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INFLAMMATORY BOWEL DISEASES IN FINLAND;

epidemiology, malignancies and mortality

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ACADEMIC DISSERTATION

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IV Nieminen U, Jussila A, Nordling S, Mustonen H, Färkkilä MA. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in IBD: A case-control observational study based on registry data. Int J Cancer. 2014;134:189-96.

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*I:Wolter Kluwer Health; II, V: Elsevier; III: Informa Healthcare; IV: John Wiley and Sons

ABBREVIATIONS

AIEC adherent invasive Escherichia coli

5-ASA 5-aminosalicylate

CD Crohn's disease

CI confidence interval

COPD chronic obstructive pulmonary disease

CRC colorectal cancer

CRP C-reactive protein

CT computed tomography

DBE double-balloon enteroscopy

EGD oesophagogastroduodenoscopy

ESR erythrocyte sedimentation rate

HUCH Helsinki University Central Hospital

GWAS genome-wide association studies

IBD inflammatory bowel disease

IBDU inflammatory bowel disease unclassified

IC indeterminate/unspecified colitis

ICD International Classification of Diseases

IHD ischaemic heart disease

IL interleukin

IPAA ileal pouch-anal anastomosis

IRR incidence rate ratio

MRI magnetic resonance imaging

NOD nucleotide oligomerisation domain

NMSC non-melanoma skin cancer

NSAID non-steroidal anti-inflammatory drug

OR odds ratio

pANCA anti-neutrophil cytoplasmic antibody with perinuclear staining pattern

PRR prevalence rate ratio

PSC primary sclerosing cholangitis

PUFA polyunsaturated fatty acid

QPATI database of the Department of Pathology

RR risk ratio

SBA small bowel adenocarcinoma

SD standard deviation

SE standard error

SIR standardized incidence ratio

SII Social Insurance Institution of Finland

SMR standardizaed mortality ratio

TLR toll-like receptor

TNF tumour necrosis factor

UC ulcerative colitis

WCE wireless capsule endoscopy

VDR vitamin D receptor

ABSTRACT

Background

Inflammatory bowel diseases (IBDs), consisting of ulcerative colitis (UC) and Crohn`s disease (CD), have in recent decades become more common in various regions of the world. Both CD and UC are lifelong gastrointestinal disorders causing considerable morbidity and are associated with excessive use of healthcare resources. In addition to the incidence of IBD, the knowledge of its prevalence is important in estimating the overall disease burden due to IBD including special services, the need for costly medical therapy and surgery, and to meet the various needs of IBD patients. Moreover, epidemiological studies may also provide clues to disease aetiology. A North-South gradient has been identified for IBD. IBD has been linked to a variety of intestinal and extraintestinal malignancies and can also lead to life-threatening complications and increased mortality. Patients with long-lasting IBD have an increased risk of developing colorectal carcinoma (CRC). Earlier studies suggest that the severity of inflammation is an independent risk factor for CRC in UC. Patients with CD are at elevated risk of developing extra-intestinal cancers in contrast to UC patients, whose risk is similar to that of the general population. Earlier studies have documented a slightly increased overall mortality for UC patients compared with the general population, but most studies have reported no increased mortality risk. In contrast to UC, overall mortality for patients with CD has been reportedly increased in most studies. This increase among CD patients has been attributed to excess mortality from gastrointestinal, respiratory and genitourinary diseases. The general aims of the present study were to evaluate the overall burden of IBD, malignancies and mortality of IBD in Finland and to assess whether the degree of microscopic inflammation is a risk factor for developing advanced colorectal neoplasia in IBD. We estimated the nationwide incidence of IBD during the period 2000–2007 and the nationwide prevalence of IBD, changed from 1993 to 2008 in Finland. In addition our aim was to test the North-South gradient of IBD in Finland and study vitamin D levels in the Health 2000 survey.

Patient and methods

Since 1986, the Social Insurance Institution of Finland (SII) has recorded all decisions on entitlements to special refunds to IBD patients in a nationwide register. In Finland, all patients diagnosed with IBD and taking medication for it at some point of the disease course are entitled to reimbursement as a part of the comprehensive national health insurance. Between 1986 and 1993 CD and UC had separate reimbursement codes and since 2000 diagnosis codes (ICD-10) have been available. Unfortunately between the years 1994 and 1999, CD and UC were recorded with the same reimbursement code, and the diagnosis codes of IBD subtypes were not registered.

New IBD cases between 2000-2007 were retrieved from the Special Reimbursement Register and the mean annual incidence rates were calculated by dividing the number of newly diagnosed IBD patients over an eight-year period (2000–2007) by the population at risk (per 100,000 persons). The register study for prevalences included all patients eligible for special reimbursement for medications for IBD in the years 1993 (n=10,958) and 2008 (31,703). The prevalence rates were calculated by dividing the number of IBD patients at the end of the year by the population at risk (per 100,000 persons). The prevalence rates for the spatial geographical study were based on the patients' places of residence at the time of IBD diagnosis. Serum 25-hydroxy vitamin D [S-25(OH)D] concentrations were measured

in a comprehensive health survey, the Health 2000 Survey, conducted in Finland in 2000–2001.
A total of 21,964 patients with IBD (16,649 with UC and 5,315 with CD) from the Special Reimbursement Register were diagnosed 1987-1993 and 2000-2007 and followed up to the end of 2010 by collating these figures with the nationwide Finnish Cancer Registry and the national computerized Cause-of-Death Register maintained by Statistics Finland. The numbers of cancers observed were compared to those expected in general population, and expressed as a standardized incidence ratio (SIR). In each cause-of-death category, the number of deaths reported was compared to that expected in general population, and expressed as a standardized mortality ratio (SMR). The role of histological inflammation as a risk factor for colorectal dysplasia or CRC was investigated in a case-control study. The hospital patient registry and the pathology database of Helsinki University Central Hospital (HUCH) between 1996 and 2008 were combined and 183 IBD patients with dysplasia or CRC were found. The control group was collected from the registry of IBD patients in HUCH.

