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Original Article

Increased Risk of High-grade Cervical Neoplasia in Women with Inflammatory Bowel Disease: A Case-controlled Cohort Study

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Abstract

Background and Aims: Women with inflammatory bowel disease [IBD] may be at higher risk for cervical intraepithelial neoplasia [CIN]. However, data are conflicting. The aim of this study was to assess the risk of high-grade dysplasia and cancer [CIN2+] in IBD women and identify risk factors.
Methods: Clinical data from adult IBD women in a multicentre Dutch IBD prospective cohort [PSI] from 2007 onwards were linked to cervical cytology and histology records from the Dutch nationwide cytology and pathology database [PALGA], from 2000 to 2016. Patients were frequency-matched 1:4 to a general population cohort. Standardised detection rates [SDR] were calculated for CIN2+. Longitudinal data were assessed to calculate CIN2+ risk during follow-up using incidence rate ratios [IRR] and risk factors were identified in multivariable analysis.
Results: Cervical records were available from 2098 IBD women [77%] and 8379 in the matched cohort; median follow-up was 13 years. CIN2+ detection rate was higher in the IBD cohort than in the matched cohort (SDR 1.27, 95% confidence interval [CI] 1.05–1.52). Women with IBD had an increased risk of CIN2+ [IRR 1.66, 95% CI 1.21–2.25] and persistent or recurrent CIN during follow-up (odds ratio [OR] 1.89, 95% CI 1.06–3.38). Risk factors for CIN2+ in IBD women were smoking and

disease location (ileocolonic [L3] or upper gastrointestinal [GI] [L4]). CIN2+ risk was not associated with exposure to immunosuppressants.

Conclusions: Women with IBD are at increased risk for CIN2+ lesions. These results underline the importance of human papillomavirus [HPV] vaccination and adherence to cervical cancer screening guidelines in IBD women, regardless of exposure to immunosuppressants.

Key Words: Inflammatory bowel disease; cervical intraepithelial neoplasia; human papillomavirus

1. Introduction

IBD is a chronic inflammatory disease characterised by an exaggerated and self-sustained immune response in the gut and extraintestinal tissues. Over the past decades, immunomodulators and biologic agents have become available widely for the treatment of Crohn's disease [CD] and ulcerative colitis [UC].[1,2] Due to their chronic inflammatory state and frequent use of immunosuppressive medication, patients with IBD are generally considered as at risk of immunocompromise.

Cervical cancer is the fourth most common type of cancer in women worldwide and virtually all such cancers result from a persistent infection with high-risk types of the human papillomavirus [hrHPV]. The development of cancer from a persistent hrHPV infection follows a stepwise progression via two stages of squamous intraepithelial lesions [low and high SIL], equivalent to the histological diagnosis of cervical intraepithelial neoplasia [CIN] 1 and CIN 2/3, respectively.[3–5] In immunocompromised women, impaired detection of oncogenic signals or decreased immunosurveillance might accelerate the progression of CIN to invasive cancer.[6] The risk of cervical neoplasia and cancer in women with IBD has been studied previously; however, results are conflicting. Some studies reported an increased incidence of cervical abnormalities,[7–11] whereas others did not find a significantly higher incidence among women with IBD.[12–15] These studies use different outcomes; solely cervical cytology results, or cervical dysplasia, or cancer risk; and both population-based and single centre IBD cohorts were studied. In addition, most of these cohorts lack details on longitudinal follow-up and detailed information on screening behaviour, urbanisation, education level, and IBD disease characteristics such as Montreal classification. The current European Crohn's and Colitis Organisation [ECCO] guideline recommends an intensified screening approach in immunocompromised IBD women,[16] and American guidelines recommend intensified screening only in IBD women using immunosuppressive medication.[17,18] However, these recommendations are based on low level of evidence.[18]

The aim of this study was to assess the detection rate and risk of CIN and cervical cancer in women with IBD as compared with the general Dutch female population, and to assess the influence of IBD disease characteristics and exposure to immunosuppressive medication. A secondary aim of this study was to assess screening behaviour and adherence to the cervical cancer screening programme for women with IBD.

2. Materials and Methods

2.1. Data collection

A multicentre cohort study was performed within the Dutch nationwide IBD biobank registry named Parelsnoer Institute [PSI]. PSI started in 2007 as a collaborative project of the eight University Medical Centres in The Netherlands, and comprises clinical data that are collected with a standardised information model and biomaterial.[19] The following data from all women in PSI were collected: year of birth; IBD type; age at time of diagnosis; Montreal classification[20] for CD location [L] and behaviour [B] and for UC extension [E]; smoking status; education level; and exposure to immunosuppressive medication [immunomodulators and biologics]. Clinical data from all female IBD patients in the PSI cohort were linked to data on cervical cytology and histology in the Dutch nationwide network and registry of histology and cytopathology [PALGA].[21] In PALGA, individuals are identified by a code derived from birth date and the first eight letters of the surname. This code was used to link the PSI and PALGA databases. All cervical records between January 2000 and December 2016 were retrieved from the PALGA database, including indication for cytological assessment, ie, within the national screening programme or by other indications. Each woman with IBD from the PSI cohort was randomly frequency-matched by age and year of first available cervical record in PALGA to four women from the general population. To correct for the higher prevalence of cervical lesions in women living in urbanised areas,[22] the four-digit postal code from each woman was used to identify women living in low [<100 000 inhabitants] and high [>100 000 inhabitants] level urbanisation areas. After matching, women without cytological or histological result [ie, hrHPV test only] within the study period were excluded [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online].

