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EDITORIAL

Recent trends in the epidemiology of inflammatory bowel diseases: Up or down?

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Abstract

Inflammatory bowel disease (IBD) is traditionally considered to be common in the Western world, and its incidence has sharply increased since the early 1950s. In contrast, until the last decade, low prevalence and incidence rates have been reported from other parts of the world including Eastern Europe, South America, Asia and the Pacific region. Recent trends indicate a change in the epidemiology of IBD with previously low incidence areas now reporting a progressive rise in the incidence, while in West European and North American countries the figures have stabilized or slightly increased, with decreasing incidence rates for ulcerative colitis. Some of these changes may represent differences in diagnostic practices and increasing awareness of the disease. The quality of studies is also variable. Additional epidemiologic studies are needed to better define the burden of illness, explore the mechanism of association with environmental factors, and identify new risk factors.

Key words: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease; Incidence; Epidemiology

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INTRODUCTION

The pathogenesis of ulcerative colitis (UC) and Crohn's disease (CD) is only partly understood. Inflammatory bowel disease (IBD) is a multifactorial disease with probable genetic heterogeneity. In addition, several environmental risk factors contribute to the pathogenesis. During the past decades, the incidence pattern of both diseases has changed dramatically, showing some common but also quite distinct characteristics of the two disorders. Differences in geographic distribution, and particularly changes in incidence over time within one area, may provide insight into possible etiological factors[1].

Several studies have been conducted on the epidemiology of IBD[1-3]. The geographical incidence of IBD varies considerably. The highest incidence rates are traditionally reported in Northern and Western Europe as well as North America, whereas lower rates are recorded in Africa, South America and Asia, including China[2]. It is more common in developed, more industrialized countries, pointing at urbanization as a potential risk factor. The incidence rate of UC varies greatly between 0.5-24.5/10^5 inhabitants, while that of Crohn's disease varies between 0.1-16/10^5 inhabitants worldwide, with prevalence rates of IBD reaching up to 396/10^5 inhabitants. Recent data from South Europe[3], East Europe[4] and Asia[5] in the mid-1990s report a rise in incidence values in some areas already comparable to rates reported from Northern Europe or North America. The gap between areas with conventionally high and low incidence rates is diminishing. A further difference is that the previously reported predominance of UC is diminishing, as CD is becoming more prevalent[6].

INCIDENCE IN THE WESTERN WORLD: NORTH/WEST EUROPE AND NORTH AMERICA

The first assessment of the incidence of IBD was carried out retrospectively in Rochester, Minnesota[7]. The reported incidence of Crohn's disease was 1.9/10^5 in 1935-1954. The incidence rates began to increase in the late 1930s in the United States and in the 1950s in North and Western Europe. From the 1960s onwards, an increasing number of studies of Crohn's disease and ulcerative colitis have been published. Most of these studies investigated the incidence retrospectively over rather short time periods and in small populations. Many of these studies were limited by incomplete case ascertainment.

The increase in the incidence of ulcerative colitis precedes the increase in the incidence of Crohn's disease by about 15-20 years. In the late 1990s, the incidence of UC leveled off to a plateau or even decreased[6], while the incidence of CD was still increasing in most European countries. Recent data, however, suggest a further increase in the incidence of IBD, at least in some North European countries. The prevalence of Crohn's disease in North America ranges from 26.0 to 198.5 cases per 10^5 persons.

The incidence rates range from 3.1 to 14.6 cases per 10^5 persons[1,7]. That of UC varied between 6.0 and 14.3 from 1981 to 1994. Both ulcerative colitis and Crohn's disease appear to be more frequent in the northern parts of the US than in the south.

Similarly, previous studies in Northern and Western Europe in the 1970s and 1980s suggested that the incidence is decreasing from north to south[8-11], but in the early nineties, the European IBD Study Group found comparable rates between Southern and Northern Europe[3]. During the period between October 1991 and October 1993, twenty European centers in twelve countries prospectively collected all newly diagnosed IBD patients, in a population-based manner using a standard protocol for case ascertainment. The overall incidence was $10.4/10^5$ for ulcerative colitis (northern centers: $11.8/10^5$ *vs* southern centers: $8.7/10^5$) and $5.6/10^5$ for Crohn's disease ($7.0/10^5$ *vs* $3.9/10^5$). For UC, the highest incidence was found in Iceland and the lowest in southern Portugal. For CD, the highest incidence rates were observed in the southeastern Netherlands and in northwestern France. Nonetheless, the excess in northern centers was less pronounced than previously reported. Similarly, gradually increasing incidence values were reported from Italy between 1978 and 1992 (from $3.8/10^5$ to $9.6/10^5$ for UC and from $1.9/10^5$ to $3.4/10^5$ for CD) in the well-known Florence study[8]. In addition, in recent publications, the incidence rate of UC in Central Greece has been reported to be as high as $11.2/10^5$, similar to that observed in high incidence North European centers[9].

