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Review Article

Review Article

Global patterns in the epidemiology, cancer risk, and surgical implications of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), mainly including ulcerative colitis and Crohn's disease, imposes a huge medical and economic burden worldwide. Recently, the diagnosis, treatment, and surveillance of IBD have advanced rapidly, which has changed the epidemiology, cancer risk, and surgery risk of IBD. Here, we reviewed the recent literature on the epidemiology, IBD-related cancer, and IBD-related surgery. We created a choropleth map to show the worldwide incidence trend for Crohn's disease and ulcerative colitis. We also found that the cancer risk and surgery risk of IBD are declining and discussed some risk factors associated with them. Based on the recent trend, we proposed several suggestions and hoped to reduce the global burden of IBD as far as possible.

Keywords: inflammatory bowel disease; ulcerative colitis; Crohn's disease; epidemiology; cancer; surgery

Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease characterized by relapsing gastrointestinal inflammation [1, 2]. It mainly includes ulcerative colitis (UC) and Crohn's disease (CD) [3]. The global burden of IBD is rapidly increasing, especially for developing and newly industrialized countries [4]. In 2017, there were an estimated 6.8 million cases of IBD, 0.83 million years of life lost, and 1.02 million years of disability attributed to IBD globally [5]. IBD has low mortality; however, its long duration and resulting hospitalizations, surgeries, ambulatory care, and pharmaceuticals have imposed a substantial burden on global healthcare systems [6]. Moreover, patients with IBD are at higher risk of developing cancer, which also exacerbates the burden. IBD-related colorectal cancer (CRC) accounts for 10%–15% of deaths in patients with IBD [7] and is also an important reason why patients with IBD undergo surgery. With various therapeutic approaches developing rapidly in the past few years, the incidence of IBD, the risk of cancer, and the risk of surgery in patients with IBD are changing. Understanding the global trend in epidemiological patterns, cancer risk, and surgery rate of IBD will give us some insight into how to allocate medical resources and reduce the burden in the future. The purpose of this review was to explore the change in epidemiology, the risk of cancer, and the risk of surgery of patients with IBD.

Epidemiology

To understand the incidence trends of UC and CD, we used data from a previous systematic review [8] and complemented literature from 1 January 2017 to 31 August 2023 by searching the PubMed database (details of literature searching strategy are provided in Supplementary Materials). The review and study that did not report an incidence or prevalence of UC, CD, or IBD were excluded. After screening, we included 103 pieces of literature on the incidence of UC, CD, or IBD and 80 on the prevalence of UC, CD, or IBD (Supplementary Tables 1–3). We extracted geographical locations, study period, population age, incidence, prevalence, and incidence trend metrics, including annual percentage change, average annual percentage change, change rate, and qualitative description. Since not all articles provide standardized incidence or prevalence, standardized incidence or prevalence was extracted if it is available, otherwise crude incidence or prevalence was used. The annual percentage change was also calculated using the Joinpoint Regression Program (Version 5.0.2, National Cancer Institute, USA), if original data were reported. The constant variance was chosen for the heteroscedastic errors option. The median year was used if the reported intervals were longer than one year.

After updating previous data with newly collected data, we identified the incidence and prevalence worldwide by the following criteria: (i) if nationwide data was available, regional data were discarded; (ii) if multiple periods for a country or region were reported, the most recent period was used; and (iii) if multiple regions within a country were reported, an average was calculated. The overall study period is from 1980 to 2021.

The incidence was stratified into five levels based on quantile (Figure 1). The regions with the highest incidence of UC and CD were North America, Europe (especially Northern Europe), and