2.2. Definitions and follow-up according to population cervical cancer screening

CIN and cervical cancer were coded according to the systemised nomenclature of medicine [SNOMED].[23] CIN1 was defined as mild dysplasia, CIN2 as moderate dysplasia, CIN3 as severe dysplasia or carcinoma in situ, and cervical cancer as invasive cervical squamous cell carcinoma or non-clear cell adenocarcinoma. CIN2+ was defined as the combination of CIN2, CIN3, and cervical cancer. Since only histological diagnoses were included as an endpoint in this study, the historical CIN classification was used instead of the two-tiered Bethesda classification for cytological screening.[24]

The number of screening episodes in a 5-year period was calculated as a proxy of screening behaviour. A screening episode started with a primary test and, if abnormal or inconclusive, this primary test was followed by a secondary test. An episode ended after 4 years following the primary test when no [adequate] follow-up test had been performed, or when follow-up had been completed according to the Dutch cervical cancer screening programme.[25] Thus, by definition, post-diagnostic follow-up smears were attributed to the same episode as the diagnosed lesion. Screening behaviour was measured for each woman by dividing the number of screening episodes by the number of 5-year follow-up periods [1: 0–5 years, 2: 5–10 years, 3: 10–15 years, 4: >15 years] during follow-up.

2.3. Statistical analysis

2.3.1. Standardised detection ratios

The primary outcome was CIN2+ detection rate, defined as the percentage of episodes resulting in a histological diagnosis of CIN2+. Standardised detection ratios [SDRs] were calculated by correcting the observed detection rates from the IBD cohort by the expected detection rates based on 5-year age categories, 5-year time periods, and urbanization level. The expected detection rates were the calculated detection rates in the matched cohort. A two-tailed *p*-value <0.05 was considered statistically significant, and 95% confidence intervals [CI] were calculated assuming a Poisson distribution.

2.3.2. Incidence rate ratios during follow-up

Follow-up for each woman started on the first available cervical record in the PALGA database [index date] and ended on December 31, 2016. Women were censored after the occurrence of the highest grade of cervical neoplasia during follow-up or end of follow-up. Incidence rates [IR] per 100 000 person-years were calculated for both the IBD cohort and the matched cohort, and incidence rate ratios [IRR] were computed. A sensitivity analysis was performed after exclusion of women with cervical neoplasia at the first screen within the study period. Kaplan-Meier survival analyses were performed for the risk of CIN1 and CIN2+ diagnoses, and statistical differences were calculated with a log-rank test. The effect of age on CIN2+ detection was visualised using attained age as time metric on the x-axis in a secondary analysis. Attained age was defined as the age at diagnosis of first occurrence of the highest CIN diagnosis during follow-up or age at end of follow-up. Cox proportional hazards regression analysis was performed to calculate hazard ratios [HRs] in order to quantify the effect of IBD on the risk of CIN2+ in the IBD cohort, adjusting for urbanisation and screening behaviour.

2.3.3. Persistent or recurrent CIN lesions

Patients with persistent or recurrent CIN or CIN2+ lesions were identified by detection of two histologically confirmed CIN or CIN2+ lesions, respectively, with a time interval of at least 18 months, since the majority of transient and productive hrHPV infections and low-grade abnormal smears regress spontaneously within this time frame.[5] Odds ratios [ORs] with 95% confidence intervals [CIs] were calculated.

2.3.4. Risk factors

Univariable and multivariable logistic regression models were performed to identify risk factors for CIN2+ within the IBD cohort. Smoking was divided in current smoking and never or former smoking if patients withdrew within 6 months before inclusion in PSI. High education level was defined as having a college or university degree. Exposure to immunosuppressive medication was defined as at least one data entry of an immunomodulator [thiopurines, methotrexate] or a biologic agent (anti-tumour necrosis factor alpha [TNFα], vedolizumab, ustekinumab) in PSI. Exposure was further subdivided in less or more than 1 year of exposure. Risk factors with a significance level of <0.20 in univariable analyses were taken into account in the multivariable analysis.

