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SPECIAL ARTICLE

The burden of inflammatory bowel disease in Europe

Johan Burisch [a,1], Tine Jess [b,1], Matteo Martinato [c], Peter L. Lakatos [d,*] on behalf of ECCO -EpiCom

[a] *Digestive Disease Centre, Medical Section, Herlev University Hospital, Copenhagen, Denmark*
[b] *Department of Epidemiology Research, Statens Serum Institut, National Center for Health Data and Disease Control, Copenhagen, Denmark*
[c] *Department of Surgical, Oncological and Gastroenterological sciences, Padua University, Italy*
[d] *1st Department of Medicine, Semmelweis University, Budapest, Hungary*

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Abstract

Inflammatory bowel diseases (IBD) are chronic disabling gastrointestinal disorders impacting every aspect of the affected individual's life and account for substantial costs to the health care system and society. New epidemiological data suggest that the incidence and prevalence of the diseases are increasing and medical therapy and disease management have changed significantly in the last decade. An estimated 2.5–3 million people in Europe are affected by IBD, with a direct healthcare cost of 4.6–5.6 bn Euros/year. Therefore, the aim of this review is to describe the burden of IBD in Europe by discussing the latest epidemiological data, the disease course and risk for surgery and hospitalization, mortality and cancer risks, as well as the economic aspects, patients' disability and work impairment.
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* Corresponding author at: 1st Department of Medicine, Semmelweis University, Koranyi S. 2/A, H-1083 Hungary. Tel.: +36 1 210 0278/1500, 1520; fax: +36 1 313 0250.
E-mail address: lakatos.peter_laszlo@med.semmelweis-univ.hu (P.L. Lakatos).
[1] Contributed equally.

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1. Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology. The diseases are thought to be the result of a disregulated mucosal immune response to commensal gut flora in genetically susceptible individuals. The impact of IBD on patients' quality of life is substantial due to early onset, fluctuating disease course and the lack of a cure. Furthermore, CD and UC account for substantial costs to the health care system and society. Descriptive epidemiological studies are important for health care system leadership, as they provide valuable information for decision making. The aim of this review is to describe the burden of IBD in Europe by discussing the occurrence of IBD, the risk for surgery and hospitalization, mortality and cancer risks, as well as the patients' disability and work impairment.

2. Incidence and prevalence in Europe

The incidence and prevalence of IBD is subject to considerable variation, both between and within geographic regions, with IBD being more common in industrialized than in non-industrialized countries. Traditionally, the highest occurrence of both UC and CD is found in the developed countries of North America[1,2] and Europe. Within Europe, the highest incidence and prevalence rates are found in Scandinavia[3–15] and the United Kingdom[16–19] while the diseases remain rare in Eastern Europe.[20–22] However, the occurrence of IBD is a dynamic process as increasing incidence rates being reported from previously low incidence areas, including not only Asia,[23] for instance, but also Eastern Europe.[24,25]

The comparison of incidence and prevalence rates in IBD across multiple studies is challenging. Detection rates and diagnostic criteria differ between studies, just as access to diagnostic procedures, such as endoscopy, may vary over time and between centers. Furthermore, methods of case assessment, as well as physicians' disease awareness, vary considerably and complete case assessment is dependent on the ability to identify all cases in the population. As such, prospective population-based studies are preferable in descriptive epidemiology compared to studies using secondary data that depend on existing hospital or public health registry systems; however such prospective population-based studies are both expensive and time consuming, and therefore rare. It is thus essential to bear in mind that observed differences between regions might either be attributed to real differences in environmental factors, lifestyle, and genetic susceptibility or simply be due to differences in methodology.

2.1. Incidence and prevalence rates

Incidence and prevalence rates from selected countries in Europe are shown in Tables 1 and 2. The incidence of CD in Europe ranges from 0.5 to 10.6 cases per 100,000 person-years while the estimates for UC range from 0.9 to 24.3 per 100,000 person-years. The highest incidence rates are observed in Scandinavia and the United Kingdom, while the lowest rates are seen in southern and Eastern Europe – suggesting a north-west/south-east gradient in IBD incidence. The European Collaborative Study on Inflammatory Bowel Disease (EC-IBD) assessed the north–south gradient in a prospective population-based cohort using uniformed diagnostic criteria and case ascertainment methods. The total incidence rates in northern Europe were 6.3 for CD and 11.4 for UC per 100,000 person-years, while in southern Europe they were for 3.6 and 8.0 per 100,000 person-years, respectively.[26]

Extrapolation of the incidence figures on the total European population (app. 731 million in 2006,[27]) despite the challenges of heterogeneous health care systems and differences in study methodology between countries and centers, would indicate a maximal estimate of 78,000 new cases of CD and 178,000 new cases of UC each year – for a combined estimate of 256,000 new cases of IBD per year. Previous reviews[28] have used the population of the European Union (27 countries, approximately 500 million in 2012[29]) which would yield 53,000 new cases of CD and 123,000 new cases of UC each year, with a combined estimate of 176,000 new cases of IBD each year.

The prevalence of CD in Europe varies from 1.5[22] to 213[12] cases per 100,000 persons, whereas the prevalence of UC in Europe varies from 2.4[22] to 294[6] cases per 100,000 persons. As for the incidence of IBD, the highest prevalence rates are found in Northern Europe. Extrapolating these numbers for the total European population indicates that there may be up to 1.6 million persons with CD and 2.1 million persons with UC in Europe, meaning a combined total of 3.7 million persons with IBD. Using the population of the European Union yields maximal estimates of 1.1 million persons with CD and 1.5 million persons with UC in Europe, for a combined total of 2.6 million persons with IBD.

Since the incidence of both CD and UC is increasing or stable in virtually every region of the world,[30] the prevalence of IBD is expected to increase further due to the early age of onset and low mortality of IBD patients. The emergence of IBD in traditionally low-prevalence regions (i.e. Eastern Europe) will further contribute to this increase. A

Table 1 Incidence rates of CD and UC in selected populations.