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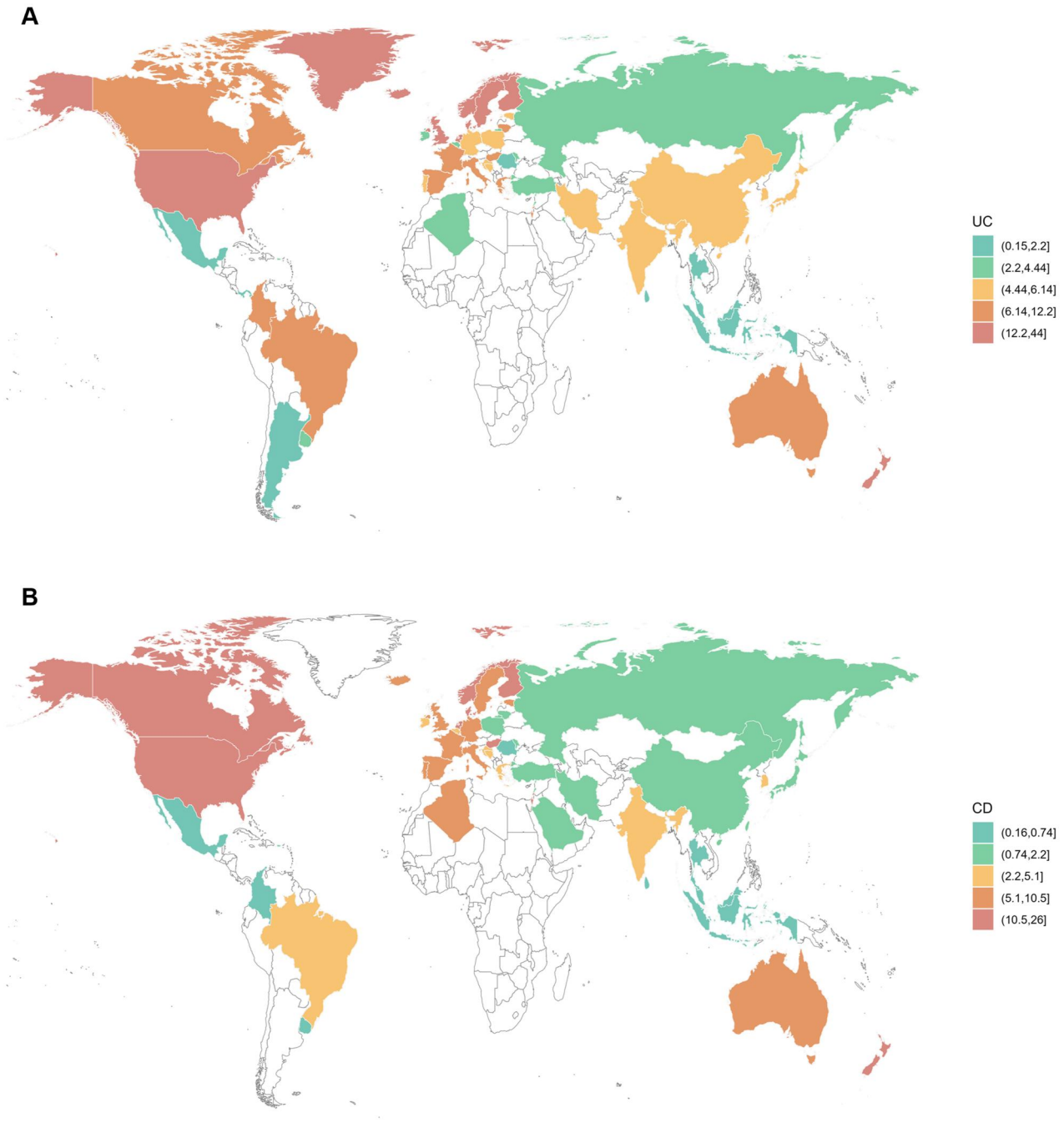

Figure 1. Map of worldwide incidence in quintiles for (A) UC and (B) CD. UC = ulcerative colitis, CD = Crohn's disease.

Oceania. Faroe Islands (44 per 100,000), Finland (35 per 100,000), and the USA (32.5 per 100,000) were the three countries with the highest incidence of UC. New Zealand (26 per 100,000), San Marino (17.9 per 100,000), and Denmark (15.6 per 100,000) were the three countries with the highest incidence of CD. The regions with the lowest incidence of UC and CD were in Asia. The Philippines (0.15 per 100,000), Brunei Darussalam (0.21 per 100,000), and Thailand (0.24 per 100,000) were the three countries with the lowest incidence of UC. The Philippines (0.16 per 100,000), Indonesia (0.25 per 100,000), and Thailand (0.28 per 100,000) were the three countries with the lowest incidence of CD.

A similar distribution was found for the prevalence of UC and CD (Figure 2). The UK (570 per 100,000), Denmark (523 per 100,000), and Norway (500 per 100,000) were the three countries with the highest prevalence of UC. The UK (26 per 100,000), Germany (322 per 100,000), and Australia (306 per 100,000) were the three countries with the highest prevalence of CD. The regions with the lowest incidence of UC and CD were in Asia. Romania (2.42 per 100,000), Sri Lanka (5.37 per 100,000), and Malaysia (8.07 per 100,000) were the three countries with the lowest prevalence of UC. Romania (1.51 per 100,000), Sri Lanka (1.77 per 100,000), and China (3.65 per 100,000) were the three countries with the lowest prevalence rates of CD.

