Risk of Cervical Abnormalities in Women With Inflammatory Bowel Disease: A Population-Based Nested Case-Control Study

HARMINDER SINGH,[*,‡] ALAIN A. DEMERS,[‡,§] ZOANN NUGENT,[§] SALAHEDDIN M. MAHMUD,[‡,§] ERICH V. KLIEWER,[‡,§] and CHARLES N. BERNSTEIN[*]

[*]Internal Medicine, and the University of Manitoba IBD Clinical and Research Centre, Winnipeg, Manitoba, Canada; [‡]Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada; and the [§]Epidemiology and Cancer Registry, CancerCare Manitoba, Winnipeg, Manitoba, Canada

Background & Aims: **We evaluated the risk of cervical abnormalities in women with inflammatory bowel disease (IBD) in a population-based, nested, case-control study.** ***Methods:*** **Cases with abnormal Papanicolaou (Pap) smears or cervical biopsies were matched with up to 3 controls (normal Pap smears) by year of birth, year of first health care coverage, and number of Pap smears in the preceding 5 years. A diagnosis of IBD before the index date was identified from the University of Manitoba IBD Epidemiology Database. Exposures to immunosuppressant drugs and corticosteroids were determined from the provincial drug prescription database. Analyses were adjusted for socioeconomic status and exposure to oral contraceptives and nonsteroidal anti-inflammatory drugs.** ***Results:*** **19,692 women with cervical cytologic and/or histologic abnormalities were matched with 57,898 controls with normal Pap smears. There was no association between cervical abnormalities and ulcerative colitis (odds ratio [OR], 1.03; 95% confidence interval [CI], 0.77–1.38). The increase in risk in women with Crohn's disease was limited to those exposed to 10 or more prescriptions of oral contraceptives (OR, 1.66; 95% CI, 1.08–2.54). The combined exposure to corticosteroids and immunosuppressants was associated with increased risk of cervical abnormalities (OR, 1.41; 95% CI, 1.09–1.81). There was no interaction between the effect of IBD and corticosteroids and/or immunosuppressants.** ***Conclusions:*** **These findings do not support an association between IBD itself and the risk of developing cervical abnormalities. An increased risk in patients given a combination of corticosteroids and immunosuppressants should be considered in managing women with IBD.**

Cervical cancer is caused by a viral infection and, consequently, immunosuppressed women, including organ transplant recipients and those with systemic lupus erythematosus, have an increased risk of cervical abnormalities.[1–4] Whether the risk of cervical abnormalities is increased similarly in women with inflammatory bowel disease (IBD), which often is treated with immunosuppression, is unknown. Although 2 recent studies showed an increased risk of cervical abnormalities in women with IBD, another observational study found no significant difference.[5–7] The results from these studies may not be generalizable because the enrolled patients were recruited from tertiary care referral IBD centers; the differences in the study results may have been owing to differences in the demographics of the subjects between the different study sites. A previous population-based study from our center suggested no increased risk for cervical cancer in IBD; however, lesser degrees of neoplasia were not evaluated in that study.[8]

The recommended screening interval between examinations for average-risk women with normal Papanicolaou's (Pap) smears is 2–3 years.[9,10] However, women with immunosuppression, such as those with human immunodeficiency virus infection or history of organ transplants, are recommended to have Pap tests every year.[9] Currently, there are no specific recommendations for women with IBD, even though many are exposed to immunosuppressive medications during the course of their disease.

The recently available human papillomavirus (HPV) vaccines protect against the acquisition of HPV types 16 and 18, if administered before the acquisition of these types. Because these 2 types are responsible for only 70% of cervical cancers, the Advisory Committee on Immunization Practices has emphasized the importance of continued cervical screening in vaccinated women.[11]

We evaluated the risk of cervical abnormalities and cervical cancer precursor lesions among women with IBD, in a population-based, nested, case-control study, using the University of Manitoba IBD Epidemiology Database, the Manitoba Cervical Cancer Screening Program Database, and the Manitoba Cancer Registry.

Abbreviations used in this paper: CI, confidence interval; HPV, human papillomavirus; MCCSP, Manitoba Cervical Cancer Screening Program; MCR, Manitoba Cancer Registry; NSAID, nonsteroidal anti-inflammatory drug; OCP, oral contraceptive pills; OR, odds ratio; Pap, Papanicolaou's; SES, socioeconomic status.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2008.10.021

Materials and Methods

Data Sources and Study Measures

Manitoba Cervical Cancer Screening Program Database and the Manitoba Cancer Registry. Cases with cervical cytologic and/or histologic abnormalities and cases of invasive cervical cancer were identified using the Manitoba Cervical Cancer Screening Program (MCCSP) database and the Manitoba Cancer Registry (MCR). The MCCSP maintains a registry of all women in Manitoba 18 years of age and older, together with the results of their Pap tests and follow-up histologic evaluations, since April 2001. Results of Pap tests are reported to the MCCSP using a standardized form and in accordance with the 2001 Bethesda system.[12] Matching controls, identified from the MCCSP database, were women with normal Pap test results.

A history of prior invasive malignancies (other than nonmelanoma skin cancers) and cervical cancer was obtained by linkage to the MCR. The MCR records all cancers diagnosed in Manitoba residents. The MCR was established in 1937 and became population-based in 1956. The coding and capture of cancer data are audited regularly by the North American Association of Central Cancer Registries and the Canadian Cancer Registry. The MCR has been shown consistently to be of high quality, including high levels of reporting completeness.[13]

Manitoba Health and Healthy Living administrative databases. Patients with IBD were identified from the University of Manitoba IBD Epidemiology Database. The University of Manitoba IBD Epidemiology Database previously was established using the Manitoba Health and Healthy Living Medical Claims and Hospital Discharge abstract databases.[14] Manitoba Health and Healthy Living is the single health insurance provider in Manitoba and uses administrative databases to collect information on ambulatory care visits, hospital admissions, diagnostic testing, and dispensing of prescription drugs. Multiple previous studies have shown the accuracy and comprehensiveness of these administrative data.[15,16] A unique personal health identification number allows deterministic linkage across the different Manitoba Health and Healthy Living databases. The case definition for IBD has been validated previously using these administrative databases.[14] Briefly, the administrative case definition of IBD includes individuals with at least 5 separate physician contacts and/or hospitalizations for an IBD diagnosis ($\geq$3 contacts for those residing in Manitoba for $\leq$2 years). Information on colposcopy, hysterectomy, and Pap test was obtained from the Medical Claims and Hospital Discharge databases.

Exposure to immunosuppressant medications (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, or infliximab), nonsteroidal anti-inflammatory drugs (NSAIDs), and oral contraceptive pills (OCPs) was determined by linkage to the provincial Drug Program Information Network. The Drug Program Information Network has been in existence since 1995 and comprehensively records all prescription drug use by residents of the province.[17] Each prescription record in the Drug Program Information Network database contains a date of dispensation, active ingredient, strength, route, the number of doses provided, and the anticipated duration of the prescription in days.

Identification of Cases and Controls

The source cohort population for this nested case-control study was identified from the MCCSP database. We excluded women with invasive malignancies, other than nonmelanoma skin cancers, or history of treatment for a cervical abnormality before January 2002. Cases were women 18 years and older who resided in Manitoba for longer than 5 years and who had an abnormal Pap test result (atypical squamous cells of undetermined significance or worse), abnormal cervical biopsy (cervical intraepithelial neoplasia 1 or worse), or cervical cancer between January 2002 and December 2006. When available, histologic results were preferred to cytologic results.

Episodes of care for cervical abnormalities for each individual were identified. An episode started with a Pap test after at least a 9-month time interval free of any procedure performed on the cervix and ended after a 9-month time interval without a cervical procedure. Cervical procedures included Pap tests, colposcopies, and any ablation or destruction of cervical lesions. The index date was defined as the date of the first event in the index episode. Only the worst cervical abnormality in the first episode of care was considered. In a sensitivity analysis, the highest grade of cervical abnormality in any of the episodes between January 2002 and December 2006 was considered, with little change in the calculated odds ratios (ORs).

Cases were matched to 3 controls with normal Pap smears by year of birth, year of first coverage in the provincial universal health care system, and number of Pap smears (categorized as 0, 1–3, and $>$3) in the preceding 5 years. The control's normal Pap test had to be reported in the same year the index case was diagnosed with abnormalities.

All cases and controls had to be residents of Manitoba for at least 5 years before the index date. The 5-year period was chosen to allow determination of exposure to the study medications (corticosteroids, immunosuppressants, NSAIDs, and OCPs) before the index date and the determination of the history of cervical screening and IBD. Women were considered to have IBD if they were diagnosed with IBD before the index date.

Statistical Analysis

SAS version 9.1 (SAS Institute Inc, Cary, NC) was used for data management and analysis. ORs and 95% confidence intervals (95% CIs) were estimated using con-