Chapter 2
The Changing Epidemiology of IBD

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Keywords  Inflammatory bowel disease • Crohn’s disease • Regional ileitis
• Kenneth Dalziel • Burrill Crohn • Ulcerative colitis • Epidemiology • North–South
gradient • West–East gradient • Appendectomy • Smoking

Key Points

• Incidence rates of IBD are increasing in areas of the world previously unaffected
  by these diseases.
• Among children, the incidence of Crohn’s disease (but not ulcerative colitis) has
  greatly increased.
• Age-specific incidence rates are highest for patients aged 20–40 years old.
• Specific population incidence rates first increase for ulcerative colitis, with an
  increase in Crohn’s disease seen 15–20 years later.
• Environmental factors associated with a decreased incidence of ulcerative colitis
  include smoking and appendicitis.
• Smoking is associated with a greater incidence of Crohn’s disease. A putative
  “North–South” in Northern America and Europe has been challenged by more
  recent studies.

Introduction

It has been possible in any given year during the last hundred years to write a
review article or a book chapter titled “The changing epidemiology of IBD”
which could make the case that what was written last year at least to some extent

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was obsolete. The reason for this is better methodology on how to deal with observational data but foremost is that the disease entities ulcerative colitis (UC) and Crohn’s disease (CD) during the last century have affected new populations or new segments of populations. Why should we be interested in such changes? There are at least three different reasons:

1. In order to fulfill our goal of finding primary prevention measures for inflammatory bowel disease (IBD), changes in the descriptive epidemiology could provide hints of the underlying causes of these diseases.
2. These changes should serve as benchmarks when new hypothesis of the etiology are presented.
3. The numbers are of interest for providers of healthcare in order to assure that there is clinical expertise available for these patient groups.

**IBD up to 1950**

During the nineteenth century, there are scattered cases of UC described especially in the British literature. Already in 1909 there was a symposia held at the Royal Society of Medicine in London, where 317 patients from different hospitals were presented [1]. In 1913, Kenneth Dalziel, a Scottish surgeon, reported nine patients with a new disease entity described as “chronic intestinal enteritis and not tuberculosis” [2]. These nine patients are the first bona fide cases of CD although other patients have been described during the same time period both from Scandinavia and Ireland [3]. However, it was not until 1932 when Dr Burrill B Crohn introduced the term “regional ileitis” [4] and CD as a defined clinical entity was established.

Different case series were presented during the first half of the twentieth century, but they have in most instances one common feature; the lack of a denominator making it impossible to assess any prevalence or incidence figures. It is therefore impossible to describe any temporal trends during this time period. To use only the number of patients as a proxy is also without meaning as it is impossible to disentangle if the increasing number of IBD patients is due to a better awareness among clinicians or reflects a real increase in incidence.

However, there are two retrospective studies in defined populations from 1935 and onward, which have tried to assess the incidence. In one study from Rochester Minnesota, the authors were able to demonstrate an annual incidence for UC of 6.0/100,000 for the period 1934–1944 and an annual incidence for CD of 1.9/100,000 for the period 1935–1954 [5, 6]. In another study from Cardiff, UK, there was an annual incidence of 0.2/100,000 for CD during the period 1935–1945 [7]. Finally, there is one study of data from the US Army where the risk of discharge for an underlying cause of UC was assessed, where Jewish ethnicity was associated with an increased risk of such discharge compared to other ethnic groups [8].

Thus, in 1950 there was a growing understanding of a correlation between UC and CD (see below), the hypothesis of a Jewish ethnicity as risk factor had been formulated, and that IBD at least in some populations constituted a clinical problem of some magnitude.
1950–1975

During this period, there were an abundance of retrospective studies published from different populations, especially in Western Europe [9–12] but also in Northern America [13]. There were some common patterns with regards to the descriptive epidemiology in all these studies; there was a strong correlation between UC and CD, i.e., populations with a high incidence or mortality of UC had also a high incidence of mortality of CD and vice versa [14]. There are at least three possible partly overlapping explanations for these correlations.

1. Misclassification of either UC or CD which would lead to a false high incidence of either one of the disease entities.
2. There are shared genetic or other environmental risk factors for the two diseases.
3. It is the same disease and UC and CD represent opposite ends of a continuous spectra.