Both the incidence and prevalence of UC were much higher than those of CD in most countries (Supplementary Figure 1). However, some countries in Southeast Asia, Western Europe, and Southern Europe, as well as New Zealand, had a higher incidence of CD than UC.

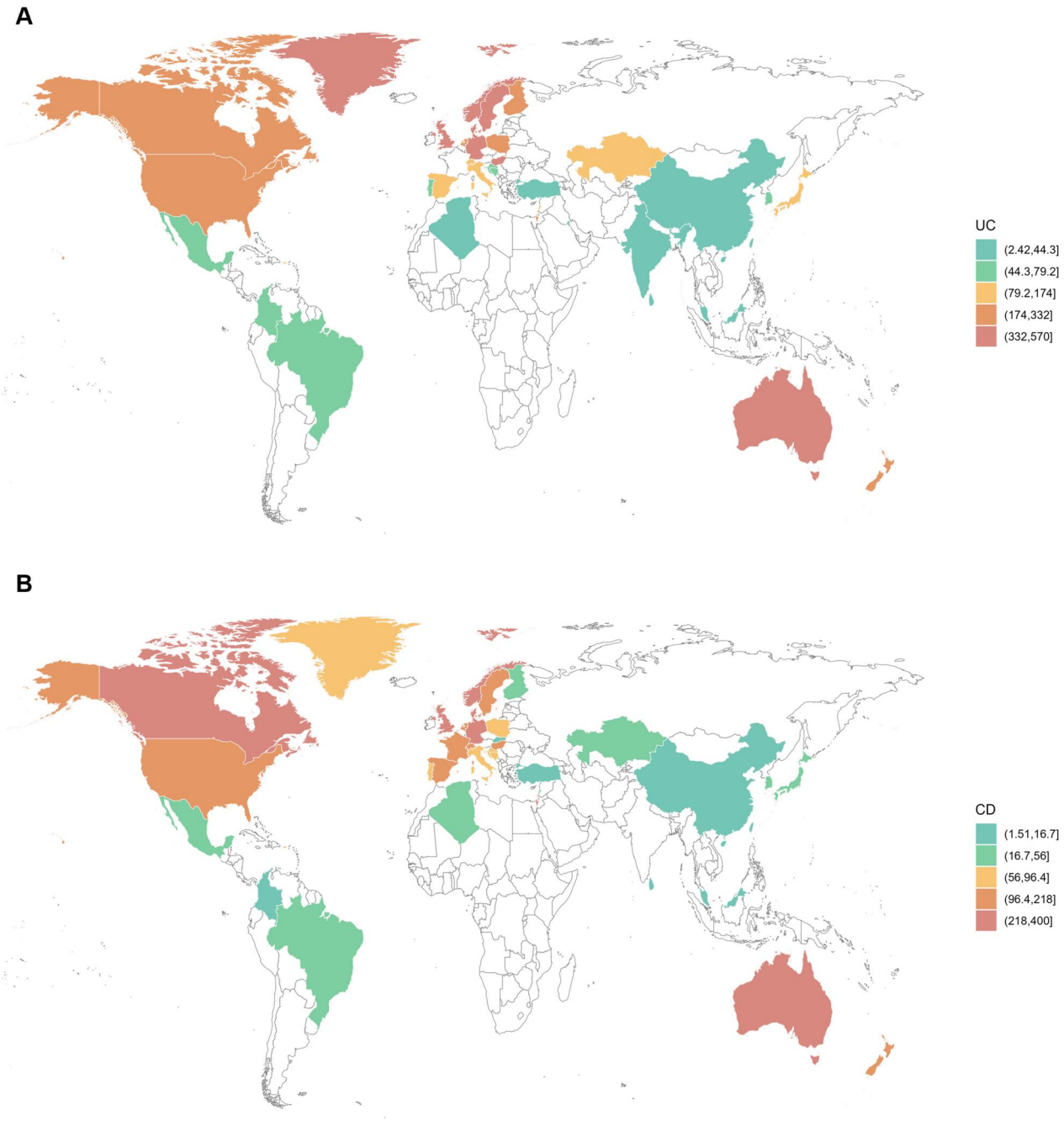

Figure 2. Map of worldwide prevalence in quintiles for (A) UC and (B) CD. UC = ulcerative colitis, CD = Crohn's disease.