In addition, we have to note that continuously increasing incidence values are still reported from some high incidence areas, e.g. Denmark and Sweden. Earlier studies have reported an incidence of $4.1/10^5$ for CD and $9.2/10^5$ for UC from the 1980s[10], while recent data in 2003-2005 indicate even higher incidence rates (CD: $8.6/10^5$, UC: $13.4/10^5$)[11]. In Stockholm, the corresponding incidence data for CD in 1990-2001 were $4.9/10^5$ in 1985-89 and $8.3/10^5$ in 1990-2001[12]. In contrast, data from the UK indicate a plateau with an incidence around $10.0/10^5$-$13.9/10^5$ for UC, while it is still increasing ($3.9/10^5$-$8.3/10^5$) in CD[13].

A further difference is that the previously reported predominance of UC is diminishing, as CD is becoming more prevalent. Furthermore, decreasing incidence values in 1988-1999 were reported from Northern France. The incidence of CD was increased slightly from $5.2/10^5$-$6.4/10^5$, while that of UC decreased from $4.2/10^5$ to $3.5/10^5$ [12].

INCIDENCE OF IBD IN OTHER PARTS OF THE WORLD: EAST EUROPE, ASIA AND SOUTH AMERICA

Until recently, only limited data was available on the epidemiology of IBD from other parts of the world. Most of these data are retrospective, hospital based surveys. One of the few exceptions is the study by Vucelic *et al*[14] from Croatia, who conducted a prospective study on the incidence of IBD in Zagreb in 1980-1989. The study was population-based, including inpatient and outpatient data, as well as general practitioners' reports. The reported incidence rate is $1.5/10^5$ inhabitants for UC and $0.7/10^5$ for CD. The prevalence of UC and CD was $21.4/10^5$ and $8.3/10^5$ respectively at the end of 1989.

In the last few years, a significant number of papers and reviews have been published on the epidemiology of IBD from Eastern Europe and Asia[4,5]. However, there is still a significant lack of data from Latin America, Africa and Australia. Most of these studies have reported a change in the epidemiology of IBD. The rise in incidence began in the early 1990s, in parallel with changes in governing systems and social environment. In Eastern Europe, a population-based epidemiology survey from Hungary[15] reported a sharp increase in incidence of UC from $1.7/10^5$ during 1977-1981 to $11.0/10^5$ during 1997-2001. In CD, a similar trend was observed (from $0.4/10^5$ to $4.7/10^5$). The ratio of UC/CD incidence rates decreased from 4.0 to 2.3 during the observed periods. The prevalence of UC and CD was $142.6/10^5$ and $52.9/10^5$ inhabitants respectively at the end of 2001. Similarly, in a prospective study Mijandrusic Sincic *et al*[16] reported much higher rates in Croatia ($7.0/10^5$ for CD and $4.3/10^5$ for UC) in 2000-2004 compared to previous reports.

In contrast, a questionnaire-based nationwide epidemiological survey[17] from Romania, over a period of one year between June 2002 and June 2003, still reported low incidence of both UC ($0.97/10^5$) and CD ($0.50/10^5$). Corresponding prevalence data were also very low ($2.25/10^5$ in UC and $1.51/10^5$ in CD). Similarly, low incidence was reported in a population-based prospective study from Estonia[18]. The data were collected between 1993 and 1998 in Tartu country (151 301 inhabitants) from the internal medicine, paediatrics and surgery departments. A total of 16 UC and 13 CD patients were diagnosed, equalling an average incidence of $1.7/10^5$ for UC and $1.4/10^5$ for CD. However, the relative small area and small absolute number of patients might have biased the data.

