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Cumulative exposure to immunomodulators increases risk of cervical neoplasia in women with inflammatory bowel disease

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Summary

Background: Women with inflammatory bowel disease (IBD) are at increased risk of high-grade cervical intraepithelial neoplasia and cervical cancer (CIN2+).

Aim: To assess the association between cumulative exposure to immunomodulators (IM) and biologic agents (BIO) for IBD and CIN2+.

Methods: Adult women diagnosed with IBD before December 31st 2016 in the Dutch IBD biobank with available cervical records in the nationwide cytopathology database were identified. CIN2+ incidence rates in IM (i.e. thiopurines, methotrexate, tacrolimus and cyclosporine) and BIO (anti-tumour necrosis factor, vedolizumab and ustekinumab) exposed patients were compared to unexposed patients and risk

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factors were assessed. Cumulative exposure to immunosuppressive drugs was evaluated in extended time-dependent Cox-regression models.

Results: The study cohort comprised 1981 women with IBD, 99 (5%) developed CIN2+ during median follow-up of 17.2 years [IQR 14.6]. In total, 1305 (66%) women were exposed to immunosuppressive drugs (IM 58%, BIO 40%, IM and BIO 33%). CIN2+ risk increased per year exposure to IM (HR 1.16, 95% CI 1.08–1.25). No association between cumulative exposure to BIO or both BIO and IM and CIN2+ was observed. In multivariate analysis, smoking (HR 2.73, 95%CI 1.77–4.37) and 5-yearly screening frequency (HR 1.74, 95% CI 1.33–2.27) were also risk factors for CIN2+ detection.

Conclusion: Cumulative exposure to IM is associated with increased risk of CIN2+ in women with IBD. In addition to active counselling of IBD women to participate in cervical screening programs, further assessment of the benefit of intensified screening of women with IBD on long-term IM exposure is warranted.

1 | INTRODUCTION

There is growing evidence that cervical neoplasia risk is increased in women with inflammatory bowel disease (IBD).[1–6] Infection with high-risk human papilloma virus (hrHPV) precedes virtually all cases of cervical intraepithelial lesions (CIN) and cervical cancer. HPV not only initiates carcinogenesis but is probably also crucial for progression along the cascade of (pre)neoplastic lesions towards cervical cancer.[7–9] The carcinogenic potential of HPV infection is determined by HPV-type, persistence of HPV infection and epigenetic alterations.[5,10] It is hypothesized that women with IBD who are exposed to HPV are at an increased risk of cervical neoplasia due to their chronic inflammatory state and frequent use of immunosuppressive drugs (IS).[5] Firstly, the (iatrogenic) immunocompromised state could result in persistence of HPV infection.[8,11] Secondly, immunosuppressive drugs may be involved in induction of carcinogenesis and accelerated progression through pre-neoplastic stages due to impaired detection of oncogenic signals (immunosurveillance).[8,12,13] The basis of the increased risk of cervical neoplasia in IBD has not been fully elucidated and the role of IS in this association is not well understood.[14–21] Recently, two studies have reported an association between the risk of cervical neoplasia and treatment with anti-tumour-necrosis factor-alpha (anti-TNF), thiopurines and 5-aminosalicylic acid (5-ASA) for Crohn's disease.[17,22] In contrast, another study reported no association between the use of immunosuppressive therapy in women with IBD and incidence of cervical neoplasia.[19] Although the incidence rate for high-grade CIN (CIN2+) lesions was significantly higher in women with IBD as compared to women from the background population (incidence rate ratio 1.66), no association between exposure to immunomodulators and biologics and the increased risk of high-grade CIN in women with IBD was detected in our previous study.[6] Currently, detailed longitudinal data on IS exposure are lacking in literature to elucidate whether IBD medication increases the risk of cervical neoplasia. Therefore, the aim of the current study was to assess the association of cumulative exposure to IS (immunomodulators (IM) and/or biologic agents (BIO)) and the development of moderate to high-grade cervical dysplasia and cervical cancer (CIN2+) in a Dutch cohort of women with IBD.

2 | METHODS

2.1 | Data resources

A cohort study using data from the Dutch IBD biobank and the Dutch nationwide network and registry of histology and cytopathology (PALGA) was performed. *The Dutch IBD biobank registry named Parelsnoer Institute (PSI)* is a collaborative biobanking project of all eight University Medical Centers (UMCs, tertiary referrals centres) in the Netherlands, founded in 2007, in which data and biomaterial of adult IBD patients are prospectively and routinely collected. Every adult patient with an established diagnosis of IBD according to the Lennard-Jones criteria,[23] treated in a UMC is eligible for inclusion. Diagnosis of IBD was confirmed by endoscopy, radiology and/or histology. After written informed consent, data are collected using a standardised information model containing 225 IBD-related items. These items include patient demographics, disease characteristics, radiographic imaging results, laboratory and endoscopy results, previous and current treatment characteristics. Thereafter, data are prospectively collected during patient visits.[24] The *Dutch nationwide network and registry of histology and cytopathology (PALGA)* database stores all cervical histological and cytological results and has a nationwide coverage of all pathology labs from 1991 onwards.[25] Since 1996, all Dutch women aged 30–60 are invited for cervical smear examination every 5 years within the national cervical cancer screening program. Women are identified by pseudonyms, based on the first eight letters of their surname and date of birth. The PALGA database also contains comprehensive information on the indication for assessment of cytology and/or histology (i.e. primary smear

within the screening programme, opportunistic screening, follow-up screening test in case of abnormal smear according to the Dutch guidelines or smear of inadequate quality).[26] Coding of diagnostic information is based on the Systematised Nomenclature of Medicine (SNOMED) as published by the College of American Pathologists in 1982.[27] Pseudonymised personal data from the PSI database were linked to the PALGA database with a unique identifier for each participant.