In addition, we qualitatively analyzed the incidence trend. For each country, the incidence trend was determined by the following criteria: (i) if nationwide data were available, the regional data were discarded; (ii) if multiple periods for a country or region were reported, the most recent period was used; and (iii) summarizing the number of literature for every country after the previous two-step screening. If the number of filtered literature that suggests the incidence trend was increasing/decreasing was more, the increasing/decreasing trend was determined. Most studies were conducted between 1980 and 2021, but the start year in 6 studies is before 1980.

The incidence trend varied from region to region (Figure 3). Regarding UC, countries exhibiting a rising incidence trend were primarily in Asia, South America, and the southern region of North America, while those displaying a declining incidence trend were predominantly in Europe. Hungary and Norway showed stable incidence trends. In terms of CD, several countries in Asia, southern Europe, and the southern region of North America exhibited a rising trend in incidence. In contrast, countries in South America and Northern Europe demonstrated a declining trend in incidence. Israel, Norway, and the UK showed a stable incidence trend. In conclusion, an upward trajectory in the incidence of both UC and CD was observed in Asia, various countries in Northern Europe, and Central America. In Southern Europe, an upward trend in the incidence of CD was observed, while a downward trend in the incidence of UC was observed. Conversely, South America exhibited a contrasting pattern, with a declining trend in CD incidence and an ascending trend in UC incidence.

