Inflammatory Bowel Disease and Cervical Neoplasia: A Population-Based Nationwide Cohort Study

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BACKGROUND & AIMS: **We examined the risk of cervical neoplasia (dysplasia or cancer) in women with ulcerative colitis (UC) or Crohn's disease (CD). We also calculated the reverse, the risk for diagnosis with cervical neoplasia before development of inflammatory bowel disease (IBD).**

METHODS: **We established a national cohort of women diagnosed with UC (n = 18,691) or CD (n = 8717) between 1979 and 2011 and a control cohort of individually matched women from the general population (controls, n = 1,508,334). Incidence rate ratios (IRRs) of screening activity and diagnosis of cervical neoplasia in women with IBD were assessed by Cox proportional hazards regression analysis. Odds ratios (ORs) of cervical neoplasia before diagnosis of IBD were calculated by using conditional logistic regression.**

RESULTS: **Women with CD underwent cervical cancer screening as often as women in the general population (IRR, 0.99; 95% confidence interval [CI], 0.96–1.02), whereas screening frequency was slightly increased in women with UC (IRR, 1.06; 95% CI, 1.04–1.08). A total of 561 patients with UC were diagnosed with dysplasia during a median follow-up time of 7.8 years, and 28 patients with UC developed cervical cancer, compared with 1918 controls. A total of 407 patients with CD were diagnosed with dysplasia during a median follow-up time of 8.3 years, and 26 patients with CD developed cervical cancer, compared with 940 controls. Patients with UC had increased risk of low-grade (IRR, 1.15; 95% CI, 1.00–1.32) and high-grade (IRR, 1.12; 95% CI, 1.01–1.25) squamous intraepithelial lesions (SILs), whereas patients with CD had increased risks of low-grade SIL (IRR, 1.26; 95% CI, 1.07–1.48), high-grade SIL (IRR, 1.28; 95% CI, 1.13–1.45), and cervical cancer compared with controls (IRR, 1.53; 95% CI, 1.04–2.27). ORs for cervical cancer were also increased 1–9 years before diagnosis of UC, compared with women without UC (OR, 2.78; 95% CI, 2.12–3.64) or CD (OR, 1.85; 95% CI, 1.08–3.15).**

CONCLUSIONS: **In a population-based nationwide cohort study, we found a 2-way association between IBD, notably CD, and neoplastic lesions of the uterine cervix. This observation is not explained by differences in screening activity.**

Keywords: Neoplasia; Thiopurines; Treatment; Cancer Risk Factor.

The risk of cervical neoplasia (ie, dysplasia or cancer) in patients with inflammatory bowel disease (IBD) remains debated. Whereas some studies suggest an increased risk of cervical neoplasia in patients with IBD,[1–3] others find risk of cervical neoplasia to be no different from that of non-IBD individuals[4–6] unless patients are smokers or have used oral contraceptives for extended time periods. The central etiologic factor for cervical dysplasia or cancer, described as necessary but not sufficient, is persistent infection with high-risk oncogenic types of human papilloma virus (HPV).[7] In addition to high-risk HPV, several other cofactors such as high parity, early age at first-time pregnancy, long-term hormonal contraception use, and immunosuppressive drug therapy have been associated with progression from chronic infection to cancer.[7,8] Most HPV

Abbreviations used in this paper: **ATC, Anatomical Therapeutic Chemical; CD, Crohn's disease; CI, confidence interval; HCD, hormonal contraceptive device; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IBD, inflammatory bowel disease; IRR, incidence rate ratio; LSIL, low-grade squamous intraepithelial lesion; NPR, National Patient Register; OR, odds ratio; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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infections spontaneously regress during the course of months to a few years, whereas others persist and progress, and it remains unclear why some people clear their infection, and others do not.[9] It may be hypothesized that the underlying immunologic changes in IBD or the treatment of IBD with immunosuppressive drugs may lead to increased risk of cervical neoplasia because of impaired ability to clear HPV infections.

The aim of the present study was to assess a national cohort of women with ulcerative colitis (UC) or Crohn's disease (CD) individually matched to a large sample of women from the general population without IBD to examine (1) the risk of cervical dysplasia and cervical cancer in women with a diagnosis of IBD; (2) the effect of IBD medications (mesalamines, corticosteroids, azathioprine, or tumor necrosis factor [TNF]-α antagonists) on the risk of cervical neoplasia; (3) the effect of hormonal contraceptive devices (HCDs) on the risk of cervical neoplasia; and, reversely, (4) the risk of cervical neoplasia before a diagnosis of IBD.

Methods

Study Population

The source population, which consisted of approximately 4 million women residing in Denmark from 1979 to 2011, was established by use of the Danish Civil Registration system, in which all Danes are registered by a 10-digit identification number.[10] The identification number is unique and constant throughout life and serves as an identifier that makes linkage between national registers possible. The Danish Civil Registration system contains continuously updated information on sex, place of birth, address, marital status, and dates of immigration, emigration, and death of all citizens. We identified patients with IBD by use of the Danish National Patient Register (NPR),[11] which contains individual-level healthcare information on hospital contacts, diagnoses, and surgical and other procedures performed in Danish hospitals since 1977 and in ambulatory outpatient settings since 1995. To minimize any impact of prevalent cases, we only included patients with a first diagnosis of IBD after January 1, 1979 by using the International Classification of Diseases, 8th and 10th revision, codes for CD (563.00-563.09 and code group K50) and UC (563.19, 569.04, and code group K51). IBD diagnoses in NPR have been found to be accurate and almost complete with validity estimates for registered CD and UC of 97% and 90%, respectively, by using a pathology register as reference.[12] To avoid diagnostic ambiguity, patients with a diagnosis of both UC and CD recorded in the NPR were not included. Individuals with a history of total hysterectomy (International Classification of Diseases-8 and -10 codes 61000, 61020, 61040, 61050, or 61100, KLCD, KLDC, KLCE, or KLCC) in the NPR before diagnosis of IBD or the index date were also excluded.

For each IBD patient we randomly sampled 50 age-matched female controls from the general population (born $\pm$ 6 months from the IBD patient) who were alive at the time of the index patient's first recorded IBD diagnosis in NPR, had no history of IBD or hysterectomy, and lived in the same municipality as the IBD patient at the time of IBD diagnosis.

Medical Treatment of Inflammatory Bowel Disease

Detailed individual-level information on medical treatment for IBD and use of HCD was extracted from the National Prescription Registry,[13] which contains information on all prescriptions redeemed from all Danish pharmacies since 1995. From the date of first recorded prescription, IBD patients were defined as "ever users" and compared with "never users" of the medication in question. As IBD medications we included azathioprine (the primary thiopurine used in Denmark; Anatomical Therapeutic Chemical [ATC] code L04AX01), mesalamine/sulfasalazine (ATC code A07EC), oral corticosteroids (ATC code H02AB), and topical corticosteroids (ATC codes A07EA01, A07EA02, and A07EA06). Treatment with TNF-α antagonists was identified by combining manually collected data, NPR procedure codes from inpatient and outpatient settings (BOHJ18A), and data from the National Prescription Registry (ATC codes L04AB01, L04B02, and L04AB04). As HCD we included oral contraceptives, vaginal ring, and intrauterine devices (ATC codes G02B, G03AA07–G03AC09).

Covariates

Information on age, sex, and municipality at diagnosis of IBD was obtained from the Danish Civil Registration system. Information on comorbidities up to 5 years before entry and during follow-up was obtained from the NPR. Comorbidities were categorized into 32 different disease groups (modified Charlson comorbidity index).

Outcomes

The primary outcomes were participation in cervical smear screening and diagnoses of cervical dysplasia and cervical cancer recorded in the Danish Cancer Registry. By use of unique reimbursement codes, which were obtained from the Danish National Health Service Register[14] where all specialists are contracted by law, we obtained information on all smear tests performed in IBD patients and controls by date of procedure. In Denmark, these procedures are mainly performed by general practitioners or private specialists in gynecology. Both are contracted with the tax-funded public health care system.

Cases of cervical dysplasia were categorized according to recommendations from the Danish Society of Obstetrics