2.2 | Study population and data collection

Female patients of 17 years and older with IBD diagnosed before 31st of December 2016 identified in the PSI database with available cervical cytological and/or histological data in the PALGA database between 1st of January 2000 and 31st of 2016 were reviewed for eligibility. For all included IBD patients, detailed information on CIN, cancer and screening history was retrieved from the PALGA database. Patient demographics and clinical IBD data including disease characteristics, smoking habits, history of malignancy, previous and current drug exposure were collected from the PSI database.

2.3 | Clinical outcome

The primary outcome of interest was the diagnosis CIN2+ in women with IBD exposed to IS (IM and/or BIO) compared to non-exposed women with IBD. Cervical intraepithelial neoplasia (CIN) was defined as all histological neoplastic lesions in the cervix categorised as mild dysplasia (CIN1), moderate dysplasia (CIN2) and severe dysplasia or carcinoma in situ (CIN3), including glandular neoplasia (such as adenocarcinoma in situ (AIS)). Cervical cancer was classified into invasive squamous cell carcinoma and invasive adenocarcinoma. CIN2+ comprises CIN2, CIN3/AIS and cervical cancer. Women with a history of any cancer except for non-melanoma skin cancer before the first recorded cervical smear were excluded for this study. Women were also excluded if IBD was diagnosed after the last recorded cervical smear or after diagnosis of high-grade cervical dysplasia or cervical cancer (i.e. CIN2+). Follow-up started from the date of IBD diagnosis (index date) and continued until the first of the following study endpoints: first occurrence of highest grade of CIN2+ diagnosis, hysterectomy or December 31st, 2016. A proxy for screening behaviour was calculated for each woman by dividing the number of screening episodes by the number of 5-year follow-up periods starting from first available cervical record to end of follow-up as described in detail in a previous article by our study group.[6]

2.3.1 | Impact of immunosuppressive drugs

The immunosuppressive drugs evaluated were IM (azathioprine, mercaptopurine, thioguanine, methotrexate, tacrolimus and cyclosporine) and BIO (infliximab, adalimumab, certolizumab, golimumab, vedolizumab and ustekinumab). Patients with any documented use of IM or BIO following IBD diagnosis were considered as being 'exposed' to immunosuppressive drugs. Patients were considered as being exposed to both IM and BIO when treated with at least one IM and at least one BIO during follow-up. Patients exposed to both IM and BIO simultaneously were considered as exposed to combination therapy. Corticosteroids were not included in the analysis due to various administration types and heterogeneity in data collection.

2.4 | Statistical analysis

Baseline demographics were expressed as median and interquartile ranges (IQR) or total count (n) and proportion (%). Chi-square tests and Mann–Whitney U tests were used to compare demographic, disease-related and treatment-related factors, between IS-exposed and non-exposed patients, including disease characteristics, drug exposure, smoking and screening behaviour. Also population density was taken into account to correct for higher prevalence of cervical lesions in women living in urbanised areas, based on postal codes retrieved from the PALGA database. Postal code areas with <100,000 inhabitants were considered low-density (rural) areas and postal code areas with ≥100,000 inhabitants were considered high-density areas (urban). We calculated incidence rates (IR) with 95% confidence intervals (95% CI) of CIN2+ lesions in IS-exposed versus non-exposed patients during follow-up expressed as number of cases per 1000 person years.

To assess the association between IS exposure and CIN2+ risk Cox-regression analyses were performed. First we assessed covariates for CIN2+. Age at diagnosis, IBD type (CD or UC/IBDU), smoking behaviour and screening behaviour were considered potential confounders. These covariates were defined at cohort entry and included in the multivariable analyses as time-fixed variables (model 1). In the second analysis, the model was extended with the effects of cumulative IM exposure, BIO exposure and exposure to combination therapy (simultaneous exposure to IM and BIO) (combination therapy) on CIN2+ risk, assessed as time-dependent variables in extended multivariable Cox-regression models. For this analysis, all IS-exposed patients with known start and stop dates and non-exposed patients were included. Baseline was set at the date of IBD diagnosis and drug exposure was assumed to start on the first documented use in the PSI database. Cumulative exposure to IM and BIO were calculated separately, as 0.5 exposure years increase for each 6 months of active exposure, until CIN2+ or end of follow-up (model 2). Hazard ratios were calculated per additional year of exposure to immunomodulators, biologics and combination therapy. We investigated the shape of the associations between cumulative drug exposure and the risk for CIN2+ using natural cubic splines. All analyses were conducted using IBM SPSS Statistics version 25.1.0 (Armonk, NY, USA: IBM) and R version 4.0.5. Statistical significance was defined as a p-value <0.05, all alternative hypotheses were 2-sided.