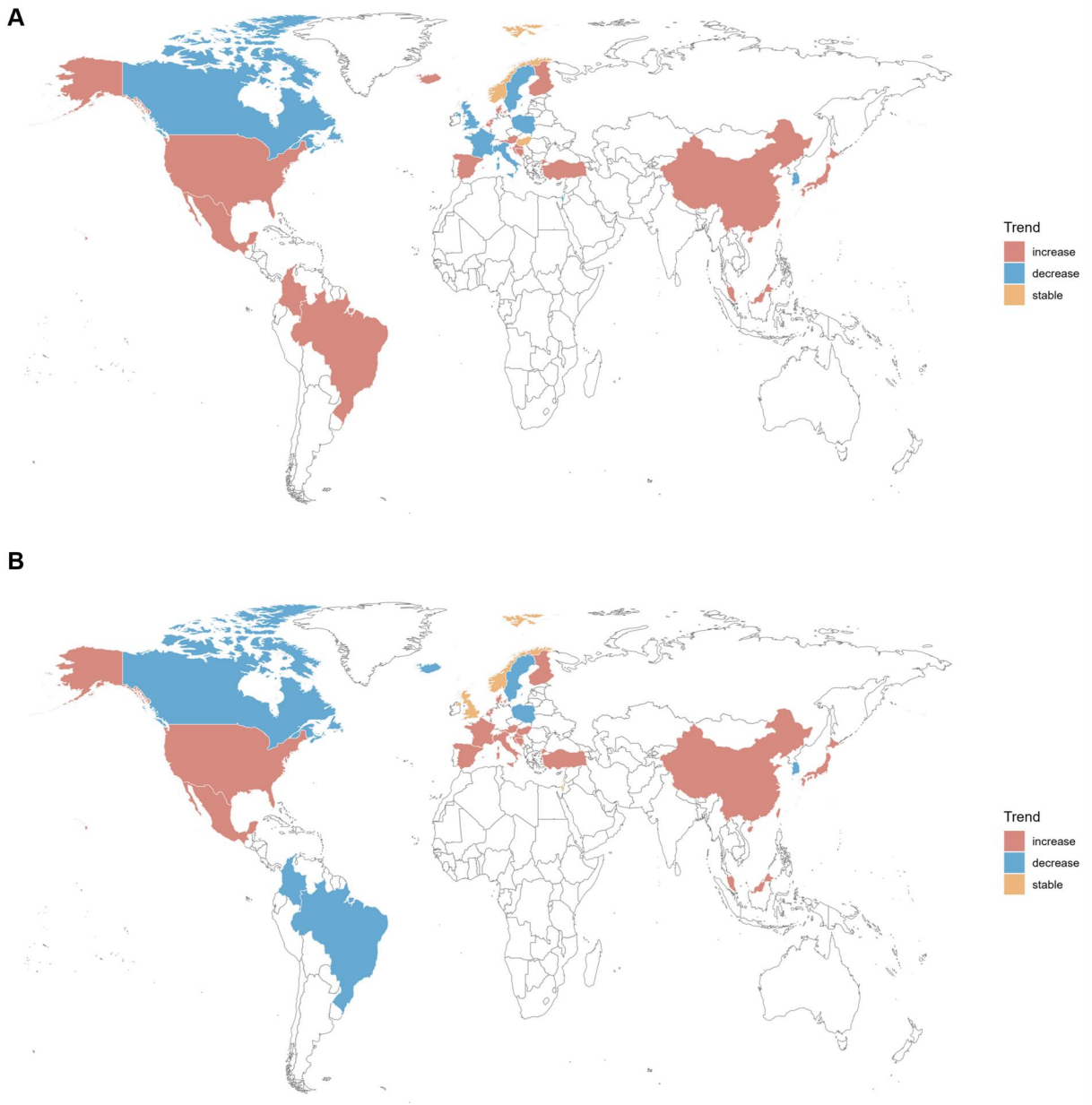

Figure 3. Map of worldwide incidence trend for (A) ulcerative colitis and (B) Crohn's disease.

Most patients develop IBD between 20 and 40 years of age, whereas about 25% of patients are diagnosed with IBD during childhood or adolescence and 10%–15% of patients develop IBD in old age [9]. Different age groups demonstrate different incidence trends. The data revealed an almost global rise in the incidence of early-onset (diagnosis at age <20 years) CD and UC during 1980–2020 (Figure 4). Recent studies found that the incidence of late-onset CD (diagnosis at age ≥60 years) is increasing in Canada (Ontario), the USA, and Denmark, but decreasing in Israel [10–14]. Similarly, the incidence of late-onset UC is rising in the USA and Denmark, but decreasing in Israel and Canada (Ontario) [10–12, 14]. In addition, China (Ningbo), Denmark, and Sweden presented an increasing trend for late-onset IBD, whereas Brazil (Rio Grande do Sul) presented a decreasing trend for late-onset IBD [15–18].

Stratified by sex, we identified that the incidence trends for males and females were identical in most countries except for the CD incidence trend in Croatia (male: increasing; female: decreasing), Iceland (male: increasing; female: decreasing), and Spain (male: decreasing; female: increasing), and UC incidence trend in China (male: increasing; female: decreasing) and South Korea (male: increasing; female: decreasing) (Supplementary Figures 2 and 3). Moreover, by comparing the unstratified incidence trend map and the stratified incidence trend map by sex, we found the distribution is similar.

Risk of cancer

Colorectal cancer

CRC is the most common cancer in CD patients. There were nearly 7.7 CRC cases among each 1000 CD patients [19]. The incidence of CRC in patients with CD reached 0.5–0.68/1,000 person-years according to a meta-analysis including papers in 1965–2008 [20, 21]. Compared with the general populations, the relative risk of CRC in CD was 2.08–2.5 and 22.01–33.2 [19, 21, 22], consistent with two other meta-analyses which reported the pooled