Similar trends in UC have been observed in Asia. Although both incidence and prevalence rates of IBD are still low compared with Europe and North America, they are rapidly increasing. An emergence of UC is apparent. In contrast, the incidence of CD is still low. An analysis of UC patients from China reported a total of 10 218 cases from 1981 to 2000[19]. Of these, 2506 were diagnosed between 1981 and 1990, and 7512 between 1991 and 2000, a three-fold increase. The most recent review [11] of Chinese literature reveals that 143 511 cases of IBD (140 120 of UC and 3391 of CD) were described during the last 15 years, with an 8.5-fold increase during the last 5 years compared with the first 5 years. In addition, though figures are still low, Leong *et al*[20] reported a three-fold increase in the incidence of CD in the Chinese population of Hong Kong, from $0.3/10^5$ in 1986-1989 to $1.0/10^5$ in 1999-2001. A hospital-based study came to the same conclusions. An estimated incidence of $0.28/10^5$ and a prevalence of $1.38/10^5$ were reported between 1950-2002 from 22 provinces of China[21].

Recent reviews from Japan also report an increase in the incidence and prevalence of IBD. Hospital-based investigations reported that the incidence of UC was $1.95/10^5$, and the prevalence was $18.12/10^5$ in 1991[21]. In a retrospective study from Seoul, South Korea, the

prevalence of UC was $7.57/10^5$, with a significant increase in incidence rates from $0.20/10^5$ in 1986-1988 to $1.23/10^5$ in 1995-1997[21]. In Thailand, UC is still uncommon, with only 40 cases reported between 1988 and 2000[22].

Singapore is also witnessing a higher prevalence of IBD, recently estimated at $6/10^5$[23]. The current prevalence of UC is $17/10^5$, whereas that of CD is lower, at $3.6/10^5$. The impact of ethnicity in various Asian populations has also been studied in Singapore, a multiracial city-state composed of Chinese, Malay and Indian groups[24]. The prevalence of UC in the three races has been calculated to be $6.2/10^5$ for Chinese, $4.8/10^5$ for Malay and $16/10^5$ for Indian subjects. Similar prevalence data were reported from a recent retrospective hospital-based study from Kuala Lumpur, Malaysia. The prevalence of UC was $17.9/10^5$ in Indians, followed by $11.2/10^5$ in Chinese and only $3.7/10^5$ in Malays between 1985 and 1998. No such marked difference was seen in CD. The prevalence rates in Chinese, Malays and Indians were $4.0/10^5$, $2.9/10^5$ and $4.9/10^5$, respectively[23].

The lower prevalence and incidence of IBD in Asia compared with the West are not universal. A population-based study from Northern India found that the prevalence rate of UC is $42.8/10^5$[25]. This unexpectedly high prevalence has been recently confirmed by another population-based study in Punjab, also in Northern India, revealing a prevalence of $44.3/10^5$ and an incidence of $6.02/10^5$[26]. However, a major limitation of these studies is that they only screened a population sample of around 22 000 and 52 000 inhabitants, respectively. Thus, the results rely on a very small number of definite cases extrapolated to the whole population of the area.

IBD in Middle-East is traditionally reported to be high among Jews from the United States and Northern Europe. In Israel, the incidence is somewhat lower and Ashkenazi Jews have a higher incidence than Sephardic Jews. In 2000, Niv *et al*[27] reported an annual incidence of $5.04/10^5$ for UC for a ten-year follow-up period between 1987-1999. The prevalence rate rose from $121.0/10^5$ to $167.2/10^5$.

In contrast, Arab countries in the Middle East still report low incidence rates. A prospective hospital-based study from Saudi Arabia[28] reported an estimated incidence of $0.5/10^5$ and prevalence of $5.0/10^5$ for IBD in children in 1993-2002. Similarly, a retrospective study from the same region estimated a $0.94/10^5$ mean incidence of CD in 1983-2002, with a gradual increase in incidence from $0.32/10^5$ to $1.66/10^5$[29]. In contrast, in Turkey the incidence of UC was as low as $0.59/10^5$-$0.69/10^5$ between 1998 and 2001, in a hospital-based study[30]. Finally, a recent case series from Teheran, Iran suggests very low incidence rates, since authors reported that only 448 IBD patients were referred to or diagnosed in two university hospitals and two private GI clinics between 1992 and 2002[31].