Later studies have shown an association between family occurrence of UC and CD, i.e., individuals with a family history of CD are at an increased risk for CD and vice versa [15]. However, such an association is not sufficient to explain the temporal trends for these diseases when they emerge. An increase in UC precludes an increase in CD with around 15–20 years [16]. During this transition period, the increase in incidence and the age distribution will change. Populations with a low annual incidence have an almost flat age-specific incidence, but during the transition from low incidence to high the increase is most pronounced in the age group of 20–40 years both for UC and CD [9, 17]. Although there have been quite a few reports about a second peak in older ages (60+), the existence of such peak remains controversial, and it has been argued that this second peak represents a delayed diagnosis made when the disease relapses [7].

There were also rather small variations in the incidence figures after the transition period 4.0–8.0/100,000 for CD and 15–20/100,000 for UC [16]. Moreover, the age-specific incidence was similar in most populations, such as Sweden and Olmsted County, USA [16, 18, 19]. It is also worth pointing out that due to the differences in the start of the transition period, the prevalence figures could vary substantially in different populations although they had the same annual incidence. This means that prevalence figures are highly unreliable tools to compare the occurrence of IBD in different populations or over time.

Other features which changed during this period were the phenotypes, such as the extent of the disease and localization. In the 1960s, ulcerative proctitis or distal colitis emerged as a specific phenotype [20] as common as pancolitis in patients with UC [16]. In the case of CD, distal ileitis had been the normal feature, but during the 1960s a new phenotype + Crohn’s colitis was described [21]. This disease entity had probably to some extent previously been categorized as UC, but it was obvious that this clinical phenotype became more frequent during the second part of the twentieth century.

During this period, the first reports were published of cigarette smoking as a protective factor against UC [22, 23]. Many exposures, especially dietary, such as
refined sugar, margarine, etc., was proposed as etiological exposures, but the results from analytical studies did not show consistent results [24]. Jewish ethnicity and high socioeconomic status were repeatedly shown to be associated with an increased risk of IBD [11, 25]. However, these studies were in most instances small and with a study design, which was not always optimal.

1975–2000

During this time period, an ever increasing number of retrospective studies were published with descriptive data from different parts of the world although mainly Western Europe and Northern America. It then became obvious that some new characteristics of IBD had emerged as follows;

1. There were reports of a North–South gradient in the occurrence of IBD both from Northern America and Europe [26] in the first half of the period an observation which was challenged in the later part of the period [27] and a “new” hypothesis emerged speculating in a West–East gradient.
2. The incidence of IBD seems to respect national borders [28, 29] although there are exceptions such as in Greece where Crete has higher incidence than the rest of the country [30, 31].
3. In some populations, a birth-cohort effect could be demonstrated [16, 32] indicating that early exposures are of importance in the etiology of IBD.
4. In line with this good hygiene during childhood was repeatedly implicated as a risk factor both directly and indirectly [33, 34].
5. Previous findings of high socioeconomic status as a risk factor for IBD was contradicted in studies from this period and even a reverse association was found [35].
6. Incidence studies from Israel did challenge the notion of Jewish ethnicity as an independent risk factor as the incidence of IBD in Israel did not differ from populations in Western Europe and Northern America [27].
7. Immigration studies especially from the UK also showed that second generation immigrants from the West Indies [36] and the Indian subcontinent [37, 38] had the same or even higher incidence of IBD as the background population casting doubts of a special vulnerability among Caucasians.
8. Minorities often with a lower socioeconomic status, such as Maoris in New Zealand [39], Bedouins in Israel [40], and Aboriginals in Canada [41] were found to be at a substantially lower risk for IBD.
9. The pattern of a higher incidence in UC compared to CD turned out not to be a generalized phenomena when studies from France [27] and some parts of Canada [42] were able to demonstrate the opposite.

During this period, the first prospective studies of the incidence in IBD were published [27, 43], highlighting the problem of indeterminate colitis [44] something which can be downplayed in retrospective studies. Indeterminate colitis
turned out to be much more common than previously thought [45] and it still remains to be established if it is an entity of its own. The most prominent prospective study was a collaborative effort from 20 European centers 1991–1993. The study was able to demonstrate that the North–South gradient seemingly was history and that the incidences of IBD in different populations throughout Europe were remarkably uniform [27].