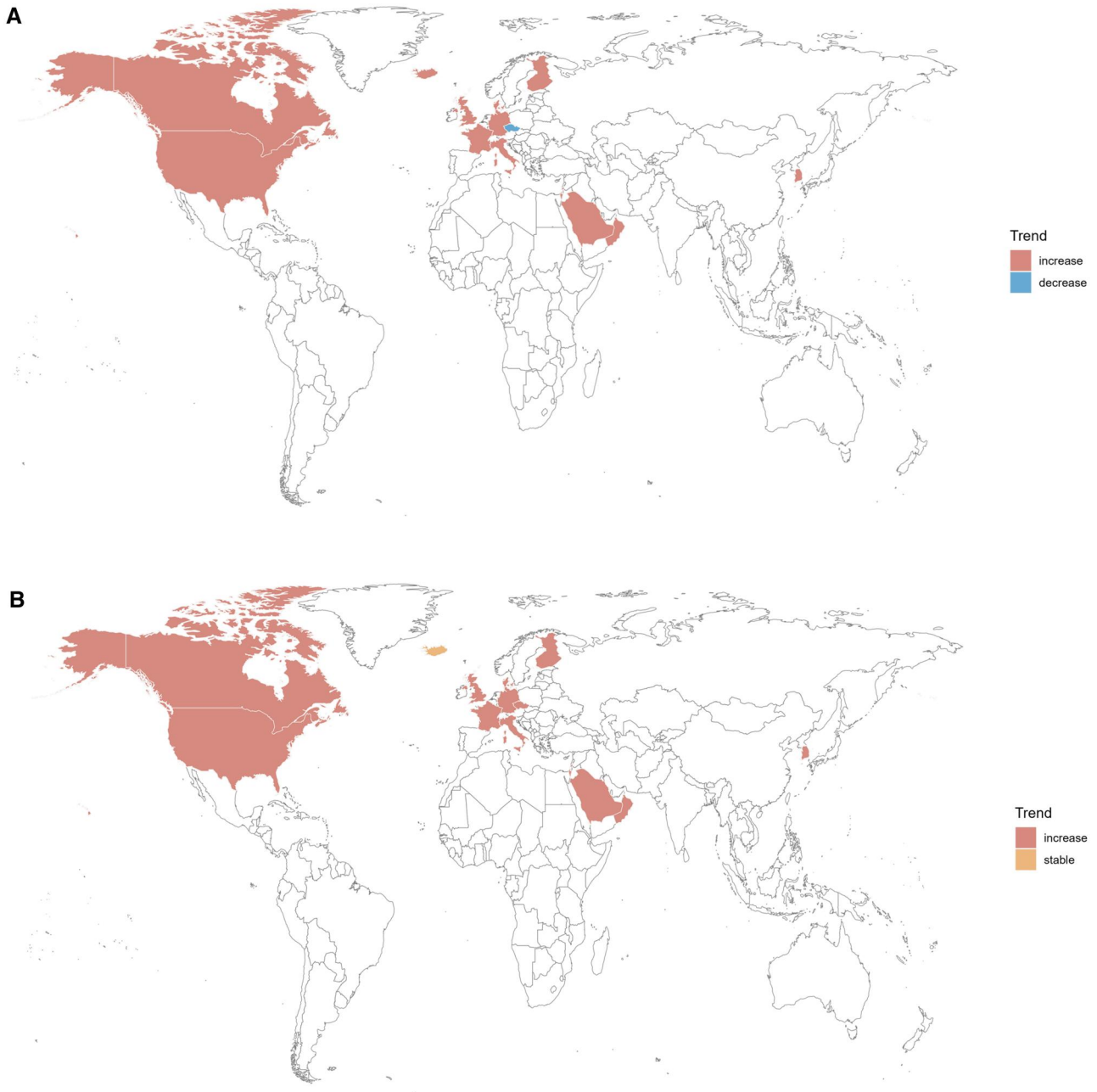

Figure 4. Map of worldwide incidence trend for (A) early-onset ulcerative colitis and (B) early-onset Crohn's disease.

standardized incidence ratio for CRC was 1.7–1.9 patients with CD [23, 24]. The relative risk and standardized incidence ratio of CRC in CD decreased approximately in 1972–2004 and 1990–2010, respectively [22, 24].

For UC, based on literature published in the twentieth century, the prevalence of CRC in patients with UC was 37/1,000 [25]. Another research included literature published from 1988 to 2018 reporting that the prevalence was 14/1,000 [26]. The CRC incidence ranged 1.58–3/1,000 according to several meta-analyses [24, 25, 27] and increased with the prolonged duration, with the incidence of the first, second, and third decades of 0.91–2/1000, 4.07–7/1,000, and 4.55–12/1,000 [25, 27]. The average pooled standardized incidence ratio for CRC was 2.4 [28]. The increased CRC incidence in patients with UC was reported between 1955 and 2000 [25], whereas a decreasing incidence was shown from 1990 to 2010 [27]. The relative risk of CRC declined from 1950 to 2013 [24], but CRC prevalence was stable from 1996 to 2018 worldwide and from 1974 to 2015 in Asia [26, 29].

Overall survival is significantly worse for patients with IBD-associated CRC than for patients with non-IBD-associated CRC (hazard ratio 1.33) [30]. When patients are stratified into CD and UC, UC patients, but not CD patients, are at increased risk of dying from CRC [31, 32].

Several factors are associated with CRC development. Patients diagnosed with IBD at a young age were at higher risk of developing CRC [21, 24, 25, 28]. In addition, the risk of developing CRC tends to increase with a prolonged IBD duration [20, 21, 24]. The mean duration of CD developing into CRC was about 18 [20, 21]. The mean age diagnosed with CRC in patients with CD was 51.5 years old [20]. Males with CD may be at higher risk of developing CRC [21, 24], while the difference was not inconclusive in patients with UC [26, 28].

Patients with CD in the UK and North America have a higher risk of CRC than patients in other countries [21, 22]. In terms of UC, patients in the UK were at higher risk, and patients in Asia and North America seemed to have a higher risk of CRC [25, 29]. However, these results may not be significant because the number of studies varies considerably from region to region.