2.4.1 | Sensitivity analyses

CIN2+ is unlikely to develop instantly after exposure to IS. To reflect an expected latency period between drug exposure and onset of an effect, we performed sensitivity analyses in which the cumulative drug exposure was lagged. Considering the uncertainty in the optimal length of the latency time window, exposure time was varied using lag periods of 6 and 12 months after the initial documented use. Secondly, we investigated robustness with regards to the assumptions about the unknown duration of exposure. While patients with unknown exposure duration were excluded from the main analyses (model 1 and 2), in these sensitivity analyses we assumed these patients to be either non-exposed or continuously exposed during the entire period.

2.5 | Ethics statement

All patients in the PSI dataset provided written informed consent. The scientific boards of the Parelsnoer Institute and PALGA approved the study. The ethics committees of all eight participating UMCs 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 (pseudonymised) 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 characteristics

In the PSI database, 2796 adult female patients were identified diagnosed with IBD before 31st of December 2016. A total of 834 patients were excluded, in the vast majority of cases due to unavailability of cervical data in the PALGA database (Figure 1). The study cohort included 1981 women with IBD; 1318 (67%) were diagnosed with CD and 663 women (33%) were diagnosed with UC or IBD-unclassified. The median follow-up time was 17.2 years [IQR 14.6 years]. Characteristics of the study population, overall and stratified by exposure to immunosuppressive treatment, are summarised in Table 1. During follow-up, 1305 patients (67%) were exposed to treatment with an IS (IM and/or a BIO). Among these patients, 1155 (89%) received IM treatment, 795 (61%) received treatment with BIO and 645 (49%) received treatment with IM and BIO either subsequently or simultaneously. Four hundred forty-nine patients (25%) were only exposed to IM and 143 patients (8%) were only exposed to BIO. At initiation of a second line of IS treatment, 58% of patients had been previously exposed to IM monotherapy and 24% to BIO monotherapy. Concomitant therapy with IM and BIO was the initial treatment in 18% of patients. Details on exposure to different IBD drug types are summarised in Table S1. Women exposed to IS were significantly younger at IBD diagnosis than unexposed women ($p < 0.001$). Also, exposed women had more ileocolonic disease ($p < 0.001$), upper GI disease ($p = 0.035$), perianal involvement ($p < 0.001$), extensive colitis ($p = 0.003$) and a history of smoking ($p = 0.008$) than non-exposed women (Table 1).

3.2 | Risk factors for CIN2+

Overall, 99 women with IBD developed CIN2+ occurred between 1st January 2000 and 31st December 2016 (IR 2.73 per 1000 PY, 95% CI 2.23–3.31). Median age at diagnosis of CIN2+ was 36.6 years [IQR 14.2]. Among patients with CIN2+, 44 developed CIN2 lesions (44%), 53 developed CIN3 lesions (54%) and 2 patients developed cervical cancer (2%). Patients with CIN2+ lesions more often had a history of smoking than patients without CIN2+ (71% vs. 59%, $p = 0.006$). Patients with CIN2+ had a significantly higher number of screening episodes per 5 years than patients without CIN2+ (1.3 vs.

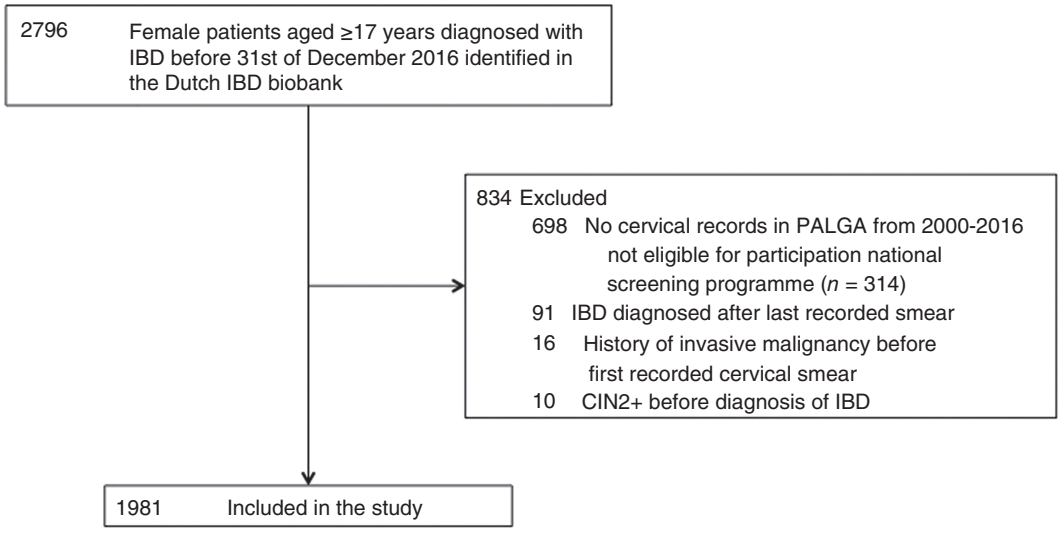

FIGURE 1 Flowchart of the study population.

TABLE 1 Patient characteristics, overall and by exposure group.

	Overall	Non-exposed to IS	Exposed to IS	
	n = 1981	*n* = 676	*n* = 1305	*p*-value
Age at inclusion in PSI (years), median [IQR]	42.0 [18.0]	46.5 [17.0]	40.0 [16.0]	0.152
Age at diagnosis (years), median [IQR]	27.8 [16.1]	30.0 [18.0]	27.0 [15.5]	<0.001
Diagnosis, *n* (%)				
Crohn's disease	1318 (67)	349 (52)	970 (74)	<0.001
UC/IBDU/IBDI	663 (33)	328 (48)	335 (26)	<0.001
CD—Montreal age at diagnosis, *n* (%)				
A1 <17 years	101 (8)	29 (8)	72 (7)	0.239
A2 17–40 years	964 (73)	245 (71)	719 (74)	<0.001
A3 >40 years	253 (19)	74 (21)	179 (19)	0.080
CD—Montreal localization, *n* (%)	*n* = 1184	*n* = 303	*n* = 885	
L1 Ileal	248 (21)	67 (23)	181 (20)	0.847
L2 Colonic	321 (27)	100 (33)	221 (25)	0.043
L3 Ileocolonic	572 (48)	123 (41)	449 (51)	0.001
L4 involvement	41 (4)	7 (2)	34 (4)	
Isolated upper GI disease	13 (1)	3 (1)	10 (1)	0.035
Perianal involvement	346 (29)	72 (24)	274 (31)	<0.001
Isolated perianal disease	30 (3)	6 (2)	24 (3)	
CD—Montreal disease behaviour, *n* (%)	*n* = 1172	*n* = 306	*n* = 860	
B1 Non-stricturing, non-penetrating	590 (50)	168 (55)	417 (48)	0.048
B2 Stricturing	239 (121)	54 (18)	185 (22)	0.144
B3 Penetrating	343 (29)	84 (27)	258 (30)	0.383
UC—Montreal disease extent	*n* = 574	*n* = 283	*n* = 291	
E1 Proctitis	43 (8)	31 (11)	12 (4)	0.002
E2 Left-sided	208 (36)	110 (39)	98 (34)	0.152
E3 Extensive colitis	323 (56)	142 (50)	181 (62)	0.003
Smoking history	*n* = 1906	*n* = 653	*n* = 1233	
Never	728 (38)	277 (42)	445 (36)	0.008
Current	522 (27)	140 (22)	417 (34)	<0.001
Former (>6 months abstinent)	656 (35)	236 (36)	371 (30)	0.002
IBD medication				
Exposure to any IBD drug	1683 (85)	378 (56)	1305 (100)	–
5ASA	1119 (57)	338 (50)	784 (60)	<0.001
Corticosteroids	1006 (51)	196 (29)	810 (62)	<0.001
IS	1305 (66)	0 (0)	1305 (100)	–
IM	1155 (58)	0 (0)	1155 (89)	–
BIO	795 (40)	0 (0)	795 (61)	–
IM and BIO	645 (33)	0 (0)	645 (49)	–
Duration therapy, years, median [IQR]				
IM (*n* = 1002)	3.5 [5.5]			
BIO (*n* = 696)	3.0 [4.5]			
Combination therapy	0.7 [2.4]			
Screening episodes/5 years	1.12 (0.54)	1.11 (0.53)	1.14 (0.55)	0.669

Note: Combination therapy defined as simultaneous exposure to IM and BIO. Data are reported as median with interquartile range.

Abbreviations: 5-ASA, 5-Aminosalicylic acid; BIO biologic agents; CD, Crohn's Disease; IBDI, IBD-indeterminate; IBDU, IBD-unclassified; IM immunomodulator; IQR, interquartile range; IS, immunosuppressive drugs (IM or BIO); UC, ulcerative colitis.

1.1, $p < 0.0001$). Also, CIN2+ patients were younger (45.2 years vs. 49.1 years, $p = 0.012$) than patients without CIN2+ (Table 2).

3.3 | Impact of immunosuppressive treatment

Sixty-eight cases of CIN2+ occurred in IBD patients that were exposed to IS (IR 3.03, 95% CI 2.37–3.82) and 31 cases in patients never exposed to IS (IR 2.23, 95% CI 1.57–3.18) (Table 3). In this analysis, women with IBD that were ever exposed to IS did not have a higher risk of CIN2+ than never-exposed women with IBD.

For the analysis of cumulative immunosuppressive exposure, 1831/1981 (92.4%) women with IBD with a detailed database record of medication use were included. Among them, 686 women (37.5%) remained non-exposed to IS, 1002 (54.7%) women were exposed to IM with a median exposure time of 3.5 years [IQR 5.5] and 696 (38.0%) women were exposed to BIO with a median exposure time of 3.0 years [IQR 4.5]. Exposure to both IM and BIO was documented in 553 patients (30.2%); 225 (12.3%) received these drugs sequentially and 328 (17.9%) patients received combination treatment at some point (Table S2). In patients exposed to both IM and BIO, exposure to combination treatment accounted for only 6.7% of the exposure time, with a median exposure time of 0.7 years [IQR 2.4].