Only limited data are available from Central and South America. A recent prospective study has reported the incidence of IBD in Puerto Rico[32]. The total incidence of IBD increased significantly between 1996 and 2000 ($3.07/10^5$ to $7.74/10^5$), being significantly higher than CD. In contrast, much lower incidence rates were reported from a population-based survey from Panama and Argentina[33] in 1987-1993. The annual incidence of UC was $1.2/10^5$ in Panama and $2.2/10^5$ in Argentina, with only a single case of CD being identified. Similarly, the incidence of both UC and CD admissions is low in Brazil with only 257 new cases (126 CD and 131 UC) diagnosed in 1980-1999[34].

Finally, Gearry *et al*[35] have recently reported one of the highest incidence rate of CD from New Zealand in 2004. The reported incidence of CD is $16.5/10^5$ and the incidence of UC is lower ($7.6/10^5$). Corresponding prevalence rates are $355.2/10^5$ and $145.0/10^5$.

INFLAMMATORY BOWEL DISEASE IN CHILDREN AND ELDERLY

It is important but difficult to study the epidemiology of IBD in children. Although both UC and CD are rare below the age of 11 years, the incidence of these diseases increases rapidly after adolescence. In the pediatric age group, several epidemiologic studies have been published with some evidence suggesting that the incidence of IBD (in particular, CD) has increased over the last ten years.

The explanation for the differences in incidence between studies is further complicated by different definitions of childhood. The upper age limit varies between 14 and 17 years of age. Furthermore, upper gastrointestinal involvement is reported to be more common in children with CD. In addition, we have to note that new diagnostic tools may lead to overinterpretation of IBD emergence, since the clinical importance of minute lesions such as small erosions diagnosed during capsule endoscopy or double-balloon enteroscopy, which may be often diagnosed as IBD in children with abdominal pain, is still to be determined. To exclude this possibility, new uniform criteria have been developed for the diagnosis of IBD in children by ESPGHAN[36].

Most of the published data come from the United States and Western Europe. The largest prospective study from the United Kingdom and Ireland has reported a well-characterized cohort of 739 children with IBD[37]. The mean incidence of CD and UC is $3.0/10^5$ and $1.5/10^5$. Higher values were reported in a prospective study from Wisconsin, United States between 2000 and 2001[38]. The mean incidence of CD and UC is $4.5/10^5$ and $2.1/10^5$, respectively.

A further population-based study from Copenhagen[39] reported that 7% of the 1161 patients diagnosed with UC and 6% of the 373 patients with CD had an onset before 15 years of age. The median age at diagnosis was 12 years (range 0-14 years), indicating a steep increase in incidence around puberty. During the 26 years of the study, no significant change in incidence was found, the mean incidence of IBD was $2.2/10^5$ (UC: $2.0/10^5$ and CD: $0.2/10^5$). In another study of a large area of Sweden, Lindberg *et al*[40] prospectively studied all patients below 16 years of age with a diagnosis of definite or probable UC and CD in 1984-1995. An increase in the incidence of UC was found (from $1.4/10^5$ to $3.2/10^5$), but only in the age group of 11-16 years, not in early childhood. The incidence of CD did not change over the time studied.

In contrast, other studies have reported a marked increase in the incidence of pediatric IBD. A slight increase in the incidence of juvenile onset CD was reported from Scotland between 1981 and 1995 with marked differences in the incidence of CD between north and south[41]. The incidence of UC and CD increased over the observed period in both south (UC: 0.9-1.6/10^5 and CD: 1.8-2.5/10^5) and north (UC: 0.9-1.8/10^5 and CD: 2.8-3.5/10^5) territories. Similarly, an increase in the incidence of CD was reported in a prospective study from northern Stockholm between 1990 and 2001[42]. The incidence in CD rose from 1.5/10^5 to 8.4/10^5 (mainly in the age group of 10-15 years), while that of UC was relatively stable at approximately 1.8-1.9/10^5, except for 1990-1992. One of the largest studies has been reported from Northern France[43]. In a prospective follow-up study, a total of 7066 patients were diagnosed, 509 (7.2%) of them were under the age of 17 years at the time of diagnosis. During follow-up, a trend for an increase in the incidence of CD was observed (from 2.1/10^5 to 2.6/10^5), while the incidence of UC remained unchanged (0.8/10^5).

In Eastern Europe, Pozler *et al*[44] have recently published the results of a retrospective study investigating the incidence of CD in the Czech Republic in children diagnosed under the age of 15 years between 1990 and 2001. A marked increase in the incidence of CD was reported from 0.25/10^5 in 1990 to 1.25/10^5 in 2001.