Country	Region	Study period	CD incidence (10^5)	UC incidence (10^5)
Eastern Europe				
Czech Republic[20]	North Bohemia	1978	NA	1.3
Estonia[21]	Tartu County	1993–1998	1.4	1.7
Hungary[24]	Western Hungary	2002–2006	8.9	11.9
Romania[22]	Nationwide	2002–2003	0.5	0.97
Southern/Central Europe				
Belgium[132]	Liege	1993–1996	4.5	3.6
Croatia[25]	Primorsko-goranska County	2000–2004	6.5	4.6
Croatia[133,134]	Zagreb	1980–1989	0.7	1.5
France[135]	Northern France	2006–2007	6.7	3.4
Germany[136]	Oberpfalz	2004–2006	6.6	3.9
Greece[137]	North-western Greece	1983–2005	2.7	0.9
Italy[138]	Florence	1990–1992	3.4	9.6
Italy[139]	8 Italian cities	1989–1992	2.3	5.2
The Netherlands[140]	South Limburg	1991–2003	6.2	7.7
Spain[141]	Navarra	2001–2003	5.9	9.6
Spain[142]	Oviedo	2000–2002	7.5	9.1
Spain[143]	Madrid	2003–2005	7.3	7.1
Northern Europe				
Denmark[3,4]	Copenhagen county	1962–1987	4.1	8.1
Denmark[5]	Copenhagen county	2003–2005	8.6	13.4
Denmark[6]	North Jutland	1978–2002	6.7	12.2
Faroe Islands[7]	Nationwide	1981–1988	3.6	20.3
Finland[8]	Tampere	1986–1999	7.2	16.5
Iceland[9]	Nationwide	1990–1994	5.5	16.5
Norway[10,11]	Southeast Norway	1990–1993	5.8	13.6
Sweden[12]	Stockholm county	1990–2001	8.3	NA
Sweden[13,14]	Örebro	1963–1987	6.1	13.1
Sweden[15]	Uppsala	2005–2007	NA	17.5
United Kingdom[16]	Derby	1991–1992	10.6	NA
United Kingdom[17]	North Tees	1990–1994	8.3	13.9
United Kingdom[18]	Cardiff	1996–2005	6.6	NA
Northern Europe[26]	8 Northern European cities	1991–1993	6.3	11.4
	Iceland, Reykjavik		8.2	24.3
	Norway, Oslo		6.9	15.6
	Denmark, Copenhagen		6.6	10.0
	Ireland, Dublin		5.9	14.8
	UK, Leicester (nonimmigrants)		3.2	9.2
	UK, Leicester (immigrants)		4.7	15.1
	The Netherlands, Maastricht		7.7	13.1
	Germany, Essen		3.5	4.3
	France, Amiens		8.1	5.6
Southern Europe[26]	12 Northern European cities	1991–1993	3.6	8.0
	Italy, Milan-Varese		3.2	10.0
	Italy, Crema-Cremona		2.7	7.5
	Italy, Reggio Emilia		4.0	7.5
	Italy, Florence		2.7	8.1
	Italy, Palermo, Sicily		5.8	8.5
	Spain, Vigo		4.8	7.0
	Spain, Sabadell		4.9	9.0
	Portugal, Braga		3.7	5.5
	Portugal, Almada		2.3	1.7
	Greece, Northwest Greece		1.0	8.5
	Greece, Heraklion, Crete		3.9	16.6
	Israel, Beer Sheva		4.3	8.5

Table 2 Prevalence rates of CD and UC in selected populations.

Country	Region	Study period	CD prevalence (10^5)	UC prevalence (10^5)
Eastern Europe				
Czech Republic[20]	North Bohemia	1968–1978	NA	17.6
Hungary[144]	Veszprem Province	1991–2001	52.9	142.6
Romania[22]	Nationwide	2004	1.5	2.4
Southern/Central Europe				
Croatia[133,134]	Zagreb	1989	8.3	21.4
Bosnia and Herzegovina[145,146]	Tuzla	2006	28.2	43.1
Italy[138]	Florence	1992	40	121
The Netherlands[147,148]	Leiden	1979–1983	48	58.4
Germany[149]	Tubingen	1984	54.6	24.8
Spain[150]	Asturias	1997	87.5	110.0
Spain[151]	Madrid	1988	19.8	43.4
Switzerland[152]	Canton of Vaud	2003–2004	100.7	105.0
Northern Europe				
Denmark[3,4]	Copenhagen county	1987	54	161.2
Denmark[6]	North Jutland	2002	151	294
Faroe Islands[153]	Nationwide	1986	31.8	157.3
Finland[8]	Tampere	1986–1999	82	205
Iceland[154]	Nationwide	1950–1979	6	72
Sweden[12]	Stockholm county	2001	213	NA
Sweden[13,14]	Örebro	1987	146	198
United Kingdom[19]	Derby	1985	85	NA
United Kingdom[17]	North Tees	1994	144.8	243.4

current inception cohort study by the Epidemiological Committee (EpiCom) is investigating the East–west gradient in the incidence of IBD, as well as differences in potential environmental risk factors between Eastern and Western Europe.[31]

The incidence and prevalence of CD and UC is increasing in Europe.
Estimated 0.3% of the European population suffers from IBD equalling 2.5–3 million persons.

3. Disease phenotype, overall disease course and relapse rates

One of the most important parameter associated with long-term outcomes is the disease phenotype. Current practice guidelines advocate the use of the Montreal classification in both CD and UC.[32] The most important variables are age at onset and disease location (terminal ileum (L1), colon (L2) and ileocolon (L3) and upper GI (L4) as modifier), behavior (non-stricturing non-penetrating (B1), structuring (B2) and penetrating (B3)) and presence of perianal disease in CD and disease extent (proctitis (E1), left-sided (E2) and extensive (E3)) in UC. Yet, there are still limited data available on the natural history of IBD in Europe.

In CD, the distribution of location is relatively homogeneous and stable with the exception of the reported variance in the frequency of the upper GI location, especially in pediatric– versus adult-onset populations. In addition, the proportion of isolated colonic disease is increasing in the last decade. An example may be the recent IBSEN cohort[33] with 27% of patients with L1, 48% L2 and 23% L3 and only 2% L4 disease at presentation. Somewhat lower rates of isolated colonic disease were reported from Denmark (L2: 30%, 43% and 37% in 1962–1987, 1991–1993 and 2003–2004).[34] Similar data were recently reported also from Eastern Europe (L1: 20%; L2: 35%, L3: 44% and all L4: 2.4%)[24] in 2002–2006.

Up to one-third of European patients may present with complicated disease phenotype at diagnosis, e.g. in the IBSEN cohort 36%, 49% and 53% of patients had presented with or developed stricturing or penetrating disease at diagnosis or after 5- or 10-years. In contrast, in previous cohorts by Cosnes et al.,[35] up to 70% of CD patients developed either penetrating or stricturing disease. Similar results were published in a Belgian study.[36] 45.9% of patients had a change in disease behavior during 10 years of follow-up, from non-stricturing, non-penetrating disease to either stricturing (27.1%) or penetrating (29.4%) disease. In contrast, disease location remained relatively stable during follow-up, with only 15.9% of patients exhibiting a change in disease location during the first 10 years. The rate of perianal complication may vary between 10 and 20% at presentation.