Smoking remained the only environmental factor which consistently was associated with IBD; as a protective factor for UC and a risk factor for CD [46, 47], in the latter case smoking also seems to aggravate the disease course [48]. Ex-smoking status, on the other hand, seems to increase the risk of UC [49]. Oral contraceptive use was also implicated as a risk factor for CD [50], especially in the USA [51], but a female predominance of CD in high incidence areas was already present before the introduction of oral contraceptives in the 1960s. Mycobacterium paratuberculosis, already hypothesized as an etiological factor by Dalziel in 1913 [2], was proposed repeatedly [52, 53] and studied extensively during this period but no causal association could be established [54]. A new association was also identified for UC as appendectomy was shown to be protective against UC [55, 56]. However, in-depth studies seemingly revealed that it was the underlying appendicitis at a younger age that was protective not the appendectomy as such [57]. This is of great interest as the change for the incidence for appendicitis also remains an enigma similar to that of IBD and interestingly early hygiene exposures has been hypothesized to be an underlying cause [58].

Thus, in the end of the last century, we were facing an epidemic of IBD so far mainly affecting Western Europe and Northern America, where it had become one of the most common patient groups for gastroenterologists. The scientific community had failed to identify any primary preventative measures as the underlying etiology remained elusive. Smoking, as a protective factor for UC, identified already in the 1950s was the only environmental factor, where a casual association had been established.

2000 and Onward

The beginning of the twenty-first century meant that some of the established facts of the descriptive epidemiology of IBD were challenged again. The notion that the maximum annual incidence for CD in high incidence population was below 10.0/100,000 was contradicted by findings from Canada, where incidence figures as high as 20/100,000 were reported [59]. However, the data source can be questioned, but incidence figures from Norway [60] and New Zealand [39] also yielded higher numbers than previously experienced. IBD in children had, during the twentieth century, been seen as a rarity [61], but reports starting in Scotland [62] and later from Sweden [63, 64] could show a remarkable increase in incidence in CD in children but a stable incidence for UC.
Outside Western Europe and Northern America, we can now follow a pattern in the incidence of IBD similar to that we experienced around 1950:

1. Eastern Europe: Incidence figures from Hungary [65] clearly indicates that the transition period is over and that Hungary now has a pattern similar to Western Europe, while Croatia seems to be in the transition period [66]. This is contrast to the neighboring countries, such as Poland [67], Romania [68], and Slovakia [69], all of which still have a low incidence.

2. Southern America and Caribbean: Puerto Rico [70] and Barbados [71] have started to show an increase in incidence, and there are indications that a similar phenomenon is under way in Chile [72] and Brazil [73].

3. Africa: With the exception of South Africa, where those with a Caucasian background have an incidence similar to that of Western Europe [25], information is scarce but there are no indications of a rise in incidence.

4. Middle East with the exception of Israel: Although there is still a low incidence, there are signs of an increase in Lebanon [74], Saudi Arabia [75], and Iran [76].

5. India: In a very thorough cross-sectional study in Punjab, the authors could report an incidence figure for UC of 6.0/100,000 [77] perhaps indicating a start of a transition to a higher incidence.

6. China: There is almost a total lack of descriptive epidemiologic data, but there are indications of an emerging raise in the urban population for UC [78] and the consensus at the 2004 Asian Pacific Week in Beijing, China was: “A progressive rise in the prevalence of IBD is discernable in most Asian Pacific countries, more so for UC than CD” [79].

7. Korea and Japan: Incidence and prevalence figures of IBD during the twentieth century indicated a low incidence [80, 81], but the number of patients which have been presented especially from Japan [82] indicates that the incidence is substantially higher than previously thought.

8. Australia and New Zealand: The incidence figures and temporal trends seem to be same as in Western Europe and Northern America [39].

The analytical studies which have been done in these low incidence populations have not yielded any new information; smoking, family history of IBD, oral contraceptive use, and appendectomy have emerged as risk or protective factors with risk estimates similar to those reported from high incidence populations [82–84]. The only exception is high socioeconomic standard which is associated with an increased risk similar to that in Western Europe and Northern America 25–50 years ago.

Conclusions

The last hundred years have taught us a lot of the descriptive epidemiology of IBD, and we can now with some certainty postulate what will happen in the next 20 years in what is at present low incidence population. There will be an increase and there
will be reasons to believe that IBD patients will, in the future, constitute a major part of the patients for gastroenterologists in Asia, Southern America, as well as East Europe. Hopefully, the access to these patient groups will enable the research community to find the underlying etiology in order to find strategies for primary prevention, but such an endeavor urgently needs new hypothesis. We do not need etiological studies of smoking, oral contraceptives without better characterization of the underlying phenotype and potential interactions with different genotypes.

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The Changing Epidemiology of IBD


Inflammatory Bowel Disease
Diagnosis and Therapeutics
Cohen, R.D. (Ed.)
2011, XIV, 322 p., Hardcover
ISBN: 978-1-60327-432-6
A product of Humana Press