2.3.5. Coverage for cervical testing

All women living in The Netherlands receive an invitation to participate in the national cervical cancer screening programme every 5 years between ages 30 and 60 years.[26] Adherence to the national cervical cancer screening programme was defined as the proportion of women with at least one primary cytology test performed within the programme. Five-year coverage rate for cervical smear testing was defined as the percentage of women within the screening age group that had at least one cervical test in the 5 years before the reference date, either within the organised screening programme or outside the programme [ie, by indication]. For 5-year coverage rates, periods of 5 consecutive years were analysed. For example: the coverage rate of 2016 is based on tests performed in the 2012–2016 period for women born between 1952 and 1986. Our results were compared with data from the nationwide monitoring of the national cervical cancer screening programme in 2016 [for the year 2010] and 2017 [for years 2011–2016].[25] These coverage rates are calculated using the number of total women in the Dutch population aged 30 to 64 years adjusted for the risk of hysterectomy as denominator from Statistics Netherlands [CBS], and a proxy of the number of screens available in each 5-year period from PALGA as numerator for each year.[25] These data were compared with the coverage rates in the IBD cohort for significant differences using two-tailed chi square tests, and *p*-value <0.05 was considered statistically significant.

2.4. Ethical approval

All patients in the PSI-IBD dataset provided written informed consent. The scientific boards of the Dutch IBD biobank and PALGA approved the study. The ethics committees of all eight participating university medical centres granted permission to link study objects from the PSI cohort to their own cervical records collected in PALGA under strict privacy procedures. Consent by women for the use of their data stored in PALGA is implicit according to the Dutch Ethical Code of reuse of data and PALGA's own privacy policy.

3. Results

3.1. Study population

A total of 2098 IBD women [median age at inclusion 42 years] were included. The matched cohort comprised 8392 women. Median follow-up was 13 years in both cohorts [range 0–16 years]. The IBD cohort comprised 1382 [66%] patients with CD and 716 [34%] patients with UC, IBD-unclassified [IBD-U], or IBD-indeterminate [IBD-I]. Within the IBD cohort, 554 [26.4%] women were smokers and 461 [34.6%] had a high education level. A total of 1030 [49%] patients were exposed to immunomodulators and 707 [34%] to biologic agents [Table 1]. CD patients were more often smokers [33.8% vs 15.0%, *p* <0.001] and were more often exposed to immunosuppresssants [immunomodulators 53.0 % vs 41.7%, biologics 42.2% vs 16.9%, *p* <0.001] than UC patients [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online]. The vast majority of patients exposed to biologics had been exposed to anti-TNFα agents. Seven patients [1%] had been only exposed to other biologics [vedolizumab, ustekinumab]. Number of screening episodes in a 5-year period was significantly higher in the IBD cohort than in the matched cohort: 30% in the IBD cohort had more than one screening episode in a 5-year period, compared with 20.9% in the matched cohort [*p* <0.001] [Table 1].

3.2. Standardised detection rates

Over the whole study period, significantly more CIN2+ lesions were detected in the IBD cohort compared with the matched cohort [SDR 1.27, 95% CI 1.05–1.52]. This difference was mainly due to more

Table 1. Patient demographics from PSI for IBD women and screening behaviour for IBD and matched women.

		IBD women *N* [%]
Total number of women		**2098**
Diagnosis	CD	1382 [66]
	UC, IBD-U or IBD-I	716 [34]
Age at IBD diagnosis	<25 years	**772 [37]**
	≥25 years	**1321 [63]**
	N/A	**5 [0]**
Smoking status[a]	Never/>6 months	1466 [70]
	Current/<6 months	554 [26]
	N/A	78 [4]
Education level[b]	Low	1352 [64]
	High	700 [33]
	N/A	46 [2]
Medication exposure[c]		
Immunomodulator	No	1068 [51]
	<1 year	237 [11]
	>1 year	793 [38]
Biologics	No	1391 [66]
	<1 year	227 [11]
	>1 year	480 [23]
Crohn's disease		
Montreal L	L1	256 [19]
	L2	277 [20]
	L3	530 [38]
	L4 or L1-3 + L4	155 [11]
	N/A	164 [12]
Montreal B	B1	495 [36]
	B2	191 [14]
	B3	192 [14]
	B1-3 + p	347 [25]
	N/A	157 [11]
Ulcerative colitis		
Montreal E	E1	56 [8]
	E2	238 [33]
	E3	346 [48]
	N/A	76 [11]

		IBD women	**Matched women**	***p*-value**
		N [%]	*N* [%]	
Total number of women		**2098**	**8379**	
Total number of screening episodes		**6654**	**23344**	
Number of screening episodes per woman in a 5 year period				
	1	1451 [69]	6595 [79]	<0.001
	>1	567 [27]	1646 [20]	
	>2	80 [4]	138 [1]	
Urbanization level	**>100000**	632 [30]	2516 [30]	0.931
	<100000	1466 [70]	5863 [70]	

Bold numbers: statistically different.

IBD, inflammatory bowel disease; PSI, Parelsnoer Institute; *N*, number; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD-unclassified; IBD-I, IBD-indeterminate; N/A, not available; L, location; B, behaviour; p, perianal disease; E, extent.

[a]Smoking was defined as current smoker or former smokers who quitted within 6 months prior to inclusion in PSI.