Results

In total, 14,214 IBD patients were identified in the period 2000-2007; 10,352 had UC and 3,862 had CD. During 2000-2007 the mean annual incidence of IBD per 100,000 inhabitantswas 34.0: in CD 9.2 and in UC 24.8. The incidence of UC was significantly higher in males (27.8) than in females (21.9). In CD the incidence rates did not differ significantly between genders. The incidence of UC increased significantly from 22.1 in 2000–2001 to 27.4 in 2006–2007. The incidence of CD increased only slightly from 8.7 in 2000-2007 to 9.4 in 2006-2007.
The nationwide point prevalence of IBD in 1993 was 216 per 100,000 inhabitants and 595 in 2008. The prevalence of UC (177) was four times higher than the prevalence of CD (38) in 1993. The prevalence of IBD and UC in Finland increased from South to North while for CD no geographical variation could be demonstrated. In the Health 2000 Survey, vitamin D levels were lower in Northern than in Southern Finland.
Overall, male patients with CD and UC had a slightly increased risk of malignancies. Patients with UC were found to have an increased risk of colon (SIR 1.81, 95% confidence interval 1.46-2.21), rectal (1.76, 1.35-2.25), biliary tract (7.26, 4.37-11.1) and thyroid cancer (1.93, 1.28-2.79). The relative risk of colorectal cancer (CRC) was highest among the youngest UC patients. In the case control study including 183 patients with IBD histological severe inflammation was present in 41.4% of patients with dysplasia and in 24.1% of patients with CRC, but in only 4.3% of the controls. Patients with severe inflammation had an odds ratio (OR) of 31.8 (95% CI 15.6-64.9) for dysplasia or carcinoma compared with patients with no inflammation and among patients with mild to moderate inflammation, the OR was 2.6 (95% CI 1.6-4.1). Disease duration increased the annual risk for dysplasia or CRC by 4.5%. Primary sclerosing cholangitis (PSC) did not elevate the risk, whereas use of thiopurines (OR = 0.09, 95% CI 0.02-0.33) protected against CRC. Patients with CD had a significantly increased SIR for cancers of the small intestine (9.97, 4.30-19.6), anus (9.51, 1.96-27.8) and biliary tract (4.93, 1.02-14.4), and for myeloma (2.84, 1.14-5.85). Males also had increased SIR for non-Hodgkin lymphomas (2.09; 95% CI 1.00–3.48). In addition the risk of basal-cell skin cancer was increased in IBD (1.29, 1.16-1.43). Males with UC had a slightly decreased risk of lung and prostate cancer.
Overall mortality was increased among patients with CD (SMR 1.33, 95% confidence interval 1.21-1.46) and UC (1.10, 1.05-1.15). SMR was significantly increased for gastrointestinal causes in CD (6.53, 4.91-8.52) and UC (2.81, 2.32-3.34). Patients with UC were found also to have increased mortality risk from pulmonary (1.24, 1.02-1.46) and

cardiovascular disease (1.14, 1.06-1.22) and cancers of the colon (1.90, 1.38-2.55), rectum (1.79 1.14-2.69) and biliary tract (5.65, 3.54-8.54), whereas mortality risk from alcohol-related deaths was decreased (0.54, 0.39-0.71). Patients with CD had a significantly increased SMR for pulmonary diseases (2.01, 1.39-2.80), infections (4.27, 2.13-7.63) and cancers of the biliary tract (4.51, 1.23-11.5) and lymphoid and hematopoietic tissue (2.95, 1.85-4.45).

Conclusion

Finland belongs to the high incidence and prevalence area of IBD. UC is almost three times more common than CD. The incidence rate of UC increased in the period 2000-2007, while the incidence rate of CD remained fairly stable. The prevalence has increased nearly threefold during the past 15 years. A clear North-South gradient was found for IBD and UC, but not for CD. The incidence of cancer among male patients with CD and CU was higher than that in general population. Patients with UC are at increased risk for CRC and biliary tract cancers and the risk of CRC was highest in the youngest patients. The degree of inflammation and the duration of the disease cumulatively increase the risk for dysplasia and CRC but, unexpectedly, PSC was not identified as a risk factor whereas use of thiopurines strongly protected against CRC. Increased overall mortality was observed in both CD and UC. The excess mortality of 14% in IBD is mainly due to deaths related to inflammation in the gut. Interventions to reduce inflammation in the gut can decrease the risk of CRC and potentially the mortality risk in IBD.

INTRODUCTION

Inflammatory bowel diseases (IBDs), Crohn´s disease (CD) and ulcerative colitis (UC) are characterized by chronic mucosal inflammation and subsequent lesions in the colon or even throughout the gastrointestinal tract with involvement of other organs. They are chronic inflammatory conditions with long-term morbidity and often requiring expensive healthcare. The aetiology of IBD has remained obscure and is thought to be multifactorial.

Over the past few years IBD has become a global disease. Western European and North American countries have been traditionally high incidence and prevalence areas. During the last decade, increasing incidence rates has also been observed in Eastern Europe and Asia. It has been suggested that the incidence of IBD has stabilized or slightly increased in Western countries with even decreasing incidence rates for UC in some Western countries. However, new epidemiological data suggest that the incidence and prevalence of the diseases are still increasing in most countries, including Western countries. A North-South gradient has been identifiedfor IBD. In Europe, higher incidence rates have been found in Northern countries. In several countries including the USA, UK and France, North-South gradients have also been reported.