The same trend has been reported from Melbourne, Australia[45] in a retrospective, hospital-based study in children diagnosed under the age of 16 years. The incidence of CD rose from 0.13/10^5 to 2.0/10^5 between 1971 and 2001.

An interesting question is the incidence of IBD in elderly populations. At least according to the published data from Western Europe, it may not be as uncommon as previously suspected. A prospective Belgian study[46] between 1993 and 1996 reported that the incidence of IBD in the elderly population (age at diagnosis > 60 years) is high (UC:4.5 and CD:3.5), was comparable to the figures for younger age groups (UC: 3.4 and CD: 4.8).

Similarly, comparable incidence rates for CD have been reported from France between 1994 and 1997[47]. The annual incidence rate is 2.5/10^5, with a higher proportion of colonic disease.

HOW CAN WE EXPLAIN THE RECENT EPIDEMIOLOGICAL TRENDS?

The incidence of IBD varies greatly worldwide. Genetic and environmental factors are assumed to play a significant role in the aetiology of the disease. The role of genetic factors is supported by ethnic and familial differences as well as twin studies[1,4], while the differences in incidence rates among various geographical areas suggest a role of certain environmental factors. It is known that the incidence differs among different ethnic groups living in the same geographic region. This fact is mostly observed in Asian countries[5,24]. Similarly, the genetic predisposition may have led to the observation that the risk for IBD in Asian immigrants surpassed that observed in UK's native population with an odds ratio of 6.1[48]. In addition, disease phenotypes may also vary among different races, e.g. in a recent study from the United States[49] reported that African American CD patients are more likely to develop upper gastrointestinal, colorectal or perianal disease, uveitis and sacroileitis compared to whites, while Hispanics are at higher risk of developing perianal disease or erythema nodosum, supporting a role of underlying genetic variations. Finally, the prevalence of identified genetic risk factors (e.g., NOD2 in CD) is also different in the different populations.

An important change in the incidence of IBD has taken place in the last few decades. In most of the Western Europe countries, the incidence rate remains relatively stable or even decreased. In contrast, continuously increasing incidence rates of CD have been recently reported from other high incidence areas such as Denmark[11] and Sweden[12]. There is also an important change in the diagnosis of CD. A new classification system has been developed[50], as well as new tools which are readily available for the investigation of the small-bowel (e.g., capsule endoscopy[51,52] and double balloon enteroscopy[53]), which may lead to a further increase in reported incidence rates. As a consequence, an unusually high upper gastrointestinal involvement (as high as 55%) has been reported in recent genetic studies in pediatric settings[54]. A similar trend is also apparent in the adult cohorts. Nonetheless, it is important to note that the clinical importance of minute lesions still needs to be determined. Capsule endoscopic examinations due to abdominal pain can reveal small lesions (angiodysplasias and small erosions) in similar percentages of subjects[55]. Since the penalty for false-positive testing is very high (unnecessary use of toxic and expensive medications, and the stigma of being diagnosed with a serious chronic disease), at present, capsule endoscopy and double balloon endoscopy should be used only in limited clinical situations rather than routinely. In addition, the interpretation of microscopic disease, especially in children is rather controversial. Nonetheless, this still does not explain the higher incidence values reported in recent studies.

In previously low-incidence areas, especially in Eastern Europe[4,15,16] and some regions in Asia[26], the disease has become more prevalent. Until now, the role of private practice is limited in Eastern Europe and most Asian countries and the majority of patients are managed in the public health care system, enabling population-based epidemiological investigations. The diligent collection of data and case ascertainment is, of course crucial.

The increased incidence rates of both UC and CD observed in Eastern Europe and Asia raise further questions. What could be the cause of this change? In the 1970s and early 1980s the lower incidence rates could be partially explained by the use of fewer up-to-date diagnostic procedures (e.g., the relative low availability of selective enterography or colonoscopy). It is also possible that greater awareness, either by physicians or by patients, may result in the diagnosis of mild cases that might have been previously unnoticed. There has also been an important change in patients' behaviour, at least in Eastern Europe, as patients tend to seek medical advice more often and with milder

symptoms than they did two decades ago. In contrast, in Eastern Europe, due to various and multiple causes, the access to health care services has not improved much. The reported incidence rates of IBD in Hungarian[15] and Croatian[16] are in a similar range, as previously observed in Nordic countries[3,56,57]. In contrast, other countries (e.g., Czech Republic, Poland, Romania and Slovakia) still report low incidence rates. These studies however, have several limitations. Some of them were retrospective surveys[44], while others were based solely on the in- and outpatient records of a single hospital, extrapolating the results to the investigated area[4]. Patients might have been unnoticed, thus the incidence rate is clearly underestimated. We believe that the increase in the incidence of IBD in Eastern Europe in the late 1980s and 1990s is real and not solely due to improved diagnosis, better health care access or more extensive search. This notion is also supported by the increase in more severe cases, which can only be interpreted as real.