[b]High education level was defined as having a college or university degree.

[c]Exposure to medication use was defined as at least one data entry of an immunomodulator [thiopurines, methotrexate] or a biologic [anti-TNFα, vedolizumab] in the database.

CIN2+ lesions in the 35 to 39 years of age group [Table 2]. No differences were observed in detection rates of CIN1 lesions [SDR 0.95, 95% CI 0.68–1.37], CIN3 lesions [SDR 1.21, 95% CI 0.94–1.55], or cervical cancer [SDR 0.30, 95% CI 0.03–1.08] [Table 2; Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online]. Significantly more CIN2+ lesions were detected in the 2006–2010 time period. Urbanisation was not a strong influencing factor for detecting CIN2+ [Table 2].

3.2.1. Incidence rate of CIN2+ during longitudinal follow-up

The risk of progression of a normal smear towards CIN2+ was higher in IBD women than in women from the matched cohort.

Table 2. Standardised detection ratios of cervical intraepithelial lesions and cervical cancer for IBD women by age, time period, and urbanisation, follow-up period 2000–2016 as compared with matched cohort.

	No. prim. tests[b]	CIN1[a]				CIN2+ [a]			
		Obs[b]	Exp[b]	SDR[b]	95% CI[c]	Obs [b]	Exp[b]	SDR[b]	95% CI[c]
Overall detection rate[b]	6654	35	35.6	0.98	0.68–1.37	**118**	**93.2**	**1.27**	**1.05–1.52**
Screening age									
<29	348	7	7.3	0.96	0.38–1.98	12	16.7	0.72	0.37–1.26
29–34	1457	11	6.4	1.72	0.86–3.08	40	35.0	1.14	0.82–1.56
35–39	1068	3	7.1	0.42	0.09–1.24	23	12.8	**1.80**	**1.14–2.70**
40–44	1136	9	6.0	1.50	0.68–2.85	17	10.2	1.67	0.97–2.67
45–49	1060	2	4.4	0.45	0.05–1.64	14	8.5	1.65	0.90–2.76
50–54	706	0	2.0			6	4.2	1.42	0.52–3.11
55–59	594	3	1.7	1.77	0.36–5.16	5	2.4	2.08	0.68–4.86
≥60	285	0	0			1	0.9	1.11	0.03–6.19
Total	6654	35	35.0	1.00	0.70–1.39	118	90.7	**1.30**	**1.08–1.56**
Time period									
2000–2005	2157	5	9.3	0.54	0.17–1.26	31	25.5	1.22	0.83–1.73
2006–2010	2006	15	11.1	1.35	0.76–2.23	38	25.7	**1.48**	**1.05–2.03**
2011–2016	2491	15	15.4	0.97	0.54–1.61	49	37.1	1.32	0.98–1.75
Total	6654	35	35.8	0.98	0.68–1.36	118	89.5	**1.26**	**1.04–1.51**
Urbanization									
High level	1962	9	13.3	0.68	0.31–1.29	43	33.4	1.29	0.93–1.73
Low level	4692	26	22.4	1.16	0.76–1.70	75	61.0	1.23	0.97–1.54
Total	6654	35	35.8	0.98	0.68–1.36	118	94.4	**1.25**	**1.04–1.50**

Bold numbers: statistically different.

IBD, inflammatory bowel disease; Obs., detection rate in the IBD cohort; Exp., detection rate in the age and year of screening matched cohort.

[a]CIN: cervical intraepithelial neoplasia; CIN1: mild dysplasia; CIN2: moderate dysplasia; CIN3: severe dysplasia or carcinoma in situ; cervical cancer: invasive cervical squamous cell carcinoma and non-clear cell adenocarcinoma; CIN2+: CIN2 or higher grade of neoplasia

[b]No. of prim tests: number of primary screening tests; detection rate is the percentage of episodes starting with a primary cytology or histology screen test resulting in a histological diagnosis of CIN or cervical cancer. SDR: standardised detection ratio: defined as observed detection rate in IBD cohort compared with the expected detection rate.

. [c]95% CI: 95% confidence interval based on a Poisson distribution.

Table 3. Observed number of CIN and cervical cancer cases, person-years, incidence rates per 1000 person-years, and incidence rate ratios for women with IBD compared with matched women from general population excluding women with an abnormal primary screen.

	Person-years	Obs-No	IR [95% CI]	IRR [95% CI]
CIN1				
IBD women	23726	18	0.76 [0.45–1.20]	0.95 [0.57–1.60]
Matched women	92956	74	0.80 [0.63–1.01]	
CIN2				
IBD women	23235	26	1.12 [0.73–1.64]	**1.83 [1.15–2.91]**
Matched women	93167	57	0.61 [0.46–0.79]	
CIN3				
IBD women	23228	28	1.21 [0.80–1.74]	**1.56 [1.01–2.41]**
Matched women	93030	72	0.77 [0.61–0.97]	
Cervical cancer				
IBD women	23383	2	0.09 [0.01–0.28]	1.14 [0.16–5.13]
Matched women	93381	7	0.07 [0.03–0.15]	
CIN2+				
IBD women	23070	56	2.43 [1.83–3.15]	**1.66 [1.21–2.25]**
Matched women	92726	136	1.47 [1.23–1.74]	

Bold numbers: statistically different.