Patients with long-lasting IBD, both UC and CD colitis, have been at increased risk of developing colorectal cancer (CRC) and CD patients are at increased risk of small intestine cancer. In most recent studies the risk of CRC has decreased and in some studies no increased risk of CRC has been seen in IBD overall. Male sex, young age at diagnosis, extensive colitis and primary sclerosing cholangitis (PSC) have been shown to increase the risk. Chronic colonic inflammation in UC or CD results in an increased risk of cell proliferation and colon carcinogenesis. Studies have supported the severity of microscopic inflammation as an independent risk factor for dysplasia and CRC in patients with long-standing UC. Patients with CD are at elevated risk of developing extra-intestinal cancers compared to UC patients, whose risk seems to be similar to that of general population. CD patients are at increased risk of developing cancer of the upper gastrointestinal tract, lung, urinary bladder and skin. Patients with UC have a significantly increased risk of liver-biliary cancer, but a decreased risk of lung cancer. Recent studies have shown an increased risk of non-melanoma skin cancers (NMSCs) in IBD patients, especially in those taking thiopurines. An increased risk of lymphoma has also been observed among IBD patients taking thiopurines.

IBD can cause increased mortality. The research on overall and cause-specific mortality in IBD is to some extent contradictory. Earlier studies have documented a slightly increased overall mortality for UC patients compared with general population but most studies have reported no increased mortality risk. In contrast to UC, overall mortality for patients with CD has been increased according to most studies. Among patients with UC mortality from CRCs, gastrointestinal, respiratory and nonalcoholic liver diseases has been increased. The increased mortality among CD patients has been attributed an excess of mortality in gastrointestinal, respiratory, genitourinary, infectious and nonalcoholic liver disease.

This thesis aims to evaluate overall burden of IBD in Finland by estimating the nationwide incidence of IBD during the period 2000–2007 and the nationwide prevalence of IBD and changes in the prevalence from 1993 to 2008 by analysing the unique, comprehensive Finnish reimbursement database. Our aim was also to test the North-South gradient

hypothesis. We moreover had an opportunity to study vitamin D levels in Finland in the Health 2000 Survey. Our aim was also to assess the long-term risks of malignant diseases and the overall and cause-specific mortality among patients with IBD in a nationwide study in Finland. Finally, our aim was to assess whether the degree of microscopic inflammation is a risk factor for developing dysplasia or CRC in IBD, and to specify the risk for developing dysplasia in patients with no inflammation to better target surveillance in IBD.

REVIEW OF THE LITERATURE

The inflammatory bowel diseases (IBDs) comprise two types of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). Ulcerative colitis was first described in the mid-1800s by the British physician Samuel Wilks (De Dombal 1968). CD, formerly called regional enteritis or terminal ileitis, is named after the American Dr. Burrill Crohn, who with his colleagues Ginzburg and Oppenheimer described the disease in 1932, as "regional ileitis" (Crohn et al.1932).

1 Aetiology and pathogenesis

Although the knowledge of immunological mechanisms has increased during the past years, the aetiology and pathogenesis of IBD remain incompletely understood. The most widely accepted general hypothesis to explain the development of IBD includes three main factors: genetic predisposition, environmental influences and the homeostasis between the intestinal microbiome and host immunity (Abraham and Cho 2009, Ventham et al. 2013) The complex interaction of these factors is ultimately believed to cause chronically relapsing inflammation of the intestinal mucosal lining and the well described phenotypes.

1.1 Genetics

Clinical observations of patients presenting with IBD suggest that genetics plays a role in the development of disease. Prevalence of CD and UC varies in different populations, patients have a first degree relative with IBD in 2 to 22% of cases and there is concordance between twins (Tysk 1988, Ornholm 2000, Ben-Horin et al. 2009, Lowe et al. 2009, Halfvarson et al. 2011). Overall, the rates of concordance between twins are more modest for CD (30.3% in monozygotic vs. 3.6% in dizygotic twins) and are somewhat higher for UC (15.4% in monozygotic vs. 3.9% in dizygotic twins) than previously shown (Cho et al. 2011, Halfvarson et al. 2011).

Genetic studies have provided many candidate loci in the past decade, and the innate and acquired immune responses have been implicated in pathogenesis. Linkage mapping studies have identified segments of human chromosomes shared among affected relatives greater than expected by chance, and described the IBD1 CD locus on chromosome 16 in 1996, where the NOD2 gene was later identified (Hugot et al. 1996, Hugot et al. 2001). The far more powerful method of genome-wide association studies (GWAS) began in IBD in 2005 (Cho et al. 2011). GWAS has been extremely productive, ultimately contributing to at least 163 independent loci for IBD, 92 further confirmed and 71 newly established in the recent International IBD Genetics Consortium Immunochip Study (Jostins et al 2012, Brant et al. 2013).

The latest data show the increasing proportion of loci common to both diseases, with relatively fewer CD- or UC-specific loci (Brant et al. 2013, Jostins et al. 2012). Most loci (67%) are associated with both CD and UC, with 38% showing equal risk for both phenotypes (Brant 2013, Jostins et al. 2012). Only 38 CD and 23 UC loci are phenotype specific. IBD shares 113 of the 163 loci with numerous traits (e.g. height) and diseases, especially other immune-mediated diseases (60 of 163 loci) (Brant 2013, Jostins et al.

2012). Considerable overlap between susceptibility loci for IBD and mycobacterial infection has been observed (Jostins et al.2012).
Numerous genes related to Th17 cell differentiation and functions are associated with IBD (Brant 2013, Jostins et al. 2012). The latest genetic data increasingly highlight the relationship between the host innate immune system and the intestinal microbiota in CD (Jostins et. al. 2012, Ventham et al. 2013). GWAS have indicated that intracellular bacterial processing by autophagy is an important pathogenic mechanism in CD. Importantly, the association between CD and NOD2 has been consistently replicated at the genome-wide significance level; NOD2 has been mechanistically linked with autophagy (Ventham et al. 2013).

Although UC susceptibility loci have primarily included genes that regulate intestinal epithelial barrier function, there is recent evidence that HLA variants are involved in the development of UC (Jostins et al. 2012, Ventham et al. 2013). HLA-DQA1 was the locus most strongly associated with UC with no corresponding increased risk in CD (Jostins et al. 2012). The HLA region, central to autoimmunity, is especially important and broad-based (affecting a large segment of the population at risk) for UC (Brant 2013, Jostins et al 2012).

1.2 Immune response

The gastrointestinal mucosa is continuously exposed to both food antigens and bacterial antigens from the extremely rich and diversified resident microbial flora. There are two basic components to the immune response: the innate and the adaptive response. The innate immune response represents our first line of defence against pathogens by the immune cells of the innate system such as dendritic cells and macrophages, but also intestinal epithelial cells and myofibroblasts (Abraham and Cho 2009, Geremia et al. 2013). This allows the initiation of rapid and effective inflammatory responses against microbial invasion but it is non-specific and does not confer long-lasting immunity. As opposed to the innate immune response, the adaptive immune system is highly specific; it confers long lasting immunity, and it is adaptable since specificity for the antigen is the result of a complex maturation and development of immune cells. The adaptive immune system is mostly based on T- and B lymphocytes that express antigen receptors on their surfaces (Mayer 2010). Intestinal homeostasis requires a controlled innate immune response to the microbiota, which is recognized by toll-like receptors and nucleotide-binding oligomerization domain (NOD)–like receptors on epithelial and immune cells (Abraham and Cho 2009, Danese 2011). This recognition process contributes to tolerance, but when the process is dysregulated, inflammation ensues (Abraham and Cho 2009).
Abnormalities in humoral and cellular adaptive immunity occur in ulcerative colitis (Danese and Fiocchi 2011). Autoimmunity seems to play a role in UC (Brant 2013, Jostins et al. 2012). In the mucosa of patients with ulcerative colitis, the homoeostatic balance between regulatory and effector T-cells (e.g.T-helper [Th] Th1, Th2, and Th17) is disturbed (Ordas et al. 2012). Evidence suggests that ulcerative colitis is associated with an atypical Th2 response mediated by non-classic natural killer T-cells producing interleukins 5 and 13 (Ordas et al. 2012). Interleukin 13 is of particular importance because it exerts cytotoxic functions against epithelial cells, including induction of apoptosis and alteration of the protein composition of tight-junctions (Ordas et al. 2012).

CD may be a disease of dysregulated microbial immune response (Jostins et al 2012, Brant 2013). In CD there is an imbalance of effector T cells (predominantly Th1 or Th17 cells) versus naturally regulatory T-cells cells in the mucosa (Baumgart and Sandborn. 2012).

1.3 Microbiota

The human gastrointestinal tract hosts more than 100 trillion bacteria and archaea which together make up the gut microbiota (Lepage et al. 2013). Archaea are prokaryotes and represent a third domain between bacteria and eukaryotic organisms. Advances in sequencing technology and the development of metagenomic and bioinformatics methods have opened up new ways to investigate the 10^{14} microorganisms inhabiting the human gut (Lepage et al. 2013). The gastrointestinal microbiome of healthy humans is dominated by four major bacterial phyla: Firmicutes, Bacteroidetes, and to a lesser degree Proteobacteria and Actinobacteria (Morgan et al. 2012).
Although multiple studies to date have failed to reveal a singleaetiological pathogenic species responsible for IBD, the current view is that while individual species may play significant roles in immunomodulation, collateral damage to the microbiome due to their loss or overabundance plays a key role in the persistence of inflammatory responses in chronic disease (Sartor 2008, Nagalinham and Lynch 2012). Dysbiosis with a decrease in beneficial bacteria, such as the Bifidobacteria, Lactobacilli, Bacteroides and Firmicutes (Sartor 2008), and an increase in pathogenic bacteria, such as adherent invasive Escherichia coli (AIEC) (Sartor 2008, Nagalinham and Lynch 2012, Fava and Danese 2011, Morgan et al. 2012) and Mycobacterium avium paratuberculosis ssp (MAP) (Feller et al. 2007) have been reported in IBD. A recent study on the intestinal mucosa, however, performed with highly sensitive methods, failed to detect the presence of MAP in newly diagnosed, treatment-naive patients with CD (Ricanek et al. 2010). MAP was not found among patients with long-lasting UC. A study of seropositivity showed a high seroprevalence for Manitobans at approximately 35%, but failed to demonstrate a difference between CD, UC and controls (Bernstein et al. 2004).
Most of the observations detailing the mechanisms of microbe–host interactions have been made in mice. Microbes associated with human IBD include Faecalibacterium prausnitzii, adherent-invasive E. coli, invasive Fusobacterium nucleatum and mucolytic bacteria such as Ruminococcus gnavus and Ruminococcus torques (Khor et al. 2011). Recent studies suggest that adherent invasive E. coli exploits host defects in phagocytosis and autophagy arising from CD-related polymorphisms to promote chronic inflammation in the susceptible host (Khor et al. 2011). Patients with IBD have a compromised mucus layer and an epithelial surface that is densely coated with bacteria; the abundant presence of Ruminococcus strains in IBD mucosa raises the possibility that such microbes may contribute to the barrier defect observed in IBD, although whether their presence is causal or correlative remains unclear (Khor et al. 2011).

1.4 Enviromental factors

Although genetic studies have provided many candidate loci, identified genetic factors account for only a modest proportion of the disease variance: 13.6% for CD and 7.5% for UC (Jostins et al. 2012). Moreover, the incidence of IBD is increasing among adults and children in both the developed and developing world (Molodecky et al. 2012). These findings demonstrate the importance of environmental factors in the pathogenesis of IBD.

1.4.1 Smoking

Smoking is the most widely studied and replicated environmental trigger for CD and UC. Current smoking has protective effect on the development of UC, current smokers have lower rate of relapse and reduced need for colectomy (Birrenbach et. al 2004, Cosnes 2008, Lakatos et al. 2007, Hansen et al. 2011, Lakatos et al. 2013). Cessation of smoking is associated with an increase in risk of UC within 2−5 years of cessation, and a recent cohort study showed that this risk could remain elevated over 20 years (Higuchi et al. 2012). Contrary to its effect on UC, smoking increases the risk of developing CD two-fold, increases the risk of disease flares and the need for steroids, and is associated with a higher rate of post-operative disease recurrence (Cosnes 2004, Cosnes 2008, Lakatos et al. 2007, Hansen et al. 2011, Higuchi et al. 2012, Lakatos et al. 2013). Despite strong epidemiological data, the mechanism by which smoking impacts IBD remains unclear as does the reason for its protective effect in UC but deleterious impact on CD. In a recent study profound shifts in the microbial composition after smoking cessation were observed with an increase of Firmicutes and Actinobacteria and a lower proportion of Bacteroidetes and Proteobacteria on the phylum level (Biedermann at al. 20l3). In addition, after smoking cessation there was an increase in microbial diversity. However, the study was not performed specifically on patients with IBD and the findings need to be confirmed in CD and UC patients.

1.4.2 Vitamin D

The main source of vitamin D is endogenous production in the skin where ultraviolet B energy in the sunlight converts 7-dehydrocholestrol to cholecalciferol (vitamin D3). Dietary contribution to vitamin D status includes foods such as egg yolk, beef liver, cod liver oil, fatty fish, fortified milk and milk products (Garg et al. 2012, Mouli and Ananthakrishnan 2014). Vitamin D from the endogenous production on exposure to sunlight as well as that absorbed from diet is metabolized within the liver to 25-hydroxyvitamin D (25(OH)D) by the enzyme vitamin D 25-hydroxylase. 25(OH)D is the major circulating form of vitamin D. 25(OH)D is biologically inactive and is activated within the proximal tubules of nephrons in the kidneys by the enzyme 25-hydroxyvitamin D-1alpha-hydroxylase (also known as CYP27B1) to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

The best measure of an individual's vitamin D status is serum 25(OH)D. Serum 25(OH)D levels of less than 20 ng/mL (50 nmol/L) indicate vitamin D deficiency. Serum 25(OH)D levels between 20 and 30 ng/mL (50 and 75nmol/L) represent vitamin D insufficiency, while levels over 30 ng/mL (75 nmol/L) represent normal values (Garg et al. 2012, Mouli and Ananthakrishnan 2014).

In addition to the role of vitamin D in calcium metabolism and bone health, there has been increasing recognition of the immunological role of vitamin D (Cantorna 2010, Guillot et al. 2010, Van Belle et al. 2011). Many autoimmune diseases have been linked to vitamin D deficiency including multiple sclerosis, rheumatoid arthritis, asthma and type 1 diabetes among others (Guillot et al. 2010, Van Belle et al. 2011). A series of systematic reviews and meta-analyses have also reported a consistent inverse relationship between serum 25-hydroxyvitamin D (25(OH)D) levels and CRC risk and for both serum 25(OH)D and vitamin D intake and CRC risk (Bernstein 2013). In a recent study on 2,809 patients with

IBD, a low plasma level of 25(OH)D was associated with an increased risk of cancer, especially colorectal cancer (Ananthakrishnan et al. 2014).

Vitamin D deficiency is more common in adults and children with IBD than healthy controls (Silvennoinen J. 1996, Jahnsen et al. 2002, Pappa et al. 2006a, Pappa et al. 2006b, Joseph et al. 2009). A deficiency of vitamin D could be a consequence of IBD itself with reduced physical activity, sunlight exposure, malnutrition, inadequate dietary intake of vitamin D, or lower bioavailability, all contributing to the deficiency (Garg et al. 2012). However, the finding that vitamin D deficiency is common even in newly diagnosed IBD patients suggests that low vitamin D itself may contribute to increased risk of IBD (Leslie et al. 2008).

A North–South gradient has long been known for IBD. In Europe, higher incidence rates have been found in Northern countries (Shivananda et al. 1996). A recent geographical study from France suggested that low sunlight exposure was associated with an increased incidence of CD (Nerich et al. 2011). In a large prospective cohort of US women, the Nurses' Health Study, higher predicted plasma levels of 25(OH)D significantly reduced the risk for incident CD and nonsignificantly reduced the risk for UC in women (Ananthakrishnan et al. 2012a). For each 1 ng/mL increase in the plasma level of 25(OH)D, there was a 6% relative risk reduction for CD.

Both UC and CD are characterized by a dysregulated mucosal immune response to intestinal microorganisms in a genetically susceptible host. Fascinating insights ascertained from the characterization of vitamin D receptor (VDR) and other vitamin D axis components in the gastrointestinal mucosa, as well as genetic associations, provide evidence for the potential involvement of vitamin D at several stages of initiation and perpetuation of inflammation in IBD (Garg et al. 2012). Studies have linked single-nucleotide VDR to increased susceptibility to CD and UC (Garg et al. 2012).

A recent study demonstrated that low plasma 25(OH)D was associated with increased risk of surgery and hospitalizations in both CD and UC, while normalization of 25(OH)D status was associated with a reduction in the risk of CD-related surgery (Ananthakrishnan et al. 2013a).

1.4.3 Diet

Diet is one of the environmental triggers most commonly reported by patients and diet has been hypothesized to play an important role in the pathogenesis of inflammatory IBDs. However, the data on any association between diet and IBD is limited. Among the dietary factors suspected to influence IBD development are macronutrients, carbohydrates, fat, and protein, in particular different subgroups such as refined sugar, fiber, saturated fatty acids, omega-3, and omega-6 fatty acids, and also food groups such as fruit, vegetables, meat and certain dairy products (Cruber et al. 2012). A recent meta-analysis concluded that only a high dietary intake of total fats, PUFAs, omega-6 fatty acids and meat confers an increased risk of CD and UC, whereas high intake of fiber and fruit was associated with decreased CD risk, and high vegetable intake was associated with decreased UC risk (Hou et al. 2011). Most earlier studies have been limited by factors including retrospective ascertainment of diet, the small number of incident cases limiting power. Recent data from the EPIC cohort and the Nurses Health Study have attempted to prospectively examine the

role of dietary factors on IBD pathogenesis (Tjonneland et al. 2009, Ananthakrishnan et al. 2013c). A nested case control study found that participants in the highest quartile of intake of linoleic acid had a two-fold increase in risk of UC (Tjonneland et al. 2009). In the analysis of the Nurses Health Study a high intake of dietary long-chain n-3 PUFAs (Polyunsaturated fatty acid) may be associated with a reduced risk of UC (Ananthakrishnan et al. 2013b). In contrast, high intake of trans-unsaturated fats may be associated with an increased risk of UC.

1.4.4 Medication

1.4.4.1 Antibiotics

Given the established crucial role of intestinal flora in the pathogenesis of IBD, it is possible that environmental factors such as antibiotics influence the risk of developing the disease through their effect on the microbiome. There have been several studies suggesting that takingantibiotic was associated with the occurrence of IBD (Ng et al. 2013a). Recent population-based studies have suggested an association including the 2–5 years prior to IBD onset where antibiotics impacting on the gut microbiome may have time to induce the changes that could help trigger IBD (Hildebrand et al. 2008, Hviid et al. 2011, Shaw et al. 2011, Virta et al. 2012). Shaw et al. in a population-based study assessed antibiotic intake in the first year life among children diagnosed with IBD (Shaw et al. 2010). The first year of life is when the gut microbiome is evolving. They found a three-fold increase in antibiotic use among children with IBD than among controls.

1.4.4.2 Aspirin, NSAIDs

The gastrointestinal adverse effects of aspirin and nonsteroidal anti-inflammatory factor are well documented. However, while their potential effect in triggering onset or relapse of IBD has been clinically suspected, only sparse high quality evidence has been available to support this. In the EPIC cohort there was a six-fold increase in risk of CD among regular users of aspirin but no association with UC (Chan et al. 2011). In contrast a recent large prospective cohort study found no association between dose, duration, or frequency of aspirin consumption and risk of either CD or UC (Ananthakrishnan et al. 2012b). However, high dose, prolonged duration, and frequent use of NSAIDs (non-steroidal anti-inflammatory drugs) were associated with an increased risk of CD and UC (Ananthakrishnan et al. 2012b).

1.4.4.3 Hormone therapy

A meta-analysis of 14 studies reported a positive association between the use of oral contraceptives and both UC and CD, with a reduced effect on discontinuation (Cornish et al. 2008). In two large prospective cohorts of US women, oral contraceptive use was associated with risk of CD (Khalili et al. 2013). The association between oral contraceptive use and UC was limited to women with a history of smoking. In a large prospective cohort of women, postmenopausal hormone therapy was associated with an increased risk of UC but not CD (Khalili et al. 2012a).

1.4.5 Stress

Stress has long been assumed to play a role in the pathogenesis of CD and UC, and to mediate a role in disease flares. Much of the literature on the role of stress or depression on disease incidence has been restricted to major life events or retrospective ascertainment of exposures, susceptible to the possibility of recall bias or reverse causality (Mikocka-Walus et al. 2007). A prospective study using the Nurses Health Study found that depressive symptoms increase the risk for CD, but not UC, among women (Ananthakrishnan et al. 2013c). Psychological factors may therefore contribute to development of CD. A reduction in the number of symptomatic relapses and need for steroids after initiation of anti-depressant therapy was found in a retrospective observational study (Goodhand et al. 2012). However, a Cochrane review could establishno benefit of psychological interventions on IBD (Timmer et al. 2011).

1.4.6 The hygiene hypothesis

The ‘hygiene hypothesis‘postulates that individuals raised in a sanitary environment are more likely to develop IBD. This hypothesis implies that the increasing frequency of immunological disorders can be attributed to the lack of childhood exposure to enteric pathogens, or alternatively to the loss of saprophytic microorganisms that may impact on regulatory T-cell development (Ng et al. 2013a) The hygiene hypothesis supports the generally negative associations with the epidemiology of Helicobacter pylori (Luther et al. 2010) and the inverse association with the prevalence of helminthic colonization (Koloski et al. 2008).

1.4.7 Appendectomy

In case–control and cohort studies from Europe and the Asia-Pacific region, appendectomy has been shown to be protective for the development of UC (Ng et al. 2013a). In contrast, the relationship between appendectomy and CD is less clear. The literature overall suggests a protective effect of previous appendectomy with confirmed appendicitis (reduction of 13–26%), particularly at a young age, and the development of UC across different geographical regions and populations, and a modest association with the development of CD (Ng et al. 2013a).

1.4.8 Breastfeeding and caesarean section

Disease expression has been proposed to be influenced by early childhood events such as mode of feeding, domestic hygiene, perinatal infections or immunizations (Ng et al. 2013a). Whether breastfeeding protects against the development of IBD remains unclear. While several studies have shown a protective effect of breastfeeding, others have shown no such association (Ng et al. 2013aa). In a recent Danish nationwide study rates of IBD with onset in childhood were moderately increased after delivery by caesarean section but the underlying mechanisms remain unclear (Bager et. al 2012). However, the possible impact of increasing caesarean section practices on the overall burden of IBD in childhood is small (Bager et al. 2012).

1.4.9 Socioeconomic factors

Overall, as IBD emerged in the developed world, it has been considered a disease of a higher socioeconomic standard of living; however, this is not a uniform finding. A recent meta-analysis demonstrated that living in an urban society was positively associated with the development of IBD; however, the consistency and strength of the association was greatest for CD (Soon et al.2012). A relationship between incidence rate and education, and incidence rate and more affluent area of residencehas also been reported in several studies (Armitage et al. 2004, Green et al. 2006, Blanchard et al. 2001). In Northern France there was a noteworthy predominance of CD in agricultural areas in contrast to most studies, and no clear link with affluence (Declercq et al. 2010). Migrant studies have demonstrated that immigrants, and particularly their offspring, from low prevalence regions acquire a similar or even greater risk of IBD than the local population (Probert et al. 1992, Carr et al. 1999, Pinsk et al. 2007).

1.5 Epigenetics

Epigenetics is defined as heritable changes in gene expression which, unlike mutations, are not attributable to alterations in the sequence of DNA (Ventham et al. 2013). The predominant epigenetic mechanisms are DNA methylation, modifications to chromatin structure, loss of imprinting and noncoding RNA (Ventham et al. 2013). An important feature of epigenetic modifications is that they are heritable between mother and daughter cells (mitotic inheritance) and between generations (meiotic inheritance). Epigenetics is one of the explanations for how cells and organisms with identical DNA can have such dramatic phenotypic differences. Epigenetic factors could mediate gene-environment interactions involved in pathogenesis (see Figure 1) (Ventham et al. 2013).

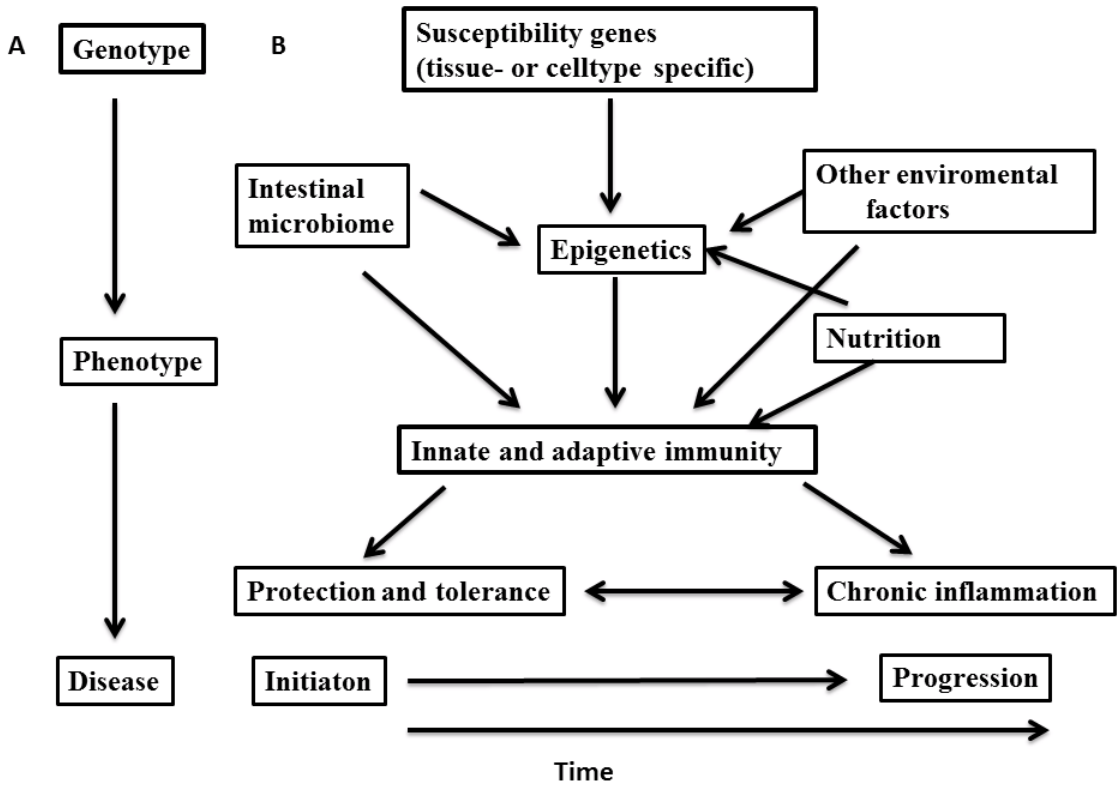

Figure 1. Roles for epigenetics in the pathogenesis of IBD. Epigenetics could mediate between the genetic environment and environmental factors to help determine the phenotype of IBD. The classic paradigm of genotype leading to phenotype and disease (A) has been expanded to embrace key aetiological factors in IBD (B). Epigenetics may interact with both genetic factors and environmental factors in affecting the immune system. The subsequent immune response has consequences for whether insults are tolerated or chronic inflammation is initiated and propagated. (Ventham et al. 2013).

2 Epidemiology

The incidence and prevalence of IBD varies greatly worldwide (Tables 1 and 2). Western European and North American countries have traditionally been high incidence and prevalence areas. During the last decade, an increasing incidence rate has been observed in Eastern Europe and Asia. New epidemiological data suggest that the incidence and prevalence of the diseases are still increasing in most countries (Molodecky et al. 2012). At present the majority of studies have been conducted in European countries, whereas there is a paucity of population-based data on the incidence and prevalence of IBD in developing countries.

2.1 Incidence

The incidence of IBD is highest in westernized nations (Table 1), with the highest rates reported in Canada [19.2 per 100,000 for UC in Nova Scotia (Bernstein et al. 2006) and 20.2 for CD (Lowe et al. 2009)], Northern Europe [UC was 24.3 in Iceland (Shivananda et al. 1996) and 10.6 for CD in the United Kingdom (Thompson et al. 1998)], and Australia [11.2 for UC and 17.4 per 100,000 for CD (Wilson et al. 2011)]. In a recent European cohort study (EccoEpiCoM) a very high incidence of UC was found on the Faroe Islands (31.8) and especially high for total IBD (83.1) (Burisch et al 2014). In a Finnish study from Tampere region (Manninen et al. 2010), the incidence of both UC and CD was reported to have increased markedly in the period 1986-1999, the incidence figures being as high as those in Sweden (Table 1, Sjöberg et al. 2013, Lapidus 2006).

In addition to variations between countries and regions in the incidence and prevalence of IBD, the ratio between UC and CD also shows geographical variations. Compared to the rest of Europe, a higher incidence rate for UC than for CD has been reported in the Nordic countries (Table 1). In Canada and Australia and New Zealand CD is the more predominant disease (Table 1).
In recent years the incidence of IBD has emerged in countries in which it has been hitherto rarely reported, including countries in Eastern Europe and Asia (Table 1). In countries undergoing westernization the incidence of UC increases first, the occurrence of UC preceding that of CD by about ten years (Molodecky et al. 2012). Globally rising rates of paediatric IBD (due primarily to the rising incidence of CD) has been demonstrated in both developed and developing nations; however, most countries lack accurate estimates (Benchimol et al. 2011, Chouraki et al. 2012). In Finland markedly increasing trends in paediatric IBD were found nationwide from 1987 to 2003 (Lehtinen et al. 2011). The increase was steeper for CD than for UC, but then latter remained more common through the study period.

2.2 Prevalence

Data on the prevalence of IBD are scarce. The highest prevalence of IBD worldwide was reported in Canada [241 for UC and 270 for CD (Green et al, 2006)] and Europe [505 for UC and 262 per 100,000 for CD in Norway (Bengtson et al. 2009)], whereas the prevalence of IBD in Asia is low. It has been estimated that approximately 0.6% of population in Canada have IBD (The Burden of Inflammatory Bowel Disease), nearly 1.2

million Americans are living with IBD (Kappelman et al. 2013) and in Europe there may be 2.6 - 3.7 million people with IBD (Burisch et al. 2013).
In the Finnish study from Tampere region (Manninen et al. 2010) the prevalence of both UC and CD 1986-1999 increased markedly with prevalence figures as high as those in Denmark (Table 2, Jakobsen et al. 2006).

2.3 Age and sex

The peak age for CD occurrence is in the age group 15–24 years and for UC in the age group 25–40 (Ekbom et al. 1991, Moum et al.1996a, Vind et al. 2006, Shivananda et al. 1996, Nerich et al. 2006, Petrisch et al. 2013, Sjöberg et al. 2013). Some studies have reported a second peak of incidence for UC and some studies for CD later in life (Sincic et al. 2006, Moum et al. 1996b, Björnsson et al. 2000, Vind et al. 2006, Jacobsen at al. 2006, Bernstein et al. 2006, Sjöberg et al. 2013).

UC occurs slightly more frequently in males (50-60%), whereas CD occurs more frequently in females (20-30%) particularly in high-incidence areas (Bernstein et al. 2006, Molinie et al. 2004, Gearry et al. 2006, Loftus et al. 2007, Ekbom et al. 1991, Moum et al.1996a, Björnsson et al. 2000, Shivananda et al. 1996, Nerich et al. 2006, Petrisch et al. 2013, Sjöberg et al. 2013). However, in low-incidence areas CD has been reported more frequently in men (Hou et al. 2009, Ng et al. 2013b).
Males seem to have a higher incidence of UC in the older age groups (Loftus et al. 2007, Ekbom et al. 1991, Moum et al.1996a, Shivananda et al. 1996, Molinie et al. 2004, Nerich et al. 2006, Sjöberg et al. 2013).

2.4 Geographic heterogeneity

A North–South gradient has long been identified for IBD. In Europe, higher incidence rates have been found in Northern countries (Table 1, Shivananda et al. 1996). In several countries including the USA, UK and France, North–South gradients have also been reported (Sonnenberg et al. 1991, Kappelman et al. 2007, Armitage et al. 2004, Nerich et al. 2006, Sonnenberg et al. 2012. In a large, multi-state sample from the United States, the prevalence of both UC and CD was lower in the South than in all other regions (Kappelman et 2007) and recently a North–South gradient was found in UC and CD based on colonic biopsies (Sonnenbetg et al. 2012). Both a Scottish study of juvenile IBD (Armintage et al. 2004) and a French study of IBD (Nerich et al. 2006) found a clear North–South gradient for CD, but not for UC. In two large prospective cohorts of US women the incidence of UC and CD was significantly lower among women residing in the southern latitudes than in those residing in the northern latitudes (Khalili et al. 2012b). Place of residence later in life (age 30 years) was more strongly related to risk. However, this pattern cannot be generalized; high incidence figures of UC have also been reported also in central Greece (Shivananda et al. 1996), Australia (Wilson et al.) and the incidence of CD is high in Australia and New Zealand (Table 1)
The recent EccoEpiCom study demonstrated an East–West gradient in IBD incidence in Europe (Burish et al. 2014). The combined annual incidence rates for CD and UC in Western Europe were twice as high as the rates in all Eastern European centres.

Table 1. Incidence rates of ulcerative colitis and Crohn's disease (per 100,000) in selected cohorts.

Location	Incidence UC	CD	Period	Case ascertainment	Population	Authors
North America						
USA, Minnesota	10.1	7.9	1970-1979	Population based	124,000	Loftus et al. 2007
	8.8	7.9	1990-2000			
USA, California	12.0	6.3	1996-2002	Medical care program	3,200,000	Herrinton et al. 2008
Canada, Manitoba	13.5	14.8	1990-2001	Population based	1,100,000	Green et al.2006
Canada	11.8	13.4	1998-2000	Population based	5,500,000	Bernstein et al. 2006
Canada, Quebec	NA	20.2	1998-2000	Population based	7,540,000	Lowe et al. 2009
South-America						
Brazil	4.43	3.5	1986-2005	Population based	534,00	Victoria et al. 2009
Europe						
EC-IBD-study			1991-1993	Population based (> 15 yrs)		Shivananda et al.1996
All centres	9.8	5.0				
All Northern centres	11.4	6.3				
All Southern centres	8.0	3.6				
Sweden, Uppsala	10.4	6.1	1965-1983	Population based	1,300,000	Ekbom et al. 1991b
Sweden, Stockholm	NA	4.6	1955-1989	Population based	1,620,000	Lapidus et al. 1997
Sweden, Stockholm,	NA	8.3	1990-2001	Population based (> 15 yrs)	1,470,000	Lapidus 2006
Sweden, Uppsala	19.2	NA	2005-2007	Population based	323,000	Rönnblom et al. 2010
Sweden, Uppsala	20.0	NA	2005-2009	Popularion based	642,000	Sjöberg et al. 2013
Norway	13.6	NA	1990-1993	Population based	966,000	Moum et al. 1996a
Norway	NA	5.8	1990-1993	Population based	966,000	Moum et al. 1996b
Denmark, Copenhagen	8.1	NA	1962-1987	Population based	550,000	Langholz et al. 1991
Denmark, Copenhagen	NA	4.1	1962-1987	Population based	550,000	Munkholm et al. 1992
Denmark, