/MPX patients.

An additional analysis compared the study group with a control group (n = 40). The mean age of the control group was 36.55±12.70 years (p = 0.107 compared to the study group). No significant difference in age was observed between CD/UC patients and controls (p = 0.107). Smoking was significantly more frequent among controls (17.5% vs. 6.6%, p = 0.038; see Table 3.)

Table 3. Patient characteristics.

	CD/UC		Controls		p
	n	n=301	n	n=40	
Age [years], mean ± SD	301	40.09±13.57	40	36.55±12.70	0.107
Smoking status, n (%)	301	20 (6.6)	40	7 (17.5)	0.038

Groups were compared using the chi-square test for smoking status and the t-test for age, as appropriate.

Deviations from the norm in the most recent cytology were observed in 6 patients in the CD/UC group (2.3%) compared to 8 controls patients (20.0%) (OR = 0.10, 95% CI [0.03; 0.34], p < 0.001). Deviations from the norm in either the most recent or previous cytology were identified in 25 patients in the CD/UC group (9.0%) versus 9 control patients (22.5%) (OR = 0.34, 95% CI [0.14; 0.91], p = 0.021; see Table 4).

Table 4. Comparison of deviation from normative values between the study group and the control group.

	CD/UC	Controls	OR (95% CI)	p
Current cytological deviation from normative values, n (%)	6 (2.3)	8 (20.0)	0.10 (0.03;0.34)	<0.001
Current or historical cytological deviation from normative values, n (%)	25 (9.0)	9 (22.5)	0.34 (0.14;0.91)	0.021

Data were presented as the number of patients (percentage of group in column). Groups were compared using the Fisher exact test. CI – confidence interval, OR – odds ratios calculated as UC/CD patients compared to controls.

Furthermore, univariable logistic regression analysis did not identify any significant predictors of deviation from the norm in current or past cytology (p > 0.05 for all predictor variables; see Table 5). The multivariable logistic regression model was also not significant.

Table 5. Univariable logistic regression analysis of deviations from normative cytology, current or historical.

Predictor Variables	OR	95% for OR	p
Ulcerative Colitis (UC)	0.73	0.31 to 1.67	0.459
Age [years]	1.01	0.97 to 1.04	0.762
Age at inflammatory bowel disease (IBD) diagnosis [years]	1.02	0.99 to 1.05	0.221
Disease duration [years]	0.95	0.89 to 1.02	0.174
Smoking status, No as baseline			
Current smoker	1.37	0.21 to 5.67	0.689
Former or electronic cigarette user	0.001	n/a	0.990
Montreal A, A1 as baseline			
A2	1432.00	n/a	0.994
A3	1.00	n/a	0.994
Montreal L, L1 as baseline			

L2	0.25	0.02 to 6.31	0.311
L3	0.37	0.04 to 7.76	0.402
L4	<0.001	n/a	0.997
N/A	<0.001	n/a	0.993
Montreal B, B1 as baseline			
B2	0.35	0.02 to 2.19	0.343
B3	1.89	0.50 to 6.83	0.327
N/A	2.19	0.29 to 11.34	0.381
Current immunosuppressive therapy	1.14	0.45 to 2.68	0.774
Current azathioprine (AZA) therapy	1.12	0.42 to 2.71	0.802
Current MP / MTX therapy	1.01	0.05 to 5.63	0.991
Previous immunosuppressive therapy	0.79	0.18 to 2.45	0.722
Previous azathioprine (AZA) therapy	0.84	0.19 to 2.62	0.799
Previous MP / MTX therapy	0.001	n/a	0.990
Current biologic or small molecule therapy	2.76	0.78 to 17.58	0.178
Previous biologic or small molecule therapy	0.52	0.17 to 1.34	0.208
Gynaecological control	n/a	n/a	n/a

CI – confidence interval, OR – odds ratio.