In UC, the distribution of the disease extent at diagnosis is variable among the different cohorts with increasing rates of proctitis. In the IBSEN cohort[37] the distribution of the disease extent was E1 in 32%, E2 in 35% and E3 in 33%. Of the patients initially diagnosed with proctitis, 28% had progressed during

the observation period, 10% to extensive colitis over the next 5-years. Similar distribution of the initial disease extent was observed in a population-based cohort from Eastern Europe (E1: 27%, E2: 51% and E3: 22%),[24] while the 5-year probability of proximal disease extension in patients with initial proctitis or left-sided colitis was 12.7%. The rate of proctitis was more variable in Denmark,[34] with 44%, 60% and 31% at diagnosis reported in 1962–1987, 1991–1993 and 2003–2004. Little data are available on the relapse rates and overall disease course in IBD from Europe. Most data were published from the Nordic countries.

In one of the early publications, the long-term disease course was reported in 185 CD patients followed-up regularly between 1960 and 78 in Copenhagen, Denmark.[38] About 45% of patients were without clinical symptoms for all the observation years. The disease activity was low in app. 30% of patients and moderate-to high in app. 25%. Continuous disease activity was observed in about 20% and intermittent symptoms were reported in 35% of patients with active disease in a given year. However, the cumulative relapse rate after 5-years was already as high as 93.1%. Similar disease course was reported in a follow-up cohort from the same region in 1991–1993.[34]

A better disease course was reported in UC during the same observation period from the Danish group[39] in 1161 patients diagnosed and followed between 1962 and 1987. After the initial one to two years, approximately 50% of UC patients were in remission in each year of follow-up, while the proportion of patients with active disease fell gradually to about 30% parallel with an increasing proportion of patients treated by colectomy. The proportion of patients in remission increased with increasing disease duration. The cumulative probability of clinical relapse was 81.6% after 5-years' disease duration, while only 1% of patients experienced continuously active disease. Interestingly, in the 1991–1993 Copenhagen cohort[34] the probability of aggressive disease during the first 5-years fell from 23.8% to 13.2%.

Somewhat different rates were published in the EC-IBD study.[40] First all types of cumulative recurrence rates were 34%, 69.2%, and 77.5% after 1, 5, and 10 years of follow-up in 358 CD patients, with similar second and third all type relapse rates (40.2%, 76.9% and 82.6% vs. 45.9 and 76.4% after 1, 5, and 10 years). Upper gastrointestinal location and 5-ASA therapy were associated with increased risk of relapses. Interestingly, relapse rates were associated to the geographic region. Higher relapse rates were reported from Copenhagen, while lower rates were observed in Greece, Italy and Norway. Relapse rates and disease course were reported more recently from the IBSEN group from Norway.[37] Of the 454 UC patients, 78% experienced at least one relapse during the first 5-years. Relapse rates were higher in females ($p=0.01$) and relapsing patients were younger ($p<0.001$), but it was not associated to disease extent. In addition, when patients were asked to self-assess their disease course, 59% experienced a decline in the severity of intestinal symptoms during the follow-up period. In contrast, only 1% of patients experienced an increase in severity, while chronic continuous symptoms were present in 9%. A relapsing course was observed in 31%, respectively. In a follow-up study of the same cohort,[41] 48% of the UC patients were in clinical remission between 5 and 10-years after diagnosis.

Similar to earlier reports, a high cumulative relapse rate (53%, 85% and 90% after 1, 5, and 10 years) was reported in 237 CD patients from the same group[33] associated with early need for steroids but not with disease phenotype or smoking habits. In contrast, approximately 44% of patients were in clinical remission during the second 5-year period and 43% experienced a decrease in the severity of disease (according to predefined disease patterns), during the follow-up period. In contrast, 3% patients experienced an increase in severity, 19% experienced chronic continuous symptoms, and 32% experienced a relapsing course.

> The majority of the patients with inflammatory diseases in Europe experience a relapsing disease course with 20–25% of patients experiencing chronic continuous symptoms.
>
> Up to 30–40% of CD patients in Europe present with complicated disease phenotype at diagnosis and a similar proportion of patients may develop complications over the next 10–15-years of follow-up.

4. Hospitalization rates

Relatively little data are available and hospitalization rates in patients with IBD vary between European countries. In the early era a significant proportion of the diagnostic workup was done on an inpatient basis leading to fairly high initial hospitalization rates as reported from the Nordic countries. As an example the hospitalization rate within the year of diagnosis was as high as 83% in CD patients diagnosed between 1962 and 1987 in Copenhagen County, Denmark. In addition, approximately 20% of patients were admitted yearly over the next 5 years[42] (Table 3).

Additional data are available from a Pan-European prospective follow-up study.[43] Data from this study confirm that hospitalization rates decline significantly from the second year after diagnosis. The cumulative risk of overall hospitalization was 52.7% at 10 years from diagnosis, but with considerable differences between countries. Rates were highest in Denmark, Ireland, Portugal while low rates were observed in Norway, Greece and Italy.

In contrast, in UC hospitalization reflects mainly the failure of medical therapy and disease severity and is associated with the need for colectomy and ultimately mortality. In a retrospective cohort from Oxford cohort, need for hospitalization for acute severe colitis was the most important predictor for colectomy.[44] Overall, 12% needed colectomy, however the rate was higher, 39.8% (74/186) in patients with one or more severe episodes compared to those not needing an admission 3.4% (19/564). Colectomy rates were increasing with subsequent admission, being 19.9%, 29.0%, and 36.6%% after one, two or three episodes, respectively. Similar findings were reported from North America with stable hospitalization rates in UC.[45,46]

A meta-analysis of hospitalization rates in IBD was published from 9 European countries based on the data of the national statistic offices in 2009.[47] Hospitalization rates varied significantly among countries between 1.2 and 4.3 discharges per 10,000 for CD and between 0.7 and 4.7 discharges per 10,000 for UC. The highest rates were found in Denmark and Scotland, while the lowest in Spain, Switzerland and the Netherlands. Numbers were similar for UC and CD in the given country with a

Table 3 Hospitalization rates in selected European cohorts in patients with Crohn's disease.

Country	Time period	Cohort type	Cohort size	Hospitalization rate
Copenhagen, Denmark[42]	1962–1987	Population-based cohort	373	83% in the 1st year after the diagnosis and 20% annually in the next 5 yrs.
EC-IBD[43]	1991–2001	Inception cohort study from referral centers	425	52.7% in the first 10-years, significant variation among countries

specific age-distribution pattern (CD: high peak in younger patients and small peak in the elderly. UC: opposite trend).

Nevertheless hospitalization is an important but partly subjective outcome measure. Need for hospitalization may be associated to multiple factors including not only disease severity but also need for diagnostic workup, health care/reimbursement policy and ethnic differences. Furthermore, the bar for hospitalization may be different in expert centers versus community settings.

Hospitalization rates are high, but slowly decreasing in patients with Crohn's disease with approximately 50% of European patients requiring hospitalization within 10-years from diagnosis. The actual rates may vary significantly between countries.
In UC, hospitalization rates remained stable and reflect disease severity and risk for colectomy.

5. Surgery in IBD in Europe: rates, trends and causes

The overall cumulative surgery rates in CD were 10–35%, 21–59% and 37–61% at 1, 5 and 10 years after diagnosis,[48] respectively. In general, surgery rates seem to have declined in the last two decades, as suggested by a recent review article by Bernstein et al.[48] focusing on surgery patterns and rates published in population-based studies. Surgical rates and risk for surgery in IBD in Europe are mainly comparable to that reported from Northern America in both CD and UC with some exceptions. Of note, the reported surgical pattern naturally varies between population-based studies and referral centers. In addition, there are some local geographic differences, e.g. higher surgical rates are still reported from Denmark or the lower colectomy rates in UC in the Mediterranean and Eastern Europe (Table 4).

Early studies reported exceedingly high surgical rates, such as the population-based Stockholm County cohort from 1955 to 1974. Reported surgery rates were 30%, 50% and 60% at 5, 10 and 15 years[49] and surgical rates did not change significantly in an update report from a follow-up cohort.[50]

Similar high rates were reported from Copenhagen in a population-based cohort some years later (1962–87).[51] 35% of CD patients had surgery during the first year after diagnosis. The cumulative probability of surgery was 61% at 10 years and 82% at 20 years. Similarly, high initial surgical rates were reported from a referral-based French cohort, with a need for early surgery as high as 15% in the first three months after the diagnosis, while the annual surgical rates remained stable over time (1978–2002).[52] In a more recent update from the Copenhagen cohort significantly lower (12%) surgery rates were reported within the year of diagnosis in incident cases diagnosed between 2003 and 2005[5] and the risk has continued to decline.[53]

The latest data from Denmark approach the low surgery rates reported from another Nordic country, in a population-based cohort from Southeastern Norway by the IBSEN group in patients diagnosed between 1990 and 1994. Cumulative probability of surgery was 14%, 27% and 38% at 1, 5 and 10 years from diagnosis with 9% having at least one reoperation.[33] Terminal ileal location, stricturing or penetrating disease and an age younger than 40 years at diagnosis were significantly associated to the risk for surgery.

The best data outside of the Nordic countries comes from the multicenter European EC-IBD inception cohort in patients diagnosed between 1991 and 1993.[43] The cumulative surgery rate after 10-years was 37.2%. After the first surgery, 2.2%, 18.5%, and 35.9% of patients need additional surgical intervention at 1, 5, and 10 years, respectively.[40] Interestingly, a geographic variability was reported. Patients from Northern European centers, especially Copenhagen, had higher risk of surgical interventions. The reason for the observed geographic differences is not well understood. Partially, this was may be explained by more aggressive disease phenotype as suggested by the authors but likely other factors may contribute such as s different attitude toward surgery.

More recently, declining surgical rates associated with increased and earlier use of immunosuppressives was reported from two population-based studies from Cardiff (Wales) between 1986 and 2003 and Hungary[54] between 1977 and 2008. In the first study surgery rates decreased during the follow-up periods from 59% to 25% 5-years after the diagnosis ($p = 0.001$) in patients diagnosed in 1986–91and 1998–2003. In the Eastern European study surgical rates were decreased in patients diagnosed after 1999. The reported surgical rates were 9.8%, 18.5%, and 21.3% after 1, 3, and 5 years after the diagnosis in patients diagnosed between 2002 and 2006.[24] Also in Denmark, the decrease in surgery was paralleled with an increasing use of immunosuppressives and biologicals, although causality was not established.[53]

Unquestionably, the reason for recent decreases in surgery rates is multifactorial. Disease phenotypes (behavior) in the more recent cohorts seems to be more mild, with a greater proportion of patients with inflammatory disease at diagnosis,[55,56] however other factors are likely to contribute. Follow-up strategy has changed significantly in the last decades and increased and earlier use of immunosuppressives may partially be regarded as a marker (one factor) of this complex change

Table 4 Surgery and colectomy rates in selected European inflammatory bowel disease cohorts.

Country	Time period	Cohort type	Cohort size	Surgery in Crohn's disease/colectomy in ulcerative colitis		
				1 year	5 years	10 years
Crohn's disease						
Sweden[49]	1955–1974	Population-based cohort	826	–	30%	50%
Denmark[5,51]	1962–1993	Population-based cohort	373	35%	–	61%
	2003–2005		562	12%		
Norway[33]	1990–2000	Population-based cohort	237	14%	27%	38%
EC-IBD[43]	1991–2001	Inception cohort study from referral centers	425	–	–	37%
UK[55]	1986–1991	Population-based cohort	105	32%	59%	–
	1992–1997		99	25%	37%	
	1998–2003		137	19%	25%	
Hungary[24,61]	1977–2008	Population-based cohort	506	15%	31%	52%
	2002–2006		163	10%	21%	
Ulcerative colitis						
Denmark[39]	1962–1987	Population-based cohort	1151	–	–	24%
Norway[41]	1990–2004	Population-based cohort	519	3.5%	–	9.8%
EC-IBD[60]	1991–2003	Inception cohort study from referral centers	771	–	–	8.7%
Hungary[24,61]	1977–2008	Population-based cohort	914	–	1.6%	3.7%
	2002–2006		220	0.5%	1.8%	2.8%

pointing towards improved medical management. This is further supported by a recent publication from Canada,[57] where authors were able to show an association between early gastroenterologist care and lower risk of surgery parallel with an increased early use of immunosupressives. Yet, exposure to immunosupressives seems to be still relatively low in the population-based studies and reoperation rates are essentially unchanged. Of note, the above surgery rates and trends were reported in mainly pre-biological cohorts with only minimal or no biological exposure, except for the recent Danish study which did not report causality.[53] Whether biological therapy directly influences long-term surgery rates and surgery trends remains unclear.

While the main aim of surgery in Crohn's disease is to eliminate the complications, the indication of colectomy and surgical therapy in ulcerative colitis is usually failure of medical therapy leading to chronic active disease or fulminate colitis. In one of the early studies from Sweden, excessive colectomy rates (20% and 45% at 5 years and 25 years) were reported in 1586 patients followed-up from 1955 to 1984.[58] Disease extent was universally identified as an important predictive factor for colectomy. Interestingly, a disease extension was observed in the majority of the patients with initial proctitis who needed colectomy later during the disease course. Similarly, high colectomy rates were reported from the Copenhagen[59] county in the same time period with 10% of patients requiring colectomy in the year of diagnosis.

Higher colectomy rates were persistently reported from the Northern-European centers, as confirmed also in the more recent EC-IBD study in patients diagnosed between 1991 and 1993.[56,60] Of note, the cumulative colectomy rate was lower (8.7%) compared to the previously reported rates. Nonetheless, the difference between northern and southern centers was significant with 25.7% 10-year cumulative colectomy risk from Denmark (HR 8.2; 95% CI, 3.6–18.6), 8.2% from Norway and the Netherlands combined (HR 2.7; 95% CI, 1.3–5.6) and only 3.9% from the south European centers. Similarly low overall colectomy rates were reported in population-based studies from Eastern Europe. The cumulative colectomy rate was 1.6% and 3.7% after 5 and 10 years' disease duration in UC patients diagnosed between 1977 and 2008.[61]

Finally, new data from the Nordic countries are showing a trend for decreasing colectomy rates. A prospective population-based study in the early 1990s from South-eastern Norway by the IBSEN group[41] revealed 3.5% and 10% colectomy rates at 1 and 10-years after the diagnosis. Similarly, lower colectomy rates were recently reported from Denmark[5] with a 10 year colectomy rate of approximately 10%.[40]

Of note, higher colectomy rates were reported from studies done in solely pediatric onset UC populations from Northern and Western Europe. In a Danish population-based study the cumulative colectomy rate in the pediatric-onset UC patients diagnosed between 1962 and 1987 was 6.4%, 26%, and 29% at 1, 10, and 20 years.[62] Colectomy rates were similar in a recent population-based French study.[63] The cumulative rate of colectomy was 8%, 15% and 20% after 1, 3, and 5 years' disease duration. Interestingly, the presence of extra intestinal manifestations (7% at diagnosis and 22% cumulatively) increased the risk for colectomy (HR 3.5; 95% 1.2–10.5).

It is not clear why colectomy rates are lower in southern and Eastern Europe. Of note however, disease severity

(assessed by disease location, extension, or episodes of acute severe colitis) is not necessarily milder in southern or Eastern European centers.

The overall cumulative surgery and reoperation rates in Crohn's disease are still high in Europe with 30–50% of patients needing a surgical intervention and up to 20% needing a reoperation after 5–10 years from the diagnosis according to population-based data. Recent data indicate a decrease in the surgical rates.

The risk of colectomy in ulcerative is approximately 10% after 10 years from the diagnosis. The unexplained geographic variation in the colectomy rates between northwest and Southeast Europe is diminishing in recent years.

6. Extra intestinal manifestations

IBD is associated with a large number of extra intestinal manifestations (EIM). In European studies, EIMs were present in as high as 20–40% of patients with CD and app. 15–20% of patients with UC.[64] In general EIMs are more common in females. The prevalence is increasing during follow-up, e.g. in a Hungarian study the frequency was higher in patients with a disease >10 years in both CD (29.9% vs. 48.9%, p=0.003) and UC (22.1% vs. 10.4%, p<0.001).[64]

Joint manifestations (peripheral or axial arthropathies) are the most common EIM in IBD, and occur in 20%–30% of patients during follow-up in studies from Hungary, Italy, Switzerland and UK.[64,65] Symptom range is relatively broad from non-inflammatory arthralgia to acute arthritis with painful swollen joints. In an Italian prospective one-year follow-up study[66] of 651 IBD patients 45.1% of CD and 36.9% of UC patients reported past or present articular symptoms during a median follow-up of 11 years. In 46% this was associated with active IBD, in 56% symptoms were intermittent and in 19% symptoms preceded IBD diagnosis, while 9.5% of patients (CD: 12.8% and UC: 7.2%) reported recent articular symptoms over the one-year prospective follow-up period.

Peripheral arthropathies can be divided into two subgroups as suggested by authors from the UK[67]: type 1 arthritis (an acute, self-limiting, pauciarticular (>5 joints) arthropathy, typically affecting large joints, associated with other EIM and its course parallels the activity of intestinal disease); and type 2 arthritis (a chronic, bilateral, symmetrical, polyarticular arthropathy affecting five or more small joints, its course runs independent to the course of intestinal disease with a prevalence of 2–4% in both CD and UC). In previous studies from Hungary and the UK, cumulative prevalence of arthritis was more common in CD compared to UC (axial 10% vs. 3% and type-1 6–11% versus 2.7–3.6%), in women and in colonic disease.[64,67]

Axial arthropathies are sacroileitis and ankylosing spondylitis (AS) with a cumulative incidence of 2–6% in IBD (20-fold higher than in the normal population).[64,65,68] In addition, arthriticular manifestations may be more frequent in CD patients with stenosing/penetrating disease and in UC in patients with pancolitis. Peripheral but not axial arthritis was more frequent in CD patients with an active disease in the Swiss IBD cohort (45.1% vs 31.3%, p=0.01).[65] In contrast, no difference in arthritis frequency was reported in UC patients with an active disease or in remission.

Erythema nodosum (EN), pyoderma gangraenosum (PG), and aphthous stomatitis are the most common cutaneous manifestations in IBD. Prevalence rates reported from France, Hungary, Switzerland and UK are app. 5–15% in CD patients, with female predominance, paralleling disease activity in up to 92% of episodes and may recur in app. 20–30% of patients.[64,65,69,70] EN is less common in UC (2–10%), however, the frequency may be higher in patients with extensive colitis. The frequency of PG is less common in both CD and UC (1–2%). In contrast, 36%–50% of patients with PG suffer from IBD. Aphthous stomatitis may be present in 1–10% of IBD patients. The course of skin manifestations is usually related to disease activity but sometimes, especially in the case of pyoderma gangrenosum, may take an independent course. Interestingly, in the Swiss IBD cohorts, only the frequency of aphthous stomatitis was linked to disease activity in patients with CD (17.1% vs 8.6%, p=0.026).[65] Finally, in a large French referral cohort patients' skin manifestations were diagnosed in 5.8% in 2402 IBD patients (5.6% EN and 0.75% PG).[70] Of note, the median delay between the IBD diagnosis and the occurrence of the first dermatologic manifestation was 3.9 years, with a trend for an earlier occurrence in CD patients (CD: 3.5 vs. UC: 5.9 yr, p=0.13) for EN, but not for PG.

The most common ocular manifestations include uveitis and episcleritis. Their prevalence is between 3 and 6% in both CD and UC in studies from Hungary, Switzerland and UK.[64,65,69] They are associated with disease activity in up to 78% of episodes, with recurrent episodes in app. 30% of patients.[69] In the Swiss IBD cohort, the frequency of uveitis was 2-fold higher in patients with active CD (12.2 vs. 5.2%), but an association was not found in UC.[65] In a Hungarian population-based cohort,[64] ocular manifestations were associated with the disease extent in UC (6.1% in pancolitis vs 1.9% in left sided colitis or proctitis, p=0.01). Furthermore, ocular manifestations may frequently occur together with other (joint or cutaneous) EIM.[64,69,70]

PSC may be present in 0.7–2% patients with CD and 2–4% of UC patients in studies from both Western and Eastern Europe.[64,65] If small-duct PSC is included, the overall prevalence ranges between 2.4 and 11%.[64,71]

In European studies, EIMs were present in as high as 20–40% of patients with CD and 15–20% of patients with UC.

7. Disability and economic burden of IBD in Europe

Little data are available on disability in patients with IBD. Unfortunately, an unequivocal definition of disability is difficult and available assessment tools are measuring different aspects of disability. In one of the early publications by Sonnenberg[72] CD and UC led to disability in significantly younger patients than other diseases with a significant socioeconomic impact. In CD disability was more

common in females, while disability from UC was similar in both sexes.

A second German study reported in 1992 that each year, about 9% and 3% of all German employees with IBD underwent a rehabilitation or were granted a disability pension and that, although they had significantly longer sick leaves, 87% were still employed before entering rehabilitation.[73] Importantly, 64% of the total social costs in CD were indirect costs such as early retirement or sick leave, while in UC this was estimated to be as high as 54%.[74]

Of note, however, a huge variation was reported in the disability rates across the world. The TREAT registry reported an overall disability rate of 25%, ranging from 20% in the US to 34% in Europe,[75] possibly reflecting differences in disease severity, local socioeconomic and societal factors, and insurance policies. In 2008 Timmer[76] summarized data in IBD patients on sick leave in the pre-biologics era. It is estimated that an IBD patient will be sick about 4 weeks per year, off from work for 3 to 6 weeks per year and hospitalized for 10 days. In concordance, IBD patients from the UK[77] reported significant interference with social activities, irrespective of the severity of the disease or disease subtype. Median days lost from "household and recreational activities" in six months was 17 in patients with UC and 20 in patients with CD. It should be noted that hospitalization rates may depend on local healthcare policies and are, therefore, difficult to compare across Europe.

In early studies, high disability pension rates were reported from Copenhagen (15% after 15 years' disease duration) in patients with CD.[42] In a more recent study performed on the IBSEN cohort after 5-year disease duration,[78] unemployment (11.7%) and sick leave (app. 50%) were more common in IBD patients compared to the Norwegian background population. In contrast, the disability pension rate was only increased in females with CD, confirming earlier data from Germany.[73] These results are in line with the results of a more recent study performed in the IBSEN cohort of patients where CD had higher impact on health related quality of life (HRQOL) compared with UC.[79] Further, women with CD had worse outcome than men in subjective health status and had higher rates of sickness, disability pension and single living.[80]

Also, in the recent update of the IBSEN cohort, the overall disability pension rate 10 years after diagnosis of IBD was 18.8% with significantly elevated RRs of 1.8 in UC and 2.0 in CD. The relative risk for disability pension was highest in patients below 40 years at diagnosis.[81] In addition, a recent Dutch study has shown that although IBD patients are as often employed as the general population, fewer people work fulltime.[82]

A recent European survey,[83] presented by the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) in partnership with the European Crohn's and Colitis Organization (ECCO), assessed burden of IBD in Europe through patients' reported data. Underemployment and unemployment due to the intestinal disease were reported in, respectively, 10% and 8% of IBD patients (2/3 in CD). Chronic disease activity was related to both under/unemployment and disability retirement. About half of the patients responded that that their life was significantly affected by IBD during their most recent flare-up. Of these, 26% had had more than 25 days of absence due to IBD and 56% of underemployed respondents worked only part-time. IBD also affects working behavior and career path. 44% of respondents said that they had lost or had had to quit a job because of IBD and 52% felt that IBD had negatively affected their education. Interestingly, Hoivik et al.[84] reported that work status and sick leave were the only variables, besides IBD related symptoms, that negatively affected HRQOL.

As mentioned initially, comparison between studies and populations is difficult due to underlying differences in definition of disability and in societies. However, recently, a comprehensive International Classification of Functioning, Disability, and Health (ICF) core set for capturing specific aspects of disability in IBD has been published, and this may lead to a more uniform and objective assessment of disability in patients in IBD.[85] Finally, it is difficult to measure the economic burden of the disease in the different European countries given the large variation in direct and indirect costs and significant differences in the health care policies. Most systematic data are available from North America.[86,87] Studies from Europe were published only in the last decade. German and English authors reported retrospectively the inpatient and outpatient costs, from the payer perspective in Ulm and Liverpool.[77,88] In year 2000, the cost for treating CD was £3416 per patient-year, and for UC, £3021 per patient-year. Inpatient and surgery costs accounted for over half of the costs, and the 10% most costly patients in CD and UC accounted for 59% and 62% of total costs. Patients requiring hospitalization had 10-fold higher costs compared to patients not hospitalized. Similar data were reported in Germany in 1997–2000. The mean cost for outpatient care was €3171 per patient-year in all 548 patients, with drugs accounting for 85% of the total costs. Costs were no different between patients with CD or UC.

The cost analysis from the EC-IBD inception cohort[43] was published in 2006. 425 CD patients and 896 UC patients were included in the analysis of eight European countries and Israel. The mean total health care cost (outpatient care, diagnostics, hospitalization, surgery, medication) in IBD was €1871 (SD €4884) per patient-year over the 10-year follow-up. The costs were higher for CD (€2548 per patient-year) compared to UC (€1524 per patient-year). Mean costs varied considerably between countries, being highest in Denmark at €3705 per patient-year and lowest in Norway at €888 per patient-year. Hospitalization accounted for 63% of the cost in CD and 45% in UC. Total and hospitalization costs were much higher in the first year after diagnosis than in the follow-up period. Interestingly, 5-aminosalicylic acid (5-ASA) derivatives were the most expensive drug category, however this was a mainly pre-biologic cohort with long-term 5-ASA use. The extent of disease was found to affect the cost in UC patients only. In contrast, in CD the costs varied significantly according to the Vienna classification phenotypes.

In a more recent publication[89] from the same cohort mean costs were analyzed over the 10-year follow-up period per 3-month treatment cycles from 13 centers. The costs for all treatment states were higher in CD with the exception of surgery. Mean costs were highest for the surgical cycles in both UC and CD (€8132/cycle and €6998/cycle), followed by drug-responsive and drug-dependent states (UC: €1760 and €839/cycle; CD: €2029 and €1033/cycle). Not surprisingly, the costs for mild disease or medical remission were the lowest (UC: €104 and €274/cycle; CD: €184 and €316/cycle). Far more economic studies will be needed in the future to assess the long-term cost-effectiveness and cost-utility of the more intense patient monitoring and advanced treatment strategy

in the future. Based on these data from the late 1990s in with a treatment strategy from the pre-biologic data, the direct economic burden associated with IBD can be estimated as high as a total of 4,681–5,596 million Euro direct costs per year in Europe. Updated cost estimation models based on new treatment algorhythms long term, incorporating the biological therapies are urgently awaited.