OBS-No, observed number; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIN2+, CIN2, 3, or cervical cancer; IBD, inflammatory bowel disease; No. number; IR incidence rate; IRR, incidence rate ratio.

After exclusion of women with an abnormal smear at first available cytopathology record, during the total of 24 159 person years, 109 IBD women were diagnosed with CIN2+, versus 320 matched women during 97 163 person years. The risk of developing a CIN2+ lesion was significantly higher in the IBD cohort; incidence rate ratio [IRR] for CIN2+ for IBD women was 1.66 [95% CI 1.21–2.25] compared with the matched cohort. This was due to an increased risk of CIN2 [IRR 1.83, 95% CI 1.15–2.91] and CIN3 [IRR 1.56,

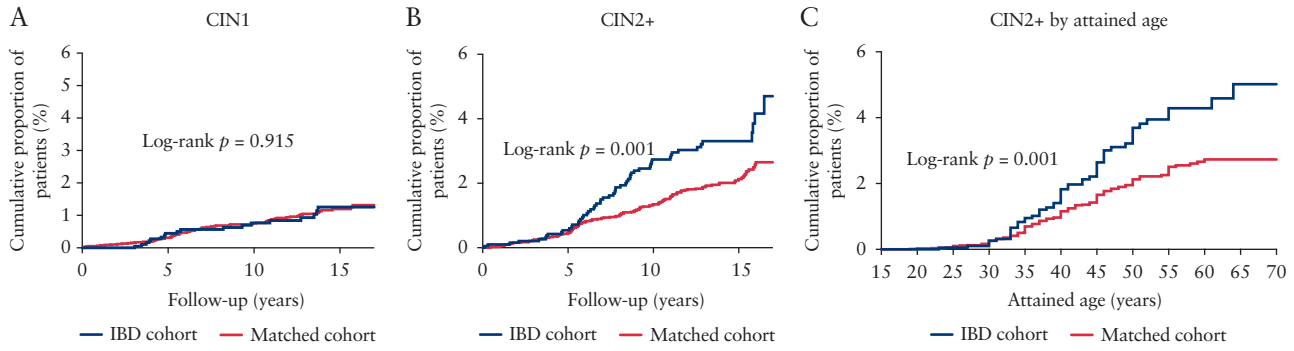

Figure 1. [A-C] Kaplan-Meier estimates for CIN1 and CIN2+ lesions as worst diagnosis for the IBD cohort and matched cohort by years of follow-up and attained age excluding women with a primary abnormal screen. A: Proportion of women with CIN1 as highest grade of dysplasia during follow-up. B: Proportion of women with CIN2+ as highest grade of dysplasia during follow-up. C: Proportion of women with CIN2+ as highest grade of dysplasia by attained age. Attained age is defined as the age at diagnosis of CIN2+ or age at end of follow-up. CIN = cervical intraepithelial neoplasia. CIN2+ = CIN2, CIN3 or cervical cancer. IBD = inflammatory bowel disease.

Table 4. Univariable and multivariable hazard ratios for different risk factors for CIN2+ over time in the study population excluding women with a primary abnormal screen.

	CIN2+			
	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Case				
No IBD	1.00	Ref	1.00	Ref
IBD	1.66	1.21–2.26	1.46	1.07–2.00
Urbanisation				
Low level	1.00	Ref	1.00	Ref
High level	1.08	0.79–1.47	1.11	0.81–1.51
Screening episodes in a 5-year period				
1 episode	1.00	Ref	1.00	Ref
1–2 episodes	1.74	1.27–2.38	1.68	1.23–2.30
>2 episodes	5.84	3.55–9.60	5.39	3.26–8.92

CIN, cervical intraepithelial neoplasia; CIN2+, CIN2, CIN 3, or cervical cancer; IBD, inflammatory bowel disease; HR, hazard ratio; CI, confidence interval; ref, reference value.

95% CI 1.01–2.41], not cervical cancer [IRR 1.14, 95% CI 0.16–5.13]. No difference was observed in women developing CIN1 as highest grade of cervical neoplasia [IRR 0.95, 95% CI 0.57–1.60] [Table 3, Figure 1A and B]. The cumulative incidence for CIN2+ as highest grade of cervical neoplasia during follow-up increased with age [Figure 1C]. Including women with prevalent lesions at the first available cytopathology record resulted in lower IRRs but still a significantly higher CIN2+ risk for IBD women [IRR 1.37, 95% CI 1.10–1.70] [Supplementary Figure 2A–C; Supplementary Table 3, available as Supplementary data at *ECCO-JCC* online]. After correcting for screening behaviour and urbanisation in a Cox proportional hazards model, CIN2+ risk in IBD women was also increased [HR 1.46, 95% CI 1.07–2.00] [Table 4].

3.2.2. Persistent or recurrent CIN lesions

In the IBD cohort, an increased risk of persistent or recurrent CIN lesions was observed. A total of 17 [0.8%] IBD women had persistent CIN lesions during follow-up, compared with 36 [0.4%] in the matched cohort [OR 1.89, 95% CI 1.06–3.38, p = 0.028]. A total of 11 [0.5%] IBD women had persistent CIN2+ lesions during follow-up, compared with 15 [0.2%] in the matched cohort [OR 2.94, 95% CI 1.08–6.1, p =0.004].

3.2.3. Risk factors for CIN2+ in the IBD cohort

In multivariable analysis, CIN2+ risk was associated with ileocolonic [L3] and/or upper gastrointestinal [GI] [L4] location in women with CD [adjusted OR 1.84, 95% CI 1.05–3.24], smoking [adjusted OR 3.20, 95% CI 1.90–5.40], and more than one or two screening episodes within a 5-year period [adjusted OR 2.00, 95% CI 1.16–3.44, and 5.02, 95% CI 1.89–13.35, respectively]. Exposure to immunomodulators or biologic agents was not associated with CIN2+ risk [Table 5].

3.3. Coverage for cervical testing

IBD women participated significantly less often in the national cervical cancer screening programme than women from the general population in 2010 and from 2012 to 2016 [Table 6]. Cervical screening outside the national programme was significantly more often performed in the IBD cohort than in the general population from 2011 to 2016 [Table 6]. In 2012, the 5-year coverage rate for total cervical screen testing was significantly higher in the IBD cohort than in the general population [82.7% vs 77.3%, p <0.001], but declined to lower rates after that year. The observed decline is most importantly explained by a decline in the number of IBD patients tested by indication [outside the national screening programme], which declined from 16.8% in the period from 2008 to 2012 to 9.7% from 2012 to 2016. In addition, the adherence rate of IBD patients to the screening programme declined slightly over the years from 2010 to 2016 [66.6% to 64.5%], a trend similar to that in the general population [69.6% to 67.4%].

4. Discussion

Results from our case-controlled cohort study show a higher detection rate of CIN2+ lesions in IBD women than in matched women from the general population. According to current guidelines, these lesions require treatment in most cases.[27] The difference in CIN2+ detection rate was highest in IBD women between the ages of 35 and 39 years. The detection rate of cervical cancer was not significantly different between the two groups, probably due to the sample size. Even after correcting for their screening behaviour, IBD women were

Table 5. Univariable and multivariable odds ratios for different risk factors for a CIN2+ diagnosis in 2000–2016 for women with IBD.

IBD cohort	CIN2+		CIN2+	
	Univariable		Multivariable	
	OR	95% CI	OR	95% CI
Screening episodes in a 5-year period				
1 episode	1.00	Ref	1.00	Ref
>1 episode	**1.64**	**1.08–2.48**	**2.00**	**1.16–3.44**
>2 episodes	**3.26**	**1.60–6.62**	**5.02**	**1.89–13.35**
Urbanisation				
Low level	1.00	Ref	1.00	
High level	**1.43**	**0.96–2.13**	1.41	0.81–2.44
Disease type				
UC	1.00	Ref	1.00	1.00
CD	**1.39**	**0.90–2.13**	0.96	0.61–1.53
Age at diagnosis				
≥25 years	1.00	Ref	1.00	Ref
<25 years	**1.60**	**1.09–2.36**	1.54	0.91–2.59
CD behaviour				
B1	1.00	Ref		
B2, B3 or all p	0.79	0.49–1.26		
CD location				
L1 or L2	1.00	Ref	1.00	Ref
L3 or all L4	**1.92**	**1.14–3.24**	**1.84**	**1.05–3.24**
UC extent				
E1 or E2	1.00	Ref		
E3	0.67	0.31–1.45		
Education level				
Low	1.00	Ref	1.00	Ref
High	**0.77**	**0.51–1.15**	0.63	0.37–1.09
Smoking status				
No	1.00	Ref	1.00	Ref
Yes	**2.59**	**1.74–3.86**	**3.20**	**1.90–5.40**
Exposure to immunomodulators				
No	1.00	Ref	1.00	Ref
<1 year	**0.42**	**0.18–0.99**	0.37	0.13–1.09
>1 year	0.89	0.59–1.33	0.91	0.54–1.55
Exposure to biologics				
No	1.00	Ref		
<1 year	0.72	0.36–1.47		
>1 year	0.96	0.61–1.54		

Bold numbers: statistically different.

