Increased risk of genital warts in inflammatory bowel disease

A Danish registry-based cohort study (1996-2018)

Elmahdi, Rahma; Thomsen, Louise T.; Iversen, Aske T.; Allin, Kristine H.; Kjær, Susanne K.; Jess, Tine

Published in:
United European Gastroenterology Journal

DOI (link to publication from Publisher):
10.1002/ueg2.12217

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Received: 2 December 2021 | Accepted: 15 February 2022

DOI: 10.1002/ueg2.12217

ORIGINAL ARTICLE

ueg journal WILEY

Increased risk of genital warts in inflammatory bowel disease: A Danish registry-based cohort study (1996–2018)

Rahma Elmahdi[1] | Louise T. Thomsen[2] | Aske T. Iversen[1] | Kristine H. Allin[1,3] | Susanne K. Kjær[2,4] | Tine Jess[1,3]

[1]PREDICT, Center for Molecular Prediction of Inflammatory Bowel Disease, Faculty of Medicine, Aalborg University, Copenhagen, Denmark

[2]Unit of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark

[3]Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark

[4]Department of Gynecology, Rigshospitalet University Hospital, Copenhagen, Denmark

Correspondence

Rahma Elmahdi, PREDICT Center for Molecular Prediction of Inflammatory Bowel Disease, Faculty of Medicine, Aalborg University, A.C. Meyers Vænge 15, Copenhagen 2450-S0056, Denmark.
Email: rahmae@dcm.aau.dk

Funding information

Danmarks Grundforskningsfond, Grant/Award Number: DNRF148; Helsefonden, Grant/Award Number: RF2272

Abstract

Background: Patients with inflammatory bowel disease (IBD) are at increased risk of human papillomavirus (HPV) related cancers such as anal squamous cell carcinoma. However, risk of non-malignant HPV infection has never been systematically studied in IBD. This study aims to assess the risk of genital warts (GW) in IBD patients.

Methods: Using the Danish nationwide registries, we identified 49,163 patients with IBD between 1996 and 2018 and matched them to 491,665 individuals from the general population by age, sex, and HPV immunisation. Cumulative incidence rates for GW in IBD and non-IBD patients were calculated by age. Cox proportional regression analysis was used to calculate hazard ratios (HR) for GW in IBD compared to matched population and in Crohn's disease (CD) compared to ulcerative colitis (UC). We undertook subgroup analysis for risk of GW by sex, year of IBD diagnosis, contraceptive exposure and IBD treatment exposure.

Results: The fully adjusted HR for GW in IBD patients compared to the matched non-IBD population was 1.33 (95% CI: 1.19–1.49) and 1.13 (95% CI: 1.01, 1.27) in CD as compared to UC. This increased risk was particularly observed in female (HR: 1.54, 95% CI: 1.33–1.79) over male (HR: 1.14, 95% CI: 0.97–1.34) IBD patients, but was also found across all periods of diagnosis with IBD, regardless of contraceptive treatment exposure, and also seen in IBD patients who had never been exposed to immunosuppressive treatment (HR: 1.33, 95% CI: 1.19–1.49).

Conclusion: In this nationwide, population-representative cohort study, we observed a 33% increased risk of GW in patients with IBD compared to the matched population and a 13% increased risk of GW in CD compared with UC. This risk was particularly increased in female over male IBD patients and seen independent of IBD treatment exposure.

KEYWORDS

cohort study, Crohn's disease, genital warts, inflammatory bowel disease, thiopurine, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD), commonly diagnosed as either Crohn's disease (CD) or ulcerative colitis (UC), is an immune mediated inflammatory disorder of the mucosa of the gastrointestinal tract that affects millions of people worldwide and over 50,000 people in Denmark alone.[1] IBD patients suffer from a range of symptoms due to inflammation, which can affect any part of the bowel and vary in disease severity. IBD sufferers are additionally at increased risk of multiple complications and co-morbidities. Among these is an increased risk of human papillomavirus (HPV)-associated cancers, including cervical and anal squamous cell carcinomas.[2,3]

Common forms of benign HPV disease include genital warts (GW). These anogenital lesions are typically caused by HPV types 6 and 11.[4] GW are common in the general population with a large population-based survey suggesting approximately 10% of women[5] and 8% of men[6] in Denmark report a previous infection causing GW.

Over the last 2 decades there has been an increasing prevalence of IBD around the world,[1] necessitating a better understanding of the underlying risks of the disease. The evidence for the risk of developing GW in IBD is largely limited to case reports and case-series studies of a small number of patients treated with TNF-α inhibitors.[7,8] These studies yield no conclusive results and do not explore the impact of immunosuppressive medication on the risk of developing GW or the risk of GW by IBD subtype. No other nationwide, population-representative cohort study exploring the risk of GW in patients with IBD has previously been undertaken. Therefore, in this population-based cohort study, we investigated the risk of developing GW in patients with IBD compared to a matched non-IBD population.

Key summary

Established knowledge on this subject

- There is an increased risk of HPV-associated cancers in inflammatory bowel disease (IBD) however, the risk of HPV-associated benign disease in IBD has never been explored in a population-based cohort.

Significant and/or new findings of this study

- We find a significantly increased risk of genital warts (GW) in Danish IBD patients compared to a matched Danish non-IBD population and in CD compared to ulcerative colitis (UC).
- There is a particularly increased risk of GW observed in female over male IBD patients and among all IBD patients, independent of IBD treatment exposure.

MATERIALS AND METHODS

Study population

The Danish National Patient Registry (NPR), established in 1977 contains information on all admissions to hospital wards in Denmark and since 1995 has also included information on all outpatient and emergency room visits. This registry can be individually linked using a unique civil registration number to the Civil Registration System, which contains up-to-date information on vital status (dead or alive), sex at birth, date of birth, date of death, and dates of immigration or emigration for all persons resident in Denmark. These registries are used to identify IBD patients and the non-IBD population.

We identified patients with CD and UC in the NPR using the International Classification of Diseases (ICD) codes (ICD-8 codes 56308-09 and ICD-10 codes K50 for Crohn's disease; ICD-8 codes 56319 and 56904 and ICD-10 code K51 for UC). All individuals over 18 years of age, diagnosed with IBD from January 1996 to January 2019 were included in the analysis if they had a minimum of two diagnoses in the NPR, or one long hospital stay (>7 days) related to an IBD diagnosis. Where more than one IBD subtype was recorded in the NPR, final subtype was assigned according to the most recent diagnosis of IBD. To generate a cohort for comparison, we randomly selected 10 individuals from the Civil Registration System, matched to the corresponding CD and UC patient for sex at birth, age (birth within a year of IBD patient) and HPV vaccination status. All individuals in the matched group were required to have no previous history of IBD diagnosis.

Cases of genital warts

Cases of GW were identified using a combination of the NPR and the Danish Prescription Registry (DPR) which contains individual-level information on all prescriptions redeemed at outpatient pharmacies in Denmark. The majority of GW presentations occur in the primary care setting with these diagnoses captured through prescription of GW medications via the DPR. ICD-10 codes A63.0A-D and ICD-8 code 09990 were used to identify GW diagnoses in the NPR. Podophyllotoxin is the first-line treatment for GW in Denmark and in order to identify cases diagnosed in primary care, Anatomical Therapeutic Chemical (ATC) codes D06BB04 (podophyllotoxin) and D06BB12 (sinecatechins) were used to identify GW specific treatment from the DPR.

HPV vaccination

HPV immunisation was identified using the Vaccination Registry, which provides a record of all vaccines administered since 2000 (i.e., 6 years prior to licensure of the first HPV vaccine), including those administered outside of the routine vaccination programme. Three doses of HPV vaccination received within 12 months, or 2 doses received within 13 months are recommended for individuals aged ≥15 years and <15 years, respectively.[9] In the Danish vaccination

program, mainly Gardasil® and Gardasil9® have been used. Both of these vaccines provide protection against HPV types 6 and 11, which account for 90% of GW. All individuals fully vaccinated at baseline were excluded. Individuals not vaccinated at baseline, who were later immunised, were censored from analysis after receiving their final dose of the HPV vaccine.

Treatment exposure in inflammatory bowel disease

Individual-level information on treatment exposure in IBD was extracted from the DPR and NPR. Patients exposed to TNF-α antagonists were identified using NPR codes for biological therapies (BOHJ18A) and DPR ATC codes (L04AB01, L04B02 and L04AB04). Those exposed to thiopurines were identified by ATC codes (L04AX01, L01BB02 and BWHB83). Oral (H02AB) or topical (A07EA01, A07EA02 and A07EA06) corticosteroids and 5-ASAs (A07EC01/2) prescriptions are also available from the DPR (Supplementary material, Table 1). IBD patients never receiving these therapies were classified in the no immunosuppressive treatment group. Exposure time of patients to each treatment group was calculated as time-varying in our analyses. Since patients switch from one medication to another over time, each patient may contribute to multiple exposure groups sequentially, in a unidirectional way (step up hierarchy: corticosteroids to thiopurines to biologics) with patients on combination therapies only contributing time to the most escalated treatment only.

Statistical analysis

We followed all individuals from baseline until first GW diagnosis, death, emigration, vaccination against HPV, reaching 70 years of age or 31 December 2018 (end of follow-up); whichever came first. We considered the first episode of GW to be the first NPR diagnosis or DPR prescription collection (described above) from baseline. To consider only incident cases of GW following IBD diagnosis, those with a diagnosis of, or prescription treatment for GW in the year before baseline were excluded. Time to event was calculated from point of cohort entry to first GW event, using age (in years) as the underlying timescale.

We used Kaplan–Meier estimator to calculate the cumulative incidence for GW in IBD patients, compared with the matched non-IBD population, as well as for CD and UC, and males and females (with and without IBD). Due to the very small number of diagnoses of GW in children with IBD and diagnoses of GW in elderly patients with IBD, we undertook both left and right censoring, excluding patients <18 years and those >70 years of age. Cox proportional regression analysis was undertaken to calculate hazard ratios (HR) and their corresponding 95% confidence intervals (CI) for GW in IBD patients compared to the matched population, CD compared with UC patients and undertook sub-group analyses by sex, contraceptive medication exposure, year of IBD diagnosis and IBD treatment exposure, adjusting for these confounders where appropriate. We used DPR prescriptions of oral and topical hormones and contraceptive devices to adjust for contraceptive medication exposure (ACT codes G03AA/B, progestogens and estrogens; G03AC/D, progestogens only and emergency contractive; and G02BA, intrauterine contraceptive devices; Supplementary material, Table 2). Interaction within co-variate groups was calculated using *t*-tests or *F*-tests and considered significant if $p < 0.05$. All analyses were undertaken in SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Sensitivity analysis

Due to the likelihood of more regular perineal examinations undertaken in IBD patients compared to the matched cohort, we assessed the potential for detection bias of GW in IBD patients. We first assessed the percentage of diagnoses coming from DPR records in the IBD population compared to the matched population and undertook a chi-squared test for significance. To assess the potential impact of the unmeasured detection bias, we calculated the E-value for the HR of GW in IBD compared with non-IBD. The E-value is the minimum strength of association between a variable and the outcome that an unmeasured confounder (e.g. increased hospital visits) might be contributing to an observed estimate, following adjustment for known confounding factors. Higher E-values indicate that the unmeasured confounding would need to be substantial to explain the observed association.[10]

RESULTS

We identified 49,163 individuals aged 18–70 years and diagnosed with IBD (68.2% UC, 31.8% CD) between 1996 and 2018 and matched them to 491,665 non-IBD individuals. The majority (86%) of IBD diagnoses were in patients <60 years old and 75.4% of all IBD patients included were diagnosed between 2003 and 2018 (Table 1). Most GW diagnoses for both IBD and matched cohort were identified via the DPR with 75.4% of total GW diagnoses identified from primary care prescriptions (Supplementary material, Table 3).

The cumulative incidence of GW in those with IBD and the matched population is shown in Figure 1. Throughout the follow-up period, those with IBD had a consistently higher incidence of GW than their non-IBD counterparts. Figure 2 shows the cumulative incidence for GW in CD and UC patients and the matched non-IBD cohort. Cumulative incidence in patients with CD was consistently higher than in patients with UC and this was also seen in female IBD patients compared with males (Figure 3).

Table 2 shows the HR for GW in the IBD, CD and UC patients compared to the matched population and subgroup analysis by sex, year of cohort entry, contraceptive exposure and IBD treatment exposure. The crude HR for GW in IBD compared to the matched population is 1.31 (95% CI: 1.24–1.39) and after adjusting for year of diagnosis, sex, contraceptive exposure and IBD treatment exposure,

TABLE 1 Baseline characteristics of study population, inflammatory bowel disease (IBD) and matched, non-IBD population aged 18–70 years in Denmark (1996–2018)

	IBD[a] population		Matched[b] population	
	N	%	N	%
All	49,163	100.0	491,665	100.0
Sex				
Female	25,863	52.6	258,627	52.6
Male	23,300	47.4	233,038	47.4
IBD subtype[c]				
Crohn's disease	15,651	31.8	156,524	31.8
Ulcerative colitis	33,512	68.2	335,141	68.2
Age group				
18–39	26,061	53.0	260,646	53.0
40–59	16,154	32.9	161,503	32.8
60–70	6948	14.1	69,516	14.1
Year of cohort entry				
1996–2002	12,101	24.6	121,013	24.6
2003–2010	17,191	35.0	171,912	35.0
2011–2018	19,871	40.4	198,740	40.4

Abbreviation: IBD, inflammatory bowel disease.

[a]Patients with a minimum two diagnoses with IBD according to International Classification of Diseases (ICD) eight and tenth edition codes identified within the Danish National Patient Registry (NPR) from 1977 to 1995.

[b]Matched for sex at birth (female or male), age (birth within 1 week of index), and vaccination status (3 doses of either Gardasil® or Gardasil9® received within 12 months, or 2 doses received within 13 months for individuals aged ≥15 years and <15 years, respectively was considered vaccinated).