Using natural cubic splines we ruled out a non-linear effect of cumulative exposure and the risk for CIN2+, hence we report from these models assuming a linear effect (Figure 2). In women with IBD, smoking and more intensive screening behaviour were covariates associated with CIN2+ (HR 2.84 and HR 1.80, respectively, Table 4, Model 1). When assessing drug exposure as time-dependent variables using Model 2, cumulative exposure to IM was associated with CIN2+. The hazard ratio associated with a 1 year longer exposure to IM was 1.16 (95% CI 1.08–1.25 $p < 0.0001$, Table 4, Model 2). There was no evidence for a significant association between cumulative exposure to BIO and CIN2+, nor for exposure to combination therapy and CIN2+. The hazard ratio of cumulative exposure to IM, BIO and combination therapy on CIN2+ risk based on model 2 is illustrated in Figure 3. Consistent with model 1, smoking during the course of IBD was strongly associated with the risk of CIN2+ lesions in all models (HR 2.73, 95% CI 1.77–4.37, $p < 0.001$, Table 4, Model 2) as was more intensive screening behaviour (HR 1.74, 95% CI 1.33–2.27, $p < 0.001$).

Sensitivity analyses considering lag time of 6 and 12 months did not meaningfully change the results (Table S3). When the 150 women with unknown exposure duration were included as being either fully non-exposed or continuously exposed, the results did not meaningfully change (Table S4).

4 | DISCUSSION

In this real-world cohort study, the association between exposure to IS and CIN2+ risk in a large cohort of women with IBD with a median follow-up of 17.2 years was assessed. Although exposure to IS, expressed as a dichotomous variable (ever versus never), did not impact CIN2+ development, we demonstrated that each year of exposure to IM (HR 1.15 per treatment year) was associated with an increased risk of CIN2+ development. Cumulative exposure to BIO and combination therapy was not associated with CIN2+. Lag time did not meaningfully change these results. Furthermore, smoking

TABLE 2 Factors associated with CIN2+ lesions.

	CIN2+ ($n = 99$)	no CIN2+ (1882)	p-value
Crohn's Disease	74 (75)	1244 (66)	0.08
Mean age at diagnosis (SD)	27.8 (10)	30.8 (12)	0.062
Mean age (SD)	45.3 (10)	49.1 (12)	0.010
Perianal involvement	22 (22)	324 (17)	0.201
Montreal E3	12 (12)	311 (17)	0.97
Montreal B2/B3	28 (28)	554 (30)	0.576
Montreal L3	41 (41)	530 (28)	0.085
Urban population density	33 (34)	561 (30)	0.456
Exposure IM ($n = 1155$)	57 (57)	1098 (58)	0.880
Exposure BIO ($n = 795$)	41 (42)	754 (40)	0.789
Exposure to any IBD drug ($n = 1662$)	82 (88)	1601 (85)	0.543
Unexposed to any IBD drug ($n = 124$)	2 (2)	122 (7)	0.074
Exposure to IS ($n = 1305$)	68 (68)	1237 (65)	0.545
Exposure to IM and BIO ($n = 645$)	30 (31)	615 (33)	0.623
Current smoking	46 (47)	476 (25)	<0.0001
Ever smoking	70 (71)	1108 (59)	0.029
Screening episodes/5 years	1.3 (0.8)	1.1 (0.5)	<0.0001

Abbreviations: BIO biologic agents; IBD, inflammatory bowel disease; IM immunomodulators; IS, immunosuppressive drugs; SD, standard deviation.

TABLE 3 Incidence of cervical neoplasia according to treatment group.

	Overall ($n = 1981$) (36,279 PY)		Unexposed to IS (13,876 PY)		Exposed to IS (22,403 PY)	
	No of events	IR per 1000PY (95% CI)	No of events	IR per 1000PY (95% CI)	No of events	IR per 1000PY (95% CI)
All CIN2+	99	2.73 (2.23–3.31)	31	2.23 (1.57–3.18)	68	3.03 (2.37–3.82)
Cervical cancer	2	0.06 (0.01–0.22)	1	0.07 (0.01–0.51)	1	0.04 (0.01–0.32)
CIN3	53	1.46 (1.11–1.91)	20	1.44 (0.93–2.23)	33	1.47 (1.05–2.01)
CIN2	44	1.18 (0.89–1.61)	10	0.72 (0.39–1.33)	34	1.52 (1.07–2.10)

Abbreviations: CI confidence interval; IR, incidence rate; PY, person years.

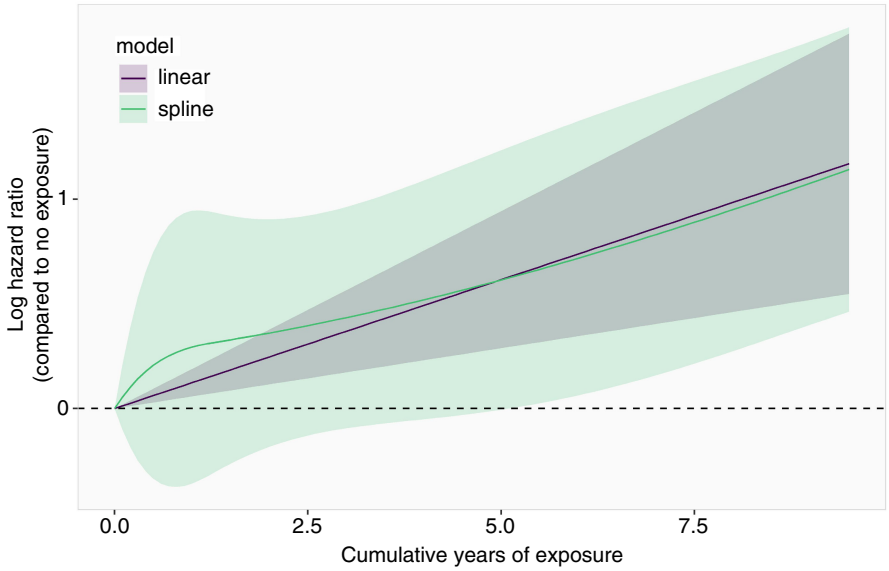

FIGURE 2 Association between cumulative exposure to immunomodulators and the risk for CIN2+ using natural cubic splines. A non-linear effect was ruled out in this model.

and more intensive screening behaviour were also risk factors for CIN2+.

We previously showed that the IR for CIN2+ lesions is higher in women with IBD than in women from the background population (IR 2.43 per 1000 person years vs. IR 1.47 per 1000 person years), however, overall exposure to IS was not a risk factor in this population. Several other studies have investigated the role of IS use and cervical abnormalities, and so far data have been conflicting. A meta-analysis reported a significant association between exposure to IS and cervical dysplasia and cancer compared to women in the general population.[2] However, data should be interpreted with caution since most studies have reported solely on *ever* versus *never* exposure only, disease severity was not taken into account and both high-grade cervical neoplasia and cervical cancer were used as outcome measures separately in the involved studies. Also, a compromised immune system due to illness of IBD itself instead of medication use might have influenced the outcome, as described in studies including women with systemic diseases.[21,28] Furthermore, most previous studies did not assess the exposure to IS as time-dependent variables, nor did consider lag time effects of drug exposure on the risk of cervical neoplasia. An increased risk of CIN2+ in IM and anti-TNF monotherapy users has been described in some available studies and mainly in CD patients; however, definition of exposure is varied among published data.[16,17,22] Cumulative exposure has only been previously investigated by a Danish study and consistent with our findings, an eight percent increase in incidence rate ratio for CIN2+ risk per redeemed azathioprine prescription in CD patients compared to matched controls was observed.[17]

In the same study, there was an increased risk of high-grade cervical dysplasia in CD patients ever exposed to anti-TNF, but an increased risk in cumulative exposure expressed by redeemed prescriptions was not identified.[17] Literature on the effect of exposure to both IM and BIO on cervical abnormalities is very limited. Marehbian et al evaluated adverse events related to drug exposure in CD patients and reported a HR of 2.34 for cervical dysplasia or HPV in CD patients exposed to both IM and BIO during follow-up compared to the general population. Compared to non-exposed CD patients, the HR was 1.52, which was lower than patients only exposed to IM (HR 1.81), but higher than patients only exposed to anti-TNF (HR 1.25).[16]

Immunity against hrHPV infection is an important process to eliminate the virus and it involves both cellular innate and adaptive

TABLE 4 Time-dependent multivariate model for CIN2+.

	Model 1			Model 2		
	HR	95% CI	*p*	HR	95% CI	*p*
Age at diagnosis (years)	1.00	0.98–1.02	0.648	1.00	0.98–1.02	0.694
Current smoking (vs. never/past)	2.84	1.82–4.46	<0.001	2.80	1.79–4.39	<0.0001
Crohn's Disease (vs. UC/IBDU)	0.91	0.55–1.51	0.912	0.95	0.57–1.58	0.840
Screening behaviour/5 years	1.80	1.37–2.36	<0.001	1.74	1.33–2.27	<0.0001
Immunomodulator exposure (cumulative)[a]				1.13	1.05–1.20	<0.0001
Biologic exposure (cumulative)[b]				1.08	0.94–1.25	0.260
Combination therapy exposure (cumulative)[c]				0.73	0.51–1.05	0.091

Abbreviations: CI confidence interval; HR, hazard ratio.

[a]Per each additional year of immunomodulator exposure.

[b]Per each additional year of biologic exposure.

[c]Per each additional year of exposure to combination therapy with an immunomodulator combined with a biologic agent. Model 1: all variables were time-fixed variables. Model 2: cumulative exposure to immunomodulators and cumulative exposure to biologic agents were assessed as time-dependent; hazard ratios, therefore, compared time after exposure with time never exposed.

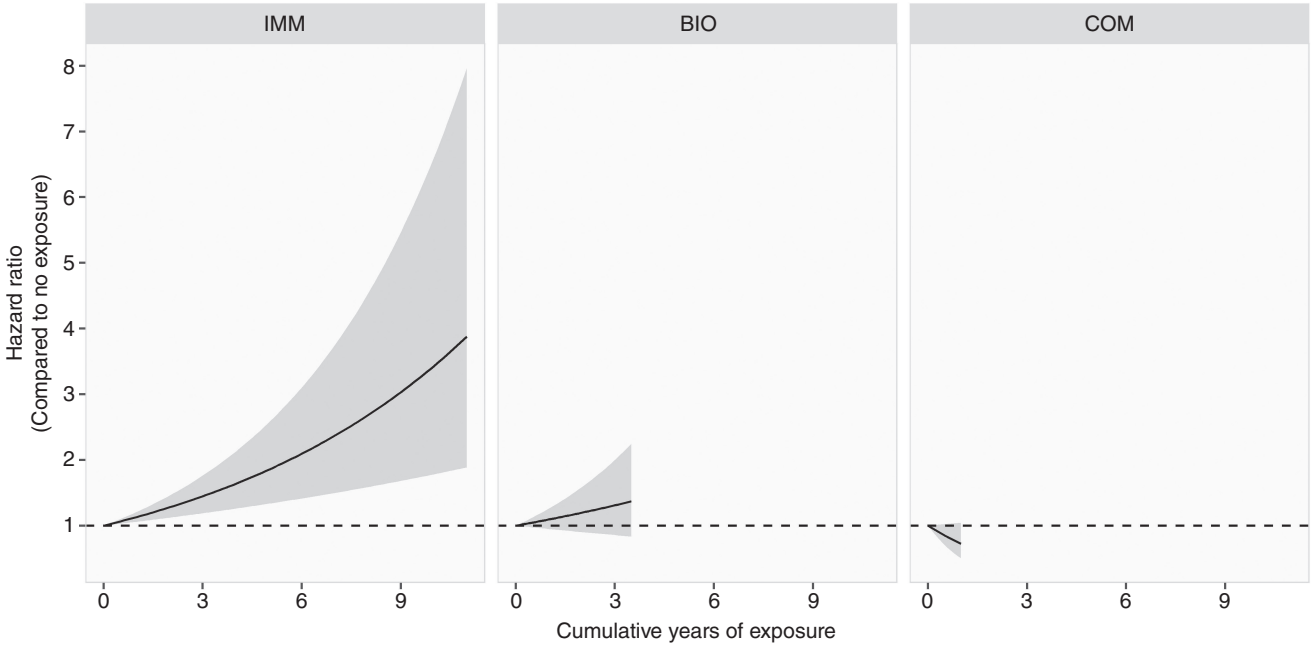

FIGURE 3 Cumulative exposure of immunosuppressive drugs and CIN2+ risk. The hazard ratio of cumulative exposure to immunomodulators (IM), biologic agents (BIO) and combination therapy (COM) compared with no exposure on CIN2+ risk using time-dependent variables (model 2). The cumulative exposure to combination therapy was very limited in our cohort.

immune responses. The mode of action of thiopurines in IBD is immunosuppression and mainly involves interference with a cellular inflammation checkpoint Rac1.[29] As a consequence, infections are well-known complications of thiopurine use and mainly the risk of viral infections (Epstein Barr virus, HPV) seems to be increased.[30] Also, thiopurines have a mutagenic potential and several mutations in tumour suppressor genes have been described upon exposure.[31] In this study we show that for each year exposure to IM the risk of CIN2+ slightly increases, supporting that IM can play a perpetuating role on the cascade from persistent HPV infection towards cervical cancer.

The malignancy promoting potential of anti-TNF agents is less clear since both anti-tumour effects and pro-tumorigenic effects have been described. TNF can either stimulate apoptosis and necrosis of tumours via the caspase pathway but also facilitate proliferation of neoplastic cells via the NF-kB pathway.[32] Previous studies have demonstrated that differences in genetic susceptibility and immune responses, including polymorphisms of TNF, are related to the incidence of HPV related lesions and cancer.[33,34] The role of exposure to anti-TNF is less clear. An important remark that should be noted is that IM have been prescribed for IBD for over 50 years, whereas BIO have been integrated in the therapeutic arsenal approximately

20 years ago. Cumulative exposure and the proportion of patients exposed to BIO were much lower in this cohort than the cumulative exposure and proportion of patients exposed to IM. CIN2 and CIN3 lesions can develop within 3–5 years following an hrHPV infection, whereas further progression to invasive cervical cancer can take up to 20–30 years.[7,35,36] Therefore, the effect of BIO exposure and CIN2+ development could have been underestimated.

Smoking was again the strongest risk factor for CIN2+ in our study population[6] and this important risk factor has been demonstrated in previous studies.[19,22] Next to HPV vaccination, counselling women with IBD to stop smoking may, therefore, be one the most important measures to lower the risk for CIN2+. Also, it should be noted that women with more intensive screening behaviour as shown by the average number of screening episodes per 5 year had a higher risk for CIN2+. We did not find evidence for more intensive screening in IS exposure, as screening behaviour was comparable in women with IBD that were exposed to immunosuppressive drugs and women that remained unexposed. Also, after correcting screening behaviour, cumulative exposure to immunomodulators remained a significant risk factor for CIN2+ in our study population.