CIN, cervical intraepithelial neoplasia; CIN2+, CIN2 or higher grade of neoplasia; IBD, inflammatory bowel disease; OR, odds ratio, CI, confidence interval; CD, Crohn's disease; B, behaviour; L, location; UC, ulcerative colitis, E, extent; p, perianal disease; Ref, reference value.

still at increased risk of CIN2 and CIN3 lesions during follow-up. Also, after excluding all women with prevalent CIN lesions at the first screen, the risk for CIN2+ remained increased. Risk factors associated with CIN2+ in IBD women were smoking and ileocolonic [L3] and/or upper GI [L4] location. Exposure to immunosuppressive medication was not identified as a risk factor.

Our study supports previous observations that IBD women are at increased risk of high-grade CIN.[7–11] In addition to previous data, we have shown that during longitudinal follow-up, women with IBD show a higher rate of progression from normal smears to CIN2+ and more often have persistent or recurrent CIN lesions than women in the general population. A higher rate of persistence of an hrHPV infection might explain both findings. Transient and productive HrHPV infections and cytological low-grade abnormal smears, histologically mostly classified as CIN1, are highly prevalent and are known to clear or regress spontaneously in many patients, especially in young women.[5,27] However, as opposed to transient or productive hrHPV infections, it is persistent or transforming infections that are essential in carcinogenesis.[5,28,29]

In our IBD cohort, ileocolonic [L3] or upper GI [L4] location in women with Crohn's disease and smoking were risk factors for CIN2+ in multivariable analysis, whereas exposure to immunosuppressants was not associated with CIN2+. Onset of IBD before the age of 25 was a risk factor in univariable analysis only. Although younger age at IBD onset has already been identified as a risk factor,[9] increased risk by disease location in Crohn's disease is a novel finding. Both young age at IBD onset and L3 and/or L4 disease location may be associated with a severe disease expression which might increase risk for CIN lesions, since chronic systemic inflammation can impair innate and adaptive cellular immune responses and may therefore result in a decreased clearance of hrHPV.[30]

Studies on immunosuppressive medication as a risk factor for CIN and cervical cancer in IBD patients display discordant results. Some studies have previously found a significant association,[8–11,15,31] but others have not.[7,13,14] In our study, exposure to immunomodulators and biologics was solely studied as: no exposure, less than 1 year, or more than 1 year. It would have been interesting to study the relation between timing of exposure to immunosuppressive medication and occurrence of CIN. Unfortunately, data on immunosuppressive medication was heterogeneously collected and data collected for the scope of this study did not allow looking into this in more detail. Further studies are needed to scrutinise the exact role for immunosuppressive medication in cervical neoplasia risk, split on duration of exposure, age of start, combination therapy, and use of corticosteroids.

Smoking was strongly associated with CIN2+ in our IBD cohort. This is consistent with previous findings, both in the general population[32,33] and among women with IBD.[8,14] In our IBD cohort, the risk of CIN2+ in active smokers was higher than the estimated 2-fold risk of CIN2+ in ever smokers in the general population,[33–35] suggesting a combined effect of IBD and exposure to cigarette smoke.

IBD women had a higher screening frequency than women from the general population, as shown by the number of screening episodes within a 5-year period. This might be explained by the fact that IBD women are referred to a gynaecologist more often or are more aware of the increased risk and request intensified screening. This more frequent screening behaviour could easily have influenced the incidence rate of CIN2+ in our study population. Undeniably, an increased number of cervical smears per individual increases the chance of detecting abnormalities. However, the hazard ratio for acquiring CIN2+ was still higher in the IBD cohort than in the matched cohort after correcting for this important confounder in multivariable analysis.

This is one of the few studies reporting on screening behaviour and adherence to a national cervical cancer screening programme among IBD patients.[13,14,36,37] Current ECCO guidelines advice is to improve the rate of adherence in IBD women, based on a study by Long *et al.*, showing a suboptimal rate of cervical smear testing in IBD patients.[16,36] Our study underlines this advice, especially since we observed a decline in screening rate over the past years, due to less frequent testing both within and outside the national screening programme.

Prevention of cervical neoplasia requires two important interventions. First, vaccination for HPV in all females up to 26 years of

Table 6. Five-year coverage rate of cervical smear testing from 2010 to 2016 in percentages for IBD women compared with women from general population.*

	Total cervical screen testing			National cervical cancer screening programme			Screens on indication [outside screening programme][a]		
	IBD	General population[c]	*p*-value[b]	IBD	General population[c]	*p*-value[b]	IBD	General population[c]	*p*-value[b]
2010	76.7%	79.0%	**0.015**	66.6%	69.6%	**0.005**	10.1%	9.4%	0.312
2011	77.5%	77.8%	0.747	66.7%	68.4%	0.118	10.8%	9.4%	**0.042**
2012	82.7%	77.3%	**<0.001**	65.9%	67.9%	**0.056**	16.8%	9.4%	**<0.001**
2013	75.2%	77.2%	**0.043**	63.8%	67.9%	**<0.001**	10.4%	9.2%	**<0.001**
2014	76.7%	76.7%	0.965	65.4%	67.7%	**0.029**	11.3%	8.9%	**<0.001**
2015	74.8%	76.3%	0.122	64.3%	67.7%	**0.001**	10.5%	8.6%	**0.002**
2016	74.2%	75.9%	0.496	64.5%	67.4%	**0.005**	9.7%	8.4%	**0.035**

Bold numbers: statistically different.