CRC risk in patients with colonic CD is higher than in patients with ileal CD [22]. No significant influence of disease extent on the risk of CRC in patients with CD was found [20, 23, 24]. However, patients with extensive UC or left-side UC are at higher risk of developing CRC [26–28]. Moreover, mucosal and histologic inflammation is also a risk factor for patients with UC [33].

The risk of CRC still exists in patients with IBD, even after colectomy. Depending on surgical procedures, the prevalence of CRC after colectomy was 0.5%–3.2%. The degree of risk, in descending order, is ileorectal anastomosis, rectal stump, and ileal pouch-anal anastomosis [34, 35]. The incidence of CRC after colectomy was 6.5/100,000 person-years [35]. Previous colorectal carcinoma or dysplasia is a critical risk factor [34, 35].

Small-bowel cancer

The prevalence of small-bowel cancer (SBC) in patients with CD was 2.3/1,000 [19], lower than that of CRC. Similarly, the average annual incidence of SBC in patients with CD was 0.15–0.3/1,000 person-years, lower than that of CRC [20, 21]. However, the hazard ratio of SBC for CD vs the general population reached 22.01–33.2 [19, 21, 22], significantly higher than that of CRC in the same population. The pooled standardized incidence ratio and standardized mortality ratio for SBC in patients with CD were reported to be 27.1 and 4.7, respectively [23, 24, 31]. In contrast to CRC, the hazard ratio of SBC for CD did not change between 1972 and 2004 [22]. Stratified analysis showed that the risk of SBC was higher in patients with small-bowel CD than in patients with ileocolic CD [21]. Moreover, patients with CD are at increased risk of dying from SBC [31].

Extraintestinal cancers

The risk of several extraintestinal cancers is also increased in patients with CD, such as lymphoma, skin cancer, hepatobiliary cancer, oral cavity cancer, breast cancer, and lung cancer [21, 36, 37]. Similarly, the risk of cancers in bile ducts, liver, pancreas, prostate, thyroid, oral cavity, and skin is higher in patients with UC [36–40]. These increased risks may be partially due to the use of immunosuppressive agents [41, 42].

Risk of surgery

Surgery is usually the last resort for the treatment of IBD, especially when the disease is severe and uncontrolled by medication. An early meta-analysis including most studies before 2000 showed that 16.3%, 33.3%, and 46.6% of patients with CD and 4.9%, 11.6%, and 15.6% of patients with UC require surgery within 1, 5, and 10 years after diagnosis, respectively [43]. A recent meta-analysis showed that after 2000, 12.3%, 18.0%, and 26.2% of patients with CD and 2.8%, 7.0%, and 9.6% of patients with UC require surgery within 1, 5, and 10 years after diagnosis, respectively [44]. Both meta-analyses found a decreasing trend in the risk of surgery over time. In general, quality of life was increased for patients with UC after undergoing surgery [45]. However, surgical treatment does not appear to improve CD patient's quality of life in the long term [46]. Moreover, patients with CD may require a second surgery. A meta-analysis in 2014 showed that the risk of a second surgery was 24.2% and 35.5% at 5 and 10 years after the first surgery [47]. Similarly, the meta-analysis in 2021 showed that the risk of a second surgery was 17.7% and 31.3% at 5 and 10 years after the first surgery. A decreasing trend for the risk of second surgery in patients with CD was also demonstrated in both studies.

The decline in surgical risk in recent years is largely due to the use of biologics. Biologics therapy was associated with lower surgical risk for patients with CD and UC, including infliximab, adalimumab, certolizumab pegol, golimumab, natalizumab, vedolizumab, or ustekinumab [48, 49]. In addition, early biologic therapy was associated with lower surgical risk for patients with CD but with higher surgical risk for patients with UC [50]. For azathioprine, different studies showed different results. A meta-analysis in 2017 showed that azathioprine was not associated with a lower surgical risk [49]. However, a population-based cohort study in the UK found that persistence with azathioprine for >12 months can reduce the risk of surgery for patients with elderly onset UC [51].

