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Sex-Based Differences in Incidence of Inflammatory Bowel Diseases—Pooled Analysis of Population-Based Studies From Western Countries

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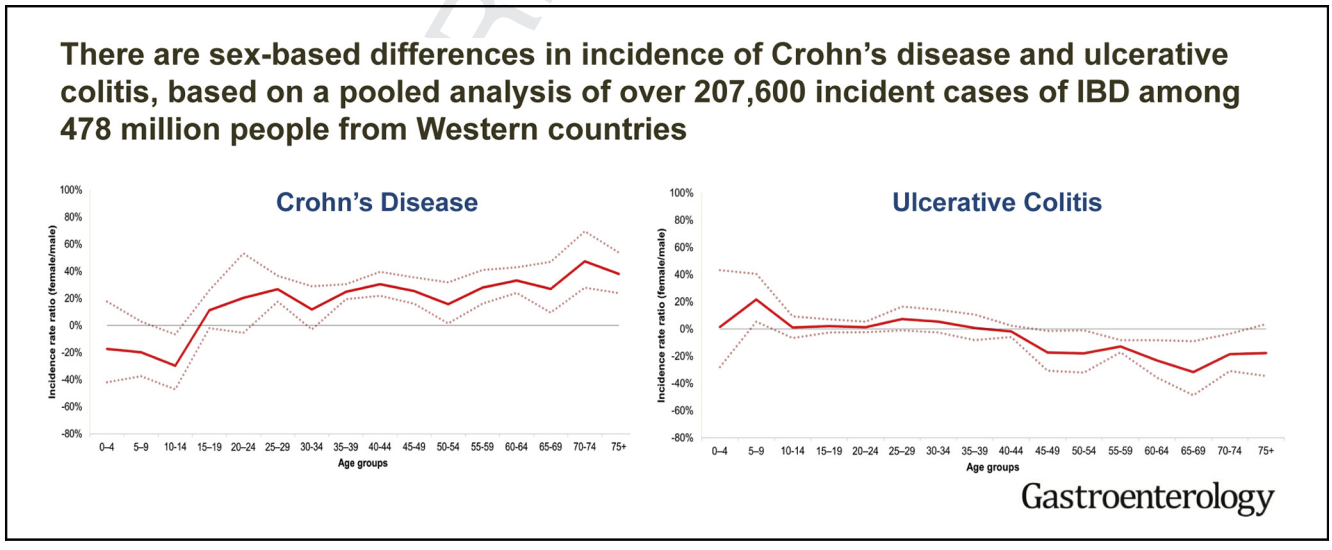

BACKGROUND & AIMS: Although the incidence of inflammatory bowel diseases (IBDs) varies with age, few studies have examined variations between the sexes. We hypothesize that sex hormones are implicated in IBD pathogenesis. We therefore used population data from established cohorts to analyze sex differences in IBD incidence according to age at diagnosis.

METHODS: We identified population-based cohorts of patients with IBD for which incidence and age data were available (17 distinct cohorts from 16 regions of Europe, North America, Australia, and New Zealand). We collected data through December 2016 on 95,605 incident cases of Crohn's disease (CD) (42,831 male and 52,774 female) and 112,004 incident cases of UC (61,672 male and 50,332 female). We pooled incidence rate ratios of CD and ulcerative colitis for the combined cohort and compared differences according to sex using random effects meta-analysis. **RESULTS:** Female patients had a lower risk of CD during childhood, until the age range of 10–14 years (incidence rate ratio, 0.70; 95% confidence interval, 0.53–0.93), but they had a higher risk of CD thereafter, which was statistically significant for the age groups of 25–29 years and older than 35 years. The incidence of UC did not differ significantly for female vs male patients (except for the age group of 5–9 years) until age 45 years; thereafter, men had a significantly higher incidence of ulcerative colitis than women. **CONCLUSIONS:** In a pooled analysis of population-based studies, we found age at IBD onset to vary with sex. Sex hormones might affect pathogenesis of IBD in patients with epigenetic and genetic risk factors. Further studies are needed to investigate mechanisms of sex differences in IBD incidence.

Keywords: Epidemiology; Estrogen; Menopause; Puberty.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are chronic inflammatory disorders of the gastrointestinal tract with marked heterogeneity in disease presentation and natural history.[1,2] The pathogenesis of IBD is complex and dictated by genetic susceptibility, dysregulation of the innate and adaptive immune systems, environmental factors, and intestinal dysbiosis. Sex differences in disease incidence and prevalence have been reported in other chronic immune-mediated disorders, such as rheumatoid arthritis, scleroderma, multiple sclerosis, and systemic lupus erythematosus, pointing to potential biological roles of sex hormones in disease pathogenesis.[3–7] Differences in IBD incidence have been reported according to the age of diagnosis, but few individual studies have examined variations in incidence according to sex and with inconsistent findings.

There is, however, accumulating evidence implicating sex hormones in susceptibility to IBD, disease symptom severity, and disease progression.[8,9] A recent meta-analysis concluded that oral contraceptive pill use is associated with an increased risk of IBD,[10] and a large cohort study of women with IBD reported changes in symptom severity during times of hormone fluctuation (eg, menstruation, pregnancy, postpartum, postmenopause).[11] Furthermore, among patients with inactive IBD at the time of cancer diagnosis, hormonal therapy, alone or in combination with cytotoxic chemotherapy, increased the risk of IBD reactivation.[12] We hypothesize that sex hormones may be implicated in IBD pathogenesis. The aim of the present study was to comprehensively assess sex differences in both CD and UC incidence according to age of diagnosis using robust population-based data.

Methods

Identification of Population-Based Studies

We reviewed a recently published comprehensive systematic review and meta-analysis describing the incidence and prevalence of IBD globally in which 260 population-based cohorts reporting incidence and prevalence rates of UC and CD were identified between 1950 and 2010.[13] An updated systematic review from 2010 to 2016 identified an additional 41 population-based studies on the incidence of UC or CD from 2010 to 2016.[14] From these 2 comprehensive studies, we identified unique population-based cohorts with incidence data reported. We additionally performed an updated search through December 2016 using this same methodology and identified 1 new population-based study that included IBD incidence data.[15] We decided a priori to include only established population-based cohorts from developed countries/provinces in the West (ie, Europe, North America, Australia, and New Zealand). This was done to maximize diagnostic accuracy and minimize heterogeneity. Because IBD is an emerging disease in the East and some developing countries, the accuracy of IBD incidence data with respect to the total population has not been established. Also,

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Abbreviations used in this paper: **CI, confidence interval; CD, Crohn's disease; ER, estrogen receptor; F:M, female-to-male ratio; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; IRR, incidence rate ratio; OCP, oral contraceptive pill; UC, ulcerative colitis.**

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