The observed changes may be at least partially explained by the differences in study design. Most of the earlier studies from Eastern Europe, and still the majority of studies from Asia[19,23], Middle-East[29,30] and Central America[33] are biased by methodological shortcomings. A great majority of them were retrospective, hospital-based surveys, which may have at least partly been responsible for the low incidence rates reported. In contrast, recent prospective, population-based studies, especially from Eastern Europe with extensive search for IBD cases[25,32] have reported much higher incidence rates from the same regions with some exceptions[20]. The situation is somewhat different in India. Though papers are prospective[25,26], results might have been biased by methodological problems. Only questionnaire-based surveys were conducted and only a limited population sample was screened. Thus, the results rely on a very small number of definite cases extrapolated to the whole population of the area.

Diet, as a luminal antigen, is thought to be an important factor in the pathogenesis of IBD[1,58]. In the last two decades, there has been a change in the lifestyle in Eastern Europe, Asia and Central America, as the standard way of living, including the diet, has become more "Westernized". This possibility is further supported by the differences in incidence and prevalence found within one region. In Eastern Europe[4,15], the change in the incidence is parallel to the change in governing system and the prevalence is clearly different between the more "Western"-type living in the western regions, as opposed to the less rapidly changing eastern parts.

This raises the possibility that the prevalence of IBD, e.g., in the eastern parts of Europe and Asia is also capable of changing in the next one or two decades. An early signal of this change might be the reported increase in the incidence of UC in many of the Asian countries. Since the change in incidence of UC precedes that in CD in most countries, it is possible that different environmental factors are responsible for the increase in the incidence of UC and CD. Alternatively, the same environmental factors may act differently in the two diseases, resulting in different epidemiological patterns. This is supported by the recent trends in the incidence of UC in Asia and the similar changes in the late 1980s and early 1990s in Eastern Europe, where the increase in the incidence of UC precedes that of CD. It is therefore, of outstanding interest to follow the temporal trends of IBD epidemiology in Asia, Eastern Europe and Central America. In addition, these studies offer a unique possibility to extensively study the role of possible environmental risk factors in the susceptibility of IBD.

Other possible environmental factors, such as perinatal events, childhood infections or measles have not been investigated outside North America and Western and Northern Europe[59,60]. Measles vaccination is however universal in Eastern Europe making the disease very rare, in addition to a low birth rate. Early childhood hygiene is also well developed, supporting a possible role of the "oversheltered child" theory[61]. The hygiene hypothesis suggests that skewing of the Th1/Th2 balance in early life is a major cause for the recent increase in allergic and autoimmune diseases. Recent data from different regions of Canada have controversial results[62,63]. Nonetheless, since early and high level of childhood hygiene has existed, at least in Eastern Europe since the early 1970s, it does not explain the epidemiological trend observed in the late 1990s. In addition, the reported prevalence of other known environmental factors (e.g., smoking, frequency of appendectomy, contraceptive and use of NSAID and antibiotics) did not change significantly in the last decades, thus it is unlikely that these factors are essential in evolution of the epidemiology trends.

The incidence of IBD varies greatly worldwide. In traditionally high incidence areas, e.g. in West European and North American countries the figures have stabilized or slightly increased, with even decreasing incidence rates for ulcerative colitis. In contrast, low prevalence and incidence rates have been reported from other parts of the world including Eastern Europe, South America, Asia and the Pacific region. Recent trends however, also indicate a change in the epidemiology in these countries, since previously low incidence areas are now reporting a progressive rise in the incidence. Some of these changes may represent differences in diagnostic practices and increased awareness of the disease. The quality of the surveys is also variable. Most probably, inadequately identified environmental factors or a combination of these factors may be responsible for the recent rapid changes. Additional epidemiologic studies are needed to better define the burden of illness, explore the mechanism of association with environmental factors, and identify new risk factors.

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