The health economic burden and permanent work disability in IBD are high in Europe with a total yearly direct healthcare cost of 4.6–5.6 bn Euros.
Unemployment (10%), sick leave (3–6 weeks/year), and permanent work disability (2-fold increased) are more common in patients with IBD than in unaffected individuals. The economic impact is even higher since IBD is affecting patients at an early age.

8. Cancer and mortality

The earliest studies on risk of cancer and mortality in patients with IBD primarily came from the US and to some extent Europe and tended to be based on highly selected patient populations referred for specialist care at tertiary centers.[90–92] This may be the reason why risk estimates were worryingly high and may have resulted in wrong information of patients and impaired possibilities to obtain reasonably priced medical and life insurances.[93]

Prognostic studies should ideally be based on unselected patient cohorts representing the broad range of disease appearance and hence producing results that are generalizable to the average IBD patient. This was recognized by Truelove and colleagues in Oxford, UK, in the 1960s and 1970s, where the group published the first important observations of a much better prognosis in 'new cases' with IBD (i.e. those diagnosed and followed at the same clinic) as compared to 'referred cases'.[94] Following this work, a number of population-based Scandinavian studies were published, which also spoke against a markedly increased risk of cancer or mortality, although the risk of colorectal cancer in patients with extensive colitis was not negligible in all studies.[95–106]

Results on prognosis from population-based studies have been collected in meta-analyses during the last decade and in addition to these, cross-European and Eastern European studies have emerged in recent years. These will be summarized in the following.

8.1. Colorectal and small bowel cancer

In year 2006, a meta-analysis was published on risk of intestinal cancer in population-based cohorts of patients with Crohn's disease. The meta-analysis was based on 6 studies, of which 4 were European, and the pooled standardized incidence ratio (SIR) of colorectal cancer was 1.9 (95% CI, 1.4–2.5), whereas the SIR of small bowel cancer was 27.1 (95% CI, 14.9–49.2).[107] Of note, the latter estimate was based on very few cases (i.e. a very low absolute risk), which only resulted in a 27-fold increased relative risk due to the extremely rare occurrence of small bowel cancer in the general population. When later adding an Italian study to the meta-analysis, nearly identical estimates were obtained.[108] However, the increased risk of especially colorectal cancer in patients with Crohn's disease was to some extent explained by the high risk observed in a large Canadian study,[109] which provided the largest weight to the meta-analysis, whereas studies from Denmark (1962–1997), Sweden (1955–1984; 1965–1983) and Israel (1970–1980) reported quite low SIRs of *1.14* (95% CI, 0.31–2.92), *0.89* (95% CI, 0.29–2.07), *2.2* (95% CI, 1.0–4.3), and *1.14* (95% CI, 0.03–6.33).[107] In line with this, a recent nationwide Danish cohort study showed no increased risk of colorectal cancer among patients with Crohn's disease,[110] and this was also the case in a study from Hungary of 501 incident CD patients (SIR, 0.99; 95% CI, 0.41–2.39).

The risk of colorectal cancer in European patients with Crohn's disease is close to that of the general population.
The relative risk of small bowel cancer in European patients with Crohn's disease is several fold increased, but it is in general a very rare disease and the absolute risk is low.

The risk of colorectal cancer in ulcerative colitis has in a former meta-analysis including highly selected studies been suggested to be markedly increased with cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years.[111] However, a recent meta-analysis based explicitly on population-based studies (8 studies of which 6 were European and the majority Scandinavian) revealed a pooled SIR of 2.4 (2.1–2.7) which was based on relatively low absolute numbers with a cumulative incidence of CRC of less than 1% at 10 years, 0.4%–2.0% at 15 years, and of only 1.1–2.5% at 20 years in studies with sufficiently long follow-up time.[112] In accordance with this finding, a recent Hungarian cohort study reported that the relative risk of CRC after a median follow-up time of 10 years was only 1.74 (95% CI, 1.01–3.0) despite a higher frequency of extensive disease and lower surgery rates in Eastern European countries than in Northern Europe.[113] Further, recent cohort studies from Sweden[114] and Denmark[110] have suggested that the risk of CRC in UC has decreased over calendar time, and that the risk of CRC today is confined to a subset of patients with extensive/long-standing disease, primary sclerosing cholangitis and young age at diagnosis.

The risk of colorectal cancer in European patients with ulcerative colitis has been twice as high as that of the general population.
However, the absolute risk is only 1–2.5% at 20 years and Scandinavian studies suggest a decrease in risk in recent years.

8.2. Extra-intestinal cancer

A meta-analysis from year 2010 on extra-intestinal malignancy in 8 population-based IBD cohort studies (of which 6 were European: 3 from Sweden, 1 from Denmark, 1 from Italy and 1 based on the EC-IBD cohort) revealed that the overall risk of extra-intestinal cancer was not increased (SIR, 1.10; 95% CI, 0.96–1.27).[115] However, patients with CD were still at increased risk of cancer of the upper gastrointestinal tract (SIR, 2.87; 95% CI, 1.66–4.96), lung (SIR; 1.82; 95% CI,

1.18–2.81), urinary bladder (SIR, 2.03; 95% CI, 1.14–3.63), and skin (SIR, 2.35; 95% CI, 1.43–3.86), whereas UC patients had an increased risk of liver-biliary cancer (SIR, 2.58; 95% CI, 1.58–4.22) and leukemia (SIR, 2.00; 95% CI, 1.31–3.06), which was counterweighted by a decreased risk of pulmonary cancer (SIR, 0.39; 95% CI, 0.20–0.74).[115] These findings may to some extent reflect differences in smoking habits between CD and UC patients, whereas the effect of IBD itself and the treatment hereof on risk of extra-intestinal cancer may have changed with changing treatment options, as the majority of included studies were several decades old. Especially, the risk of skin cancer and lymphoma in IBD has been debated following the introduction of thiopurines[116–119] and biologicals,[120] but it is difficult to differentiate between an increased baseline risk and an increased risk related to drug exposure.[121] Concerning the risk of lymphoma, a recent Hungarian study of 1420 patients followed for 19,293 person-years observed 3 lymphomas, all occurring in patients who had never received thiopurines or biologicals and the risk was not higher than among non-IBD individuals (SIR, 1.37; 95% CI, 0.44–4.26).[122] In contrast, a study from the French CESAME cohort (n=19,486 IBD patients) found a multivariate-adjusted hazard ratio of lymphoproliferative disorder of 5.28 (2.01–13.9, p=0.0007) when comparing patients receiving thiopurines with patients who had never received these drugs.[117] However, the French study may have been influenced by selection bias and a recent unselected nationwide Danish cohort study of 45,986 patients with inflammatory bowel disease (1997–2008) reported a more modestly increased risk of lymphoid tissue cancer in IBD patients using thiopurines (RR, 2.40; 95% CI, 1.13–5.11) when compared to unexposed IBD patients and adjusting for propensity scores and a number of potential confounders.[123] In line with this, a General Practice Research Database study in the UK reported an OR of 3.22 (95% CI, 1.01–10.18) for lymphoma in ever users of azathioprine as compared to non-users.[118] A Dutch study pathology register study of 17,834 IBD patients found no overall increased risk of lymphoma in IBD, but suggested an association between AZA/6-MP use and EBV-positive lymphoma.[124] The risk of cancer following treatment with biologicals still needs to be investigated in long-term observational studies, as done in a recent Danish nationwide cohort study suggesting no overall increased risk of cancer in anti-TNF-α exposed IBD patients compared to unexposed patients.[125]

Finally, the 15-year follow-up of the EC-IBD cohort suggested no increased overall risk of cancer among patients with IBD (independent of treatment).[126]

> The overall risk of extra-intestinal cancer is not markedly increased in European patients with IBD despite an increased risk of cancer of the upper gastrointestinal tract, lung, skin and urinary bladder in Crohn's disease and an increased risk of biliary-liver cancer and leukemia in UC counterweighted by a decreased risk of lung cancer.
>
> Thiopurines may increase the risk of lymphoid tissue cancer and non-melanoma skin cancer among European IBD patients, but drug effects are to some extent difficult to differentiate from the baseline increased risk of these cancers.

8.3. Mortality

In a meta-analysis from year 2010 on mortality in CD based on 9 population-based studies of which 8 were European (including an EC-IBD study), the pooled SMR was 1.39 (95% CI, 1.30–1.49). Mortality was increased from cancer, chronic obstructive pulmonary disease, gastrointestinal disease, and genitourinary disease.[127] A recent nationwide Danish study on mortality in IBD confirmed a 50% increased mortality in CD which did, in contrast to what was observed for UC, not decrease over time, hence suggesting that changes in treatment have not improved survival.[128] However, in contrast to the 40–50% increased mortality in the majority of former studies, a population-based cohort study from Finland (1986–2007) of 1915 adult IBD patients showed no increased mortality from CD. This may be due to the fact that an increased mortality from diseases of the digestive system was counterweighted by reduced mortality from mental and alcohol-related behavioral disorders when comparing IBD patients to the general Finnish population.[129] Still, another recent population-based study (Netherlands; 1991–2003) also questioned the suggested increased mortality from CD (SMR, 1.1; 95% CI, 0.7–1.6), despite a significantly increased mortality from gastrointestinal causes (SMR, 7.5; 95% CI, 2.8–16.4) in this patient group.[130]

> Mortality is up to 40% increased in European patients with Crohn's disease as compared to the general population.

In a meta-analysis from year 2007 on mortality in UC based on 10 population-based studies (8 European including EC-IBD) no increased overall mortality was observed (standardized mortality ratio, SMR, 1.1; 95% CI, 0.9–1.2), although an excess mortality was seen in patients with extensive colitis, in the first years after diagnosis and in Scandinavian patients.[131] In particular, increased mortality from gastrointestinal diseases, non-alcoholic liver diseases, pulmonary embolisms, and respiratory disease (pneumonia) was observed, but this was counterweighted by reduced mortality from pulmonary cancer.[42] The studies of the meta-analysis were, however, not recent and a more recent nationwide Danish study reports a decreasing overall mortality among patients with UC during the last three decades, primarily explained by decreased mortality from CRC.[128] A decrease in mortality from CRC among patients with UC was also observed in a recent Swedish study,[114] whereas a recent population-based Dutch study showed decreased mortality from overall cancer in UC.[130] Population-based studies on mortality among IBD patients from Eastern Europe are lacking.

> Mortality is not increased in European patients with ulcerative colitis as compared to the general population.

9. Summary and conclusion

In conclusion, the incidence and prevalence of IBD have increased in the last few decades throughout Europe. The current estimated prevalence of IBD is approximately 0.3%

of the European population with a significant geographic variation (North/West to South/East gradient). Studies are underway (e.g. ECCO EpiCom initiative) to further explore the factors associated and responsible for these trends.

Since IBDs affect mainly young individuals in their early adulthood and impact all aspect of the affected individual's life they account for substantial direct and indirect costs to both health care system and society. There seems to be a change in the natural history of IBDs as suggested by the recent studies. However, about half of the patients have frequent relapses or continuous active disease and may develop extra intestinal manifestations. In addition up to 2/3 of the patients with CD patients still develop complications requiring hospitalization and/or surgery although some recent studies suggest a decrease in the surgical rates. Surgical rates have also decreased in UC with 10–15% of patients ultimately requiring colectomy. However, there is an unexplained geographic variation in the colectomy rates between north/west and south/east Europe. The factors reported to be associated with these changes include an altered patient monitoring (more complex, tight patient control) and an optimized, tailored treatment strategy including now a more systematic use of biologicals. Future studies are needed to determine if these drugs can further improve long-term disease outcomes.

New data from Europe suggest that the risk of cancers is lower compared to that previously reported; e.g. the colorectal cancer is close to that in the general population in CD and about 2-fold (1–2.5% after 20-years) in UC according to data from Scandinavia and Hungary. In addition, the risk of extra intestinal cancers is not markedly increased in the European patients.

Nonetheless, the long-term disability rate, economic and social impact of IBD in Europe is enormous. Unfortunately, still app. 20% of the IBD patients in Europe will end up with disability pension and further 10% and 25% have to face unemployment or part time employment problems. In addition sick leave is affecting up to half of the patients and even direct health care costs may be as high as 2–3000€ in average. However, a restructuring of the costs is currently occurring and in a short term study from The Netherlands anti-TNFs already accounted for as high as 2/3rd of the direct costs in CD and 1/3rd in UC with a 3-month total cost of €1626 in CD and €595 in UC).[155] Further Pan-European epidemiological and follow-up studies as well as strategic disease modifying trials are needed to investigate the role of tight control and early patient profile stratification in the disease management hopefully leading to superior long-term outcomes, improved quality of life, decreased disability rates and ultimately normal life.

Conflict of interest

None.

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