The major strengths of our study are its national scale, large study population, long-term follow-up and data from prospectively maintained registers on IS exposure and cervical neoplasia. The time-dependent approach to exposure classification avoided the introduction of immortal time bias (person-time accumulated between date of diagnosis and date of treatment initiation) that can potentially lead to overestimation of the treatment effect.[34] Also, we were able to correct for important confounders such as smoking, screening behaviour and IBD-related factors such as age at diagnosis. Several limitations have to be noted. First, insufficient information on hrHPV status, corticosteroid and oral contraceptive use, pregnancies and sexual behaviour could have prevented identification and control of confounding factors. Second, possible confounding by disease severity and therapy response is a concern as these guide treatment regimens. Third, women without cervical records were not included in this analysis and this may have affected our results. Fourth, a 5-year screening interval, as recommended by Dutch national guidelines, might be considered long. Care providers might already perform stricter screening in this population based on extrapolation of data from other populations with long-term immunocompromised state or other national guidelines (USA, Germany).[37] More frequent screening increases the chance of detecting abnormalities, whereas less frequent screening could lead to detection of more severe CIN abnormalities that would have been detected in an earlier stage with more frequent screening. Last, heterogeneity of drug regimen and sample size hamper evaluation of the association of combination therapy with IM and BIO and CIN2+ risk. No significant effect in patients exposed combination therapy was observed, suggesting that CIN2+ risk is higher in patients exposed to only IM than in patients exposed to combination therapy. However, only 6.7% of exposure time in the patients exposed to both IM and BIO during follow accounted for exposure to combination treatment. This limited exposure time is probably explained by top-down treatment, in which patients are treated with combination treatment with anti-TNF and thiopurines for 6–12 months, and monotherapy with anti-TNF or thiopurines thereafter. Since the exposure time to combination therapy was limited in our cohort, we believe no definitive conclusion can be drawn on its effect on CIN2+ development.

Since HPV vaccination was only introduced in the Netherlands in 2008 for girls turning 13 years, our outcomes are likely unaffected by this vaccination program. Future large prospective studies will be necessary to assess the risk of cervical neoplasia associated with long-term exposure to biologic agents and the effect of HPV vaccination.

Guidelines for cervical screening in IBD vary significantly due to conflicting definitions of the immunocompromised status (as compared to patients suffering from HIV) and conflicting evidence concerning cervical abnormalities.[38] The finding of the association between cumulative exposure and CIN2+ may have implications on the strategies for cervical cancer prevention. Vaccination for HPV should be strongly encouraged in all women with IBD ideally in a pre-treatment setting. Normal immunogenic response to HPV vaccination has been reported in patients on immunosuppressive medication; therefore, vaccination should not be retained in women on active medical treatment.[39] Also, adherence to national cervical cancer screening programs should be strongly encouraged in all women with IBD, especially since testing rates in women with IBD remain low.[6,20,40] The findings of this study support an intensified screening strategy in women with IBD on long-term immunomodulator treatment. However, the optimal interval of cervical screening has not been proven in our study, so no recommendation on screening interval can be provided based on these results. We advocate further investigation, in particular to assess cost-effectiveness of intensified screening before implementation of a recommendation on a shorter interval in the international IBD guidelines. This study should further alert physicians on the risks of long-term IM therapy in IBD patients and should encourage them to consider stopping medication in patients with long-term remission. Lastly, although this cohort only included women, IBD is also a risk factor for other HPV-associated neoplasia such as head, neck and anogenital cancers.[41–43] Future studies should investigate the impact of immunosuppressive exposure in other HPV-associated cancers and the efficacy of HPV vaccination in male IBD patients.

In conclusion, long-term exposure to IM is associated with an increased risk of CIN2+ in women with IBD. Physicians should stress the importance of HPV vaccination and cervical cancer screening for all women with IBD. These results imply that further investigation is required to assess the benefit of intensified screening in women with IBD on long-term immunomodulator treatment.

AUTHOR CONTRIBUTIONS

J. E. Kreijne: Conceptualization (equal); data curation (equal); formal analysis (lead); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); writing – original draft (lead); writing – review and editing (equal). **R. L. Goetgebuer:** Conceptualization (equal); data curation (lead); formal

analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); validation (lead); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **N. S. Erler:** Conceptualization (equal); formal analysis (equal); methodology (equal); validation (equal); visualization (supporting); writing – review and editing (equal). **N. K. De Boer:** Conceptualization (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **A. G. Siebers:** Data curation (equal); writing – review and editing (supporting). **G. Dijkstra:** Conceptualization (supporting); resources (supporting); writing – review and editing (supporting). **F. A. van Kemenade:** Conceptualization (supporting); methodology (supporting); writing – review and editing (supporting). **F. Hoentjen:** Writing – review and editing (supporting). **B. Oldenburg:** Conceptualization (supporting); writing – review and editing (supporting). **A. E. van der Meulen-de Jong:** Writing – review and editing (supporting). **C. I. J. Ponsioen:** Writing – review and editing (supporting). **M. J. Pierik:** Writing – review and editing (supporting). **C. J. van der Woude:** Conceptualization (equal); funding acquisition (lead); methodology (supporting); project administration (supporting); supervision (supporting); writing – review and editing (supporting). **A. C. De Vries:** Conceptualization (equal); formal analysis (supporting); investigation (supporting); methodology (equal); supervision (lead); writing – review and editing (lead). All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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