4. Discussion

This study analysed cervical cytology results among women with inflammatory bowel disease (IBD) and compared these findings to a healthy control group. Significant differences were observed in the prevalence of cytological abnormalities between IBD patients and controls. Deviations from normal cervical cytology were identified in 2.3% of the IBD group, compared to 20.0% in the control group (OR = 0.10, 95%CI [0.03; 0.34], $p < 0.001$). This marked difference suggests that IBD patients may have a lower risk of cervical cytological abnormalities than the general population, or that protective factors, such as novel therapies, may contribute to this reduced risk. Additionally, when both the most recent cytology results and past records were considered, the prevalence of deviations was 9.0% for IBD patients and 22.5% for controls (OR = 0.34, 95%CI [0.14; 0.91], $p = 0.021$).

These findings indicate that patients with IBD may have a lower incidence of cervical abnormalities compared to healthy individuals, which contrasts with some previous studies suggesting an increased risk of cervical intraepithelial neoplasia (CIN) in this population. This observation may be related to the introduction of new medications, such as biologics and small molecules, which could reduce inflammation and potentially influence women's health. Despite concerns regarding elevated CIN risk in IBD patients, particularly those receiving long-term immunosuppressive therapy, the present data are consistent with reports indicating that IBD patients are not at higher risk for abnormal CIN [4,8]. However, data from Singh et al. suggest that increased risk may be associated with the combined use of corticosteroids and immunosuppressants, which should be considered in the management of women with IBD. [8,9].

The data demonstrated that abnormalities in cervical cytology were identified more frequently among CD patients than those with UC, both in the most recent results (3.8% vs. 0.8%) and in cumulative findings over time (10.3% vs. 7.7%) [10,11]. Although these differences did not reach statistical significance, the odds ratios suggest a potential trend toward increased cytological abnormalities in CD [12,13]. This finding is consistent with the results of Rungoe et al., who reported a bidirectional association between IBD, particularly CD, and neoplastic lesions of the uterine cervix in a population-based study [14].

The association between specific immunosuppressive therapies and cytological abnormalities was also examined. Although no statistically significant associations were identified, a slightly higher proportion of cytological abnormalities was observed among azathioprine users compared to those receiving methotrexate or mercaptopurine. This observation, while not definitive, aligns with existing data indicating that thiopurine therapy may increase susceptibility to viral infections, including

persistent HPV infection, which is a key driver of cervical dysplasia. The absence of HPV status in the dataset constitutes a significant limitation for interpreting this potential association [15]. According to the current European Crohn's and Colitis Organization (ECCO) guidelines, patients receiving thiopurine treatment may have an increased risk of high-grade cervical dysplasia and cancer; therefore, these women are encouraged to participate in available screening programs [16].

These results reinforce the importance of regular monitoring and adherence to cervical cancer screening programs in women with IBD, particularly those exposed to immunosuppressive or biological agents. The ECCO guidelines underscore the necessity of routine gynaecological monitoring in this population [16,17].

Furthermore, smoking remains a significant risk factor for abnormal cervical smears, as emphasised by Lee et al. [9]. Although recent meta-analyses of high-quality, unselected population-based studies do not demonstrate a statistically significant increase in cervical cancer risk among patients with IBD, these studies do report a higher incidence of low-grade cervical lesions compared to the general population [18].

Several limitations affect this study. The retrospective design and the relatively small number of cytological abnormalities reduce the statistical power to detect robust associations in multivariate analyses. Additionally, the absence of HPV testing data represents a significant limitation, given that persistent HPV infection is a primary mechanism in cervical dysplasia development. Future prospective studies with larger cohorts, standardised HPV testing, and extended follow-up are required to better define the risk profile of IBD patients and to optimise screening strategies [5,16,19,20].

In conclusion, cervical cytological abnormalities were less frequent in women with IBD compared to healthy controls, which may be attributable to protective factors such as advanced therapies. Considering the retrospective design, limited number of cytological abnormalities, and lack of HPV data, prospective studies with larger cohorts, standardised HPV testing, and a comprehensive approach are warranted.

Institutional Review Board Statement: The study received approval from Ethical Commission Board (Nr. 106/2025).

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