IBD: inflammatory bowel disease.

[a]Opportunistic, indicative or secondary tests only.

[b]Chi-square tests were used to test for significant differences and two-tailed *p*-value <0.05 was considered statistically significant.

[c]The coverage rates in Monitors 2016 [for year 2010] and 2017 [for years 2011 to 2016] are calculated using a denominator that is calculated with the following data: all women aged 30 to 64 years in the Dutch population, as reported by CBS on 1 January of each year. The year corresponds with the year at the end of the 5-year coverage period. The population is adjusted per 5-year age group for the risk of hysterectomy.

age, preferably before sexual activity, is recommended for all women as primary prevention strategy.[16] Normal immunogenic response to HPV vaccination has been reported in patients on immunosuppressive medication.[38] HPV vaccination was only introduced in The Netherlands in 2008 for girls turning 13 years. Since this vaccinated population has not reached the screening age of 30 years during the study period, reported associations are in all probability unaffected by this vaccination programme. Data regarding efficacy in terms of decreasing incidence of cervical dysplasia in immunocompromised individuals are expected in the following years. Given the burden of other HPV-related [penile, oral, and anal] cancers in men, vaccination in young males is also highly worth considering.[39,40] Next to that, secondary prevention by means of screening for premalignant cervical lesions within in a national cervical cancer screening programme is advised. ECCO recommends that IBD women follow European guidelines on cervical cancer screening for the general population[16,41] and an intensified screening approach for immunocompromised women. American guidelines also suggest intensified screening for IBD women using immunosuppressive medication, but not for all women with IBD.[17,18] This risk stratification is not fully substantiated by our data. A decision on an intensified screening programme in IBD women requires careful consideration of burden to patients, costs, and benefits. Based on available evidence, we recommend encouraging all IBD women to adhere to national cervical cancer screening programmes, and increased awareness among physicians is warranted.

Despite the novel longitudinal data presented in this multicentre cohort study, a few limitations of this study warrant consideration. Since our IBD cohort comprises only patients from tertiary referral centres, reflecting a population with more severe disease,[42] results of this study might not be completely generalisable to all IBD patients. Also, we did not have data on several other possible confounders such as sexual behaviour and oral contraceptive use.[43] It has been shown that a higher proportion of women with inflammatory bowel disease have sexual dysfunction compared with matched controls.[44] Since sexual activity is a strong risk factor for CIN,[32] it might be hypothesised that the association with IBD is even stronger. Unfortunately, we were not able to draw conclusions on hrHPV status, since these data were only collected limitedly. Also, there was not enough power to identify risk factors for persistent or recurrent lesions, in particular exposure to immunosuppressive medication. Furthermore, we were not able to collect data from PALGA before the year 2000. Some women might have had a history of CIN before the index date of our follow-up period, which may have put them at higher risk of a subsequent lesion. Last, a group of women in the IBD cohort might have had a CIN2+ diagnosis before their IBD diagnosis. We did not exclude these women, based on the fact that IBD is a chronic disease that often starts years before the actual date of diagnosis. Moreover, since higher rates of cervical neoplasia were detected even to up to 10 years before IBD diagnosis,[9] we believe that including these women in the cohort was justified.

In conclusion, this study demonstrates that IBD is a risk factor for high-grade cervical neoplasia, especially in women who smoke or who have a severe CD phenotype. Close surveillance of low-grade lesions and treatment of high-grade CIN is warranted, given that persistent lesions were more prevalent in women with IBD, possibly reflecting a decreased clearance of hrHPV. Vaccination for HPV and adherence to cervical cancer screening programmes should be strongly encouraged in all IBD women, regardless of immunosuppressant use.

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of Interest

RG, JK, FJvK, AS, CA, IdK, and JM: have no competing interests to report. ACdeV: has participated in advisory board and/or received financial compensation from the following companies: Janssen, Takeda, Abbvie and Tramedico. CJvdW: has served on advisory boards and/or received financial compensation from the following companies: MSD, FALK Benelux, Abbott Laboratories, Mundipharma Pharmaceuticals, Janssen, Takeda, and Ferring during the past 3 years. GD: has unrestricted research grants from Abbvie and Takeda; fees for advisory boards for Mundipharma and Pharmacosmos; received speaker's fees from Abbvie, Takeda, and Janssen Pharmaceuticals. FH has served on advisory boards, or as speaker, or consultant for Abbvie,

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Author Contributions

Study concept and design: JK, AV, FK, JW. Data acquisition: RG, JK, CA, IdK, AS. Analysis and interpretation of data: RG, CA, JK, AV, IdK. Drafting of the manuscript: RG, JK. Critical revision of the manuscript for important intellectual content: all authors. All authors approved the final version of the manuscript for publication.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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