[c]In cases where more than one IBD subtype is recorded (Crohn's disease and ulcerative colitis), subtype is assigned according to last recorded subtype in the (NPR).

the HR of GW in IBD remained increased at 1.33 (95% CI: 1.19–1.49) compared with the non-IBD population. CD patients have an increased hazard for GW with HR 1.45 (1.32–1.58) compared with the matched population. This was higher than the HR for GW in UC at 1.24 (95% CI: 1.15–1.33) and direct comparison of GW in CD to UC patients using Cox proportional regression analysis showed a significantly increased risk of GW in CD (adjusted HR:1.13, CI: 1.01, 1.27; Table 3).

Female IBD patients had an adjusted HR for GW of 1.54 (95% CI: 1.33–1.79) compared to matched female patients, significantly higher than that seen in male IBD patients (adjusted HR: 1.14, 95% CI: 0.97–1.34) compared to the matched male population. An increased adjusted HR for GW was seen in all IBD patients compared with the matched population regardless of year of diagnosis (1996–2002 HR: 1.21, 95% CI, 1.05–1.39; 2003–2010 HR: 1.39, 95% CI: 1.23–1.57; 2011–2018 HR: 1.39, 95% CI: 1.18–1.64). Furthermore, an increased HR of GW in IBD was seen across all treatment groups, compared to the matched population. The HR of GW was numerically higher in IBD patients treated with thiopurines (adjusted HR: 1.50, 95% CI: 1.34–1.67) than other medication groups, and the adjusted HR for GW was lowest among IBD patients treated only with corticosteroids or 5-ASAs (1.19, 95% CI: 1.10–1.30). Of note, the adjusted HR for GW in IBD patients was also increased in those not treated with any immunosuppressive therapies (HR: 1.33, 95% CI: 1.190–1.49) compared with matched individuals.

Among those with IBD, 78.9% of GW diagnoses came from a recorded DPR prescription, compared with 84.2% of GW diagnoses in the matched population (Supplementary material, Table 3) and this difference was of borderline significance ($p = 0.05$). E-value calculation indicated that the observed HR for GW in the IBD population, compared to the matched population of 1.33 (95% CI: 1.19–1.49) could be explained by an unmeasured confounder associated with both IBD and GW with a HR of at least 1.98. An unmeasured confounder associated with both the exposure and the outcome with a HR of at least 1.89 would lead us to consider this result non-significant by moving the confidence interval to include the null.

DISCUSSION

In this population-based cohort study of over 491,665 IBD patients, we observed a 33% increased risk for GW in IBD patients compared with their matched counterparts and this was particularly seen in female over male IBD patients. We additionally observed a 13% increased risk for GW in CD patients compared with UC patients. There was an increased risk for GW in all IBD patients, independent of treatment exposure (including IBD patients never exposed to immunosuppressive therapy) compared to the matched population.

Although this is the first cohort study exploring non-malignant anogenital HPV disease in IBD, our finding of an increased risk of GW in IBD patients is supported by evidence of a similarly increased risk for high-risk HPV in IBD. Rungoe et al. identified an increased risk of high-grade lesions in female patients with UC (IRR: 1.12, 95% CI: 1.01–1.25) and CD (IRR: 1.28, 95% CI: 1.13–1.45) in a Danish nationwide cohort study[2] and an increased risk of HPV associated anal squamous cell carcinoma (SCC) in IBD has been identified elsewhere, including in population studies from England, Finland and the UK.[11–13]

The increased risk of GW in Crohn's disease compared to UC, which we observe even after adjusting for treatment exposure, is also in keeping with findings from several others studies investigating the risk of high-risk HPV infection of the cervix, where CD is commonly found to be the unfavourable IBD subtype for persistent HPV infection.[2,14,15] HPV-associated anal SCC is also consistently more strongly associated with CD subtype than UC,[13,16] however these findings may be confounded by the increased risk of anal SCC in the context of anal fistulating disease in CD compared with UC, where disease activity is limited to the colon. This may also be the case in our findings.

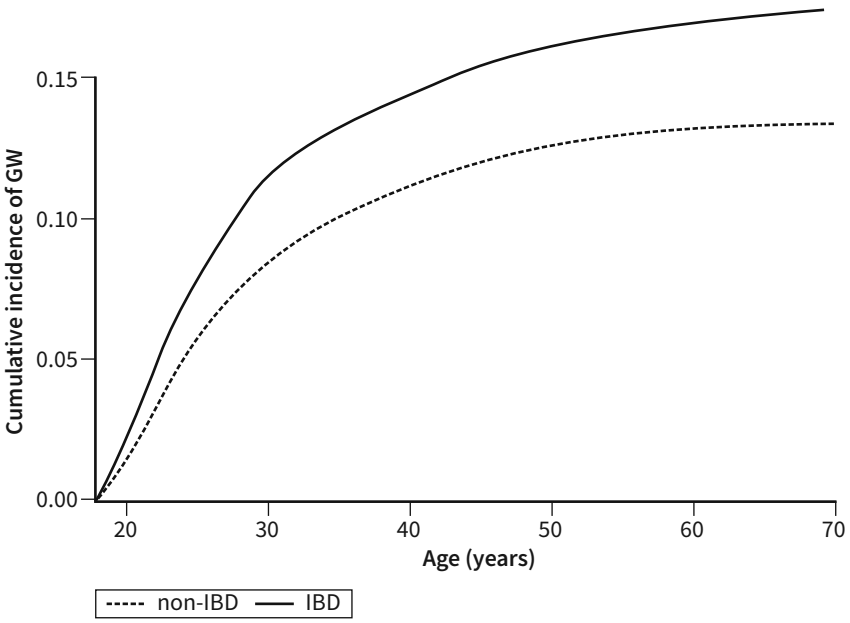

FIGURE 1 Kaplan–Meier survival analysis curves for cumulative incidence of genital warts (GW) at age 18–70 years from 1996 to 2018 in Danish IBD patients and matched non-IBD population*. Cumulative incidence for GW in IBD compared to the matched non-IBD calculated using Kaplan–Meier. CD, Crohn's disease; GW, genital warts; IBD, inflammatory bowel disease; UC, ulcerative colitis. *Censoring outcomes for IBD population: Attained age 70 years = 6411; Emigration or death = 3986; HPV vaccination = 550; End of study period follow-up = 36,801. Event outcomes for IBD population: GW diagnosis = 298; GW treatment prescription = 1117. Censoring outcomes for matched population: Attained age 70 years = 67,856; Emigration or death = 35,598; HPV vaccination = 4548; End of study period follow-up = 370,309. Event outcomes for matched population: IBD diagnosis = 2549; GW diagnosis = 1703; GW treatment prescription = 9094

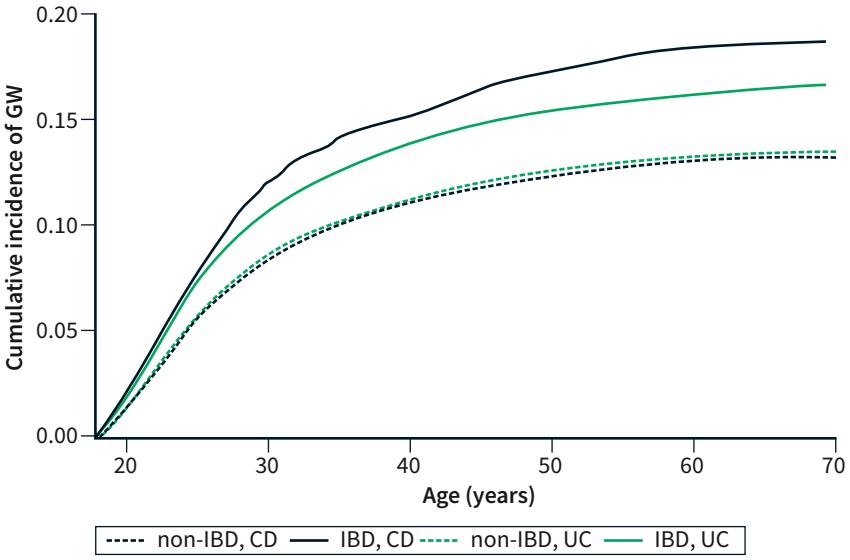

FIGURE 2 Kaplan–Meier survival analysis curves for cumulative incidence of genital warts (GW) at age 18–70 years from 1996 to 2018 in Danish Crohn's disease patients and ulcerative colitis patients. Cumulative incidence for GW in IBD compared to the matched non-IBD calculated using Kaplan–Meier. CD, Crohn's disease; GW, genital warts; IBD, inflammatory bowel disease; UC, ulcerative colitis

Female patients with IBD appear at particularly increased risk of GW compared with their matched counterparts with a 54% increased risk of GW. This observation is in keeping with findings from a cohort study exploring the risk of GW in renal transplant recipients in a Denmark[17] where an almost 5-fold increased risk of GW was found among female renal transplant recipients and

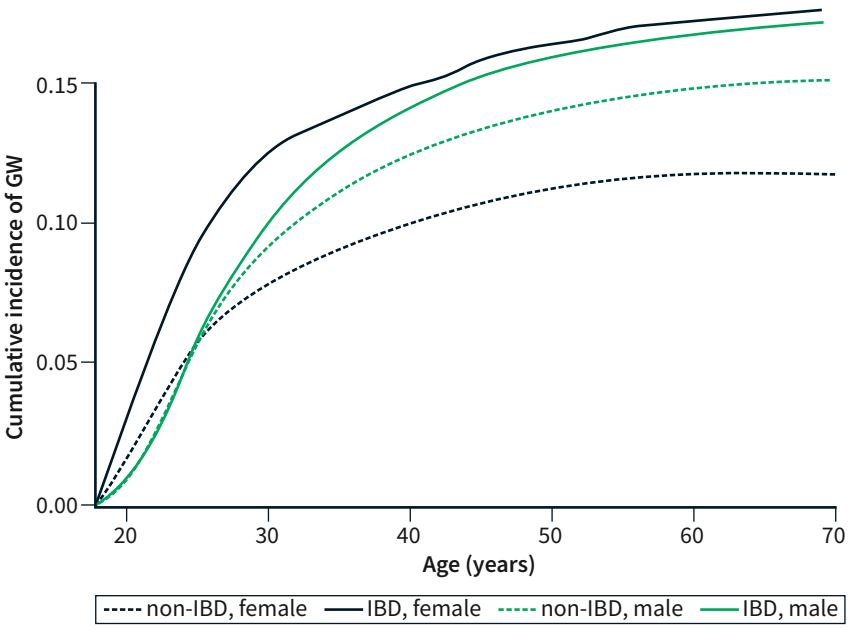

FIGURE 3 Kaplan–Meier survival analysis curves for cumulative incidence of genital warts (GW) at age 18–70 years from 1996 to 2018 in Danish female IBD patients, male IBD patients, matched female population, and matched male population. Cumulative incidence for GW in IBD compared to the matched non-IBD calculated using Kaplan–Meier. CD, Crohn's disease; GW, genital warts; IBD, inflammatory bowel disease; UC, ulcerative colitis

test for interaction showing this to be more pronounced than in males ($p < 0.01$). An increased risk for HPV-related anal SCC diagnosis is also seen for female patients with IBD. In a direct comparison of female IBD patients to their male conterparts, Wewer et al. found a 65% increased risk of HPV-related anal SCC in a cohort of Danish CD patients (HR: 1.65, 95% CI: 1.20–1.72).[18]

We observed an increased risk of GW in IBD patients not treated with any class of immunosuppressive medication compared to their matched non-IBD counterparts, and these findings are in keeping with a case-control study by Handisurya and colleagues who investigated the risk of GW in 109 IBD patients and found no increased risk for low-risk anogenital HPV infection in IBD patients treated with TNF-α inhibitors compared to those receiving alternative (thiopurines) or no treatment.[19] Previous cohort studies assessing the risk of persistent high-risk HPV infection in IBD have shown an increased risk of cancer in this patient group even in the context of no exposure to immunosuppressive treatment, and in the years preceding diagnosis with IBD.[2,20] This supports our observations which indicate that the increased risk of GW seen in IBD may not be due to treatment with immunosuppressive medication alone, but may be the result of the underlying chronic inflammation which is seen IBD itself. This is further supported by our observation in this work that those treated only with anti-inflammatories such 5-ASAs or with topical/oral corticosteroids have a numerically lower HR for GW (HR: 1.19, 95% CI: 1.10, 1.30) than those with IBD who are untreated (HR: 1.33, 95% CI: 1.19, 1.49).

Strengths and limitations

The primary strength of this study is the population-representative cohort study design combining data from several nationwide registries. Therefore the reliability of outcomes such as GW diagnosis are not affected by recall bias or incomplete data that are commonly found in survey studies or administrative health database cohorts. IBD diagnoses identified via the NPR in this study have previously been assessed against histological records and found to be highly valid.[21] We were also able to match IBD patients to a random selection of the general population by age, sex, and vaccination against HPV. This is particularly important due to HPV infection being highly age dependent, and HPV vaccination being highly effective for immunisation against almost all GW disease. The potential limitations of this study include the risk of detection bias for GW in our IBD cohort, with IBD patients being more likely to have regular clinical contact and undergo a perineal examination as part of that contact. There was borderline significant difference in the percentage of diagnoses coming from prescriptions, with IBD patients having a higher number of clinically recorded GW diagnoses than the matched population. Using the E-value, however we estimated that the observed HR of 1.31 for GW in IBD versus non-IBD could be explained by a potential confounder (e.g., increased detection) associated with IBD and GW diagnosis with HR of 1.95, or at least 1.79 for our findings to be considered insignificant. Although it is therefore possible, we do not consider it likely that detection bias alone would be able to fully explain the strength of association of the results. Another potential limitation is the lack of information on smoking, which is known to

TABLE 2 Hazard ratio for the diagnosis or treatment prescription for genital warts (genital warts event) in inflammatory bowel disease (IBD) compared to matched non-IBD population, Denmark (1996–2018)

Variable	GW events (N)	Crude HR (95% CI)	*p*-value	Partially adjusted HR[a] (95% CI)	*p*-value	Fully adjusted HR[b] (95% CI)	*p*-value
Total	1415	1.31 (1.24, 1.39)		1.31 (1.24, 1.39)		1.33 (1.19, 1.49)	
Sex							
Female	729	1.49 (1.38, 1.61)	<0.0001	1.49 (1.38, 1.61)	<0.0001	1.54 (1.33, 1.79)	<0.0001
Male	686	1.16 (1.07, 1.26)		1.16 (1.08, 1.26)		1.14 (0.97, 1.34)	
Contraceptive use							
Yes		1.42 (1.31, 1.55)	0.022	1.43 (1.31, 1.55)	0.008	1.46 (1.28, 1.66)	0.007
No		1.25 (1.16, 1.34)		1.22 (1.14, 1.31)	0.008	1.25 (1.11, 1.41)	
Year of cohort entry							
1996–2002	463	1.20 (1.09, 1.32)	0.060	1.20 (1.09, 1.32)	0.061	1.21 (1.05, 1.39)	0.069
2003–2010	717	1.38 (1.28, 1.49)		1.38 (1.27, 1.49)	0.061	1.39 (1.23, 1.57)	
2011–2018	235	1.38 (1.20, 1.58)		1.38 (1.20, 1.58)	0.061	1.39 (1.18, 1.64)	
IBD treatment exposure							
No immunosuppressive treatment	330	1.34 (1.20, 1.50)	<0.0001	1.35 (1.21, 1.50)	<0.0001	1.33 (1.19, 1.49)	<0.0001
Corticosteroids (oral/topical) or 5-ASA	577	1.20 (1.11, 1.31)		1.20 (1.11, 1.31)	<0.0001	1.19 (1.10, 1.30)	
Thiopurines	313	1.54 (1.38, 1.73)		1.51 (1.35, 1.69)	<0.0001	1.50 (1.34, 1.67)	
Biologicals	195	1.29 (1.12, 1.49)		1.33 (1.16, 1.54)	<0.0001	1.32 (1.15, 1.53)	

Note: Hazard ratios calculated using Cox proportional regression analysis for incidence of GW in those diagnosed with IBD compared to the matched non-IBD population.

Abbreviations: GW, genital warts; HR, hazard ratio; IBD, inflammatory bowel disease.

[a]Partial adjustment - adjusted for year of entry and sex, where relevant.

[b]Full adjustment - adjusted for year of entry, sex, contraceptive exposure, and IBD treatment exposure, where relevant.

TABLE 3 Hazard ratio for the diagnosis or treatment prescription for genital warts (genital warts event) in Crohn's disease (CD) compared to ulcerative colitis (UC), Denmark (1996–2018)

GW events (N)				
CD patients	UC patients	Crude HR (95% CI)	Partially adjusted HR[a] (95% CI)	Fully adjusted HR[b] (95% CI)
568	847	1.16 (1.04, 1.29)	1.17 (1.06, 1.31)	1.13 (1.01, 1.27)

Note: Hazard ratios calculated using Cox proportional regression analysis for incidence of GW in those diagnosed with IBD compared to the matched non-IBD population.

Abbreviations: GW, genital warts; HR, hazard ratio; IBD, inflammatory bowel disease.

[a]Partial adjustment - adjusted for year of entry and sex, where relevant.

[b]Full adjustment - adjusted for year of entry, sex, contraceptive exposure, and IBD treatment exposure, where relevant.

impact the risk of chronic infection with HPV and is less common in UC patients, but more common in CD patients, compared with the general population.[22,23] This is unlikely to be a systematic cause of bias for our overall analysis of IBD compared to the matched general population, or be a contributor to the increased HR for GW in CD as directly compared to UC observed in this study.

CONCLUSION

In this nationwide, population-representative cohort study, we observed an overall 31% increased risk of GW in patients with IBD compared to matched population and a 13% increased risk of GW in CD compared to UC. This increased risk was particularly high in female IBD patients and observed independent of treatment exposure.

ACKNOWLEDGEMENTS

Corresponding Author, Rahma Elmahdi is the guarantor of this submission and takes responsibility for the integrity of the work as a whole, from inception to submitted article. This work was supported by the Danish National Research Foundation (grant no. DNRF148). Rahma Elmahdi was also supported by Helsefonden-bevillengen (RF2272).

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Rahma Elmahdi, Louise T. Thomsen, Tine Jess, Susanne K. Kjær and Aske T. Iversen designed the study. Aske T. Iversen analysed the data. All authors interpreted the analyses. Rahma Elmahdi, Louise T. Thomsen, and Aske T. Iversen drafted the first version of the manuscript. Rahma Elmahdi, Tine Jess and Kristine H. Allin finalised the manuscript. All authors contributed substantially and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to National Health Registry access restrictions. The data will be shared on reasonable request to the corresponding author.

ORCID

Rahma Elmahdi https://orcid.org/0000-0002-7013-9548
Susanne K. Kjær https://orcid.org/0000-0002-8347-1398

REFERENCES

1. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020;5:17–30.
2. Rungoe C, Simonsen J, Riis L, Frisch M, Langholz E, Jess T. Inflammatory bowel disease and cervical neoplasia: a population-based nationwide cohort study. Clin Gastroenterol Hepatol. 2015;13:693–700.e1.
3. Jess T, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. Am J Gastroenterol. 2013;108:1869–76.
4. Formana D, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30.
5. Kjær SK, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. J Infect Dis. 2007;196:1447–54.
6. Munk C, Nielsen A, Liaw KL, Kjaer SK. Genital warts in men: a large population-based cross-sectional survey of Danish men. Sex Transm Infect. 2012;88:640–4.
7. Handisurya A, Lázár S, Papay P, Primas C, Haitel A, Horvat R, et al. Anogenital human papillomavirus prevalence is unaffected by therapeutic tumour necrosis factor-alpha inhibition. Acta Derm Venereol. 2016;96:494–8.
8. Somasekar A, Alcolado R. Genital condylomata in a patient receiving infliximab for Crohn's disease. Postgrad Med. 2004;80:358–9.
9. Thomsen SB, Allin KH, Burisch J, Jensen CB, Hansen S, Gluud LL, et al. Outcome of concomitant treatment with thiopurines and allopurinol in patients with inflammatory bowel disease: a nationwide Danish cohort study. United European Gastroenterol J. 2020;8:68–76.
10. Haneuse S, Vanderweele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. JAMA. 2019;321:602–3.
11. Segal JP, Askari A, Clark SK, Hart AL, Faiz OD. The incidence and prevalence of human papilloma virus–associated cancers in IBD. Inflamm Bowel Dis. 2021;27:34–9.
12. Jussila A, Virta LJ, Pukkala E, Färkkilä MA. Malignancies in patients with inflammatory bowel disease: a nationwide register study in Finland. Scand J Gastroenterol. 2013;48:1405–13.
13. Ruel J, Ko HM, Roda G, Patil N, Zhang D, Jharap B, et al. Anal neoplasia in inflammatory bowel disease is associated with HPV and perianal disease. Clin Transl Gastroenterol. 2016;7:e148.
14. Andersen NN, Pasternak B, Basit S, Andersson M, Svanström H, Caspersen S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA. 2014;311:2406–13.
15. Goetgebuer RL, Kreijne JE, Aitken CA, Dijkstra G, Hoentjen F, de Boer NK, et al. Increased risk of high-grade cervical neoplasia in women with inflammatory bowel disease: a case-controlled cohort study. J Crohns Colitis. 2021;15:1464–73. https://doi.org/10.1093/ecco-jcc/jjab036
16. Wisniewski A, Fléjou J-F, Siproudhis L, Abramowitz L, Svrcek M, Beaugerie L. Anal neoplasia in inflammatory bowel disease: classification proposal, epidemiology, carcinogenesis, and risk management perspectives. J Crohns Colitis. 2017;11:1011–18.
17. Larsen HK, Thomsen LT, Haedersdal M, Dehlendorff C, Schwartz Sørensen S, Kjaer SK. Risk of genital warts in renal transplant recipients—a registry-based, prospective cohort study. Am J Transplant. 2019;19:156–65.
18. Wewer MD, Zhao M, Nordholm-Carstensen A, Weimers P, Seidelin JB, Burisch J. The incidence and disease course of perianal Crohn's disease: a Danish nationwide cohort study, 1997–2015. J Crohns Colitis. 2021;15:5–13.
19. Handisurya A, Lázár S, Papay P, Primas C, Haitel A, Horvat R, et al. Anogenital human papillomavirus prevalence is unaffected by therapeutic tumour necrosis factor-alpha inhibition. Acta Derm Venereol. 2016;96:494–8.
20. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal pap smears in women with inflammatory bowel disease. Am J Gastroenterol. 2008;103:631–6.

21. Fonager K, Toft Sørensen H, Nørby Rasmussen S, Møller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. Scand J Gastroenterol. 1996;31:154–9.
22. Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, et al. Environmental factors in inflammatory bowel disease: a case-control study based on a Danish inception cohort. J Crohns Colitis. 2011;5:577–84.
23. Burisch J, Pedersen N, Cukovic-Cavka S, Turk N, Kaimakliotis I, Duricova D, et al. Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe - an ECCO-EpiCom study. J Crohns Colitis. 2014;8:607–16.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Elmahdi R, Thomsen LT, Iversen AT, Allin KH, Kjær SK, Jess T. Increased risk of genital warts in inflammatory bowel disease: a Danish registry-based cohort study (1996–2018). United European Gastroenterol J. 2022; 10(3):287–95. https://doi.org/10.1002/ueg2.12217