Age of onset is an important risk factor for surgery. Patients with pediatric-onset CD showed a lower risk of surgery at 1 and 5 years after diagnosis, but a higher risk at 10 years after diagnosis (all ages: 18.7%, 28.0%, 39.5%; pediatric: 8.9%, 15.5%, 44.1%), whereas patients with pediatric-onset UC showed a higher risk of surgery at 1, 5, and 10 years after diagnosis (all ages: 4.0%, 8.8%, 13.3%; pediatric: 5.7%, 14.1%, 21.0%) [44]. Of the British population, patients with late-onset CD (≥60 years old) were at lower risk of surgery at 1, 5, and 10 years after diagnosis (late-onset: 9.5%, 14.6%, 17.9%; adult-onset: 12.2%, 19.0%, 24.4%), while patients with late-onset UC had a similar risk of surgery to patients with adult-onset CD (late-onset: 2.2%, 4.5%, 5.8%; adult-onset: 2.2%, 5.0%, 7.7%) [51]. However, of the population in Ontario, Canada, elderly UC (≥65 years old) were at higher risk of surgery and elderly CD had a similar risk to young-adult CD [52]. Besides, the risk of surgery is higher in patients with *Clostridium difficile* infection (odds ratio 1.9–2.23) [53, 54]. Sex, geographic location, disease extent, and disease behavior were not associated with the risk of surgery, except for the 1-year risk of surgery of ileum-dominant CD [44].

Discussion

Overall, the global burden of IBD is still growing. Many countries show an increasing incidence trend for IBD, and most countries with a decreasing incidence trend exhibit very high incidence and prevalence. Moreover, the cost is still high and may be higher due to the application of biologics [55]. Therefore, resource allocations, clinician training, prevention strategies, and treatment development need to evolve with the changing epidemiology. For regions with increasing incidence trends but low incidence and prevalence, gastroenterologists should improve the capabilities of diagnosing and treating IBD, researchers should investigate the difference in clinical characteristics of IBD between home and other countries, and governments should encourage the development of clinical practice guidelines. In addition, population-level interventions, based on previous experience (such as avoiding unnecessary antibiotics), to reduce exposure to modifiable risk factors are necessary. Meanwhile, it is critical to explore the factors that contribute to the decline in incidence and develop preventive strategies. For regions with stable or decreasing incidence trends but high incidence and prevalence, more effective diagnostic and treatment strategies are needed to minimize the negative health impacts and maximize cost-effectiveness, such as optimizing patient selection, dosing, and discontinuation of biologics.

Moreover, given IBD is most often diagnosed in the young and early-onset IBD is growing, clinicians should be serious about screening for early-onset IBD. Meanwhile, it remains unclear whether some treatments that can be used in adults are safe and effective when used in children. Therefore, research is also needed on the efficacy and safety of some novel biologics, such as vedolizumab, in children and adolescents.

Fortunately, the CRC risk in patients with IBD has exhibited a stable or declining trend since 1990. However, given that the prevalence of IBD is expected to increase constantly in the next few decades, the absolute cases of CRC will increase. So, we suggest active colonoscopy screening and surveillance in IBD patients to early detect and treat cancer, especially in regions with high incidence and prevalence. Surveillance and endoscopic resection of dysplasia can reduce the risk of cancer and cancer-associated death [56, 57]. The recommended time of screening initiation is 8–10 years according to several guidelines [58], and chromoendoscopy may be a better choice [59]. Early detection of SBC remains an unsolved problem. Capsule endoscopy and enteroscopy may help screen SBC, but the high cost limits its application. It is also unclear when to screen for SBC. Therefore, exploring the procedures for screening small bowels is necessary.

Besides, identifying which patients are at high risk of developing cancer is important, as it can help reduce unnecessary medical expenses. However, there is still no reliable way to predict which patients will develop cancer. What we know is just risk factors, such as young age at diagnosis, long duration of disease, extensive lesion, history of dysplasia, family history of CRC in a first-degree relative, etc. Therefore, more research needs to be done to develop clinical approaches for predicting and preventing IBD-related cancer.

The risk of surgery is also declining but the reason behind it remains elusive. The causes are possibly multifactorial, including the evolution of therapies, especially biologics, early diagnosis, and the development of clinical management [60]. We speculate that as the understanding of inflammatory bowel disease grows and diagnostic and therapeutic techniques continue to evolve, the place of surgery in treatment will diminish. But for now, surgery is still an effective way to improve the quality of life for patients with CD in the short term and cure patients with UC. Therefore, given that surgery is the last resort, clinicians should explore strategies to improve the quality of life in the long term after surgery and avoid second surgery in patients with CD.

Supplementary Data

Supplementary data are available at *Gastroenterology Report* online.

Authors' Contributions

Y.Z. and X.C. collected the data and drafted the manuscript. Y.Z. analyzed the data. H.Y. and L.W. revised the manuscript. H.Y. worked on the final approval of the version to be published. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that there are no conflicts of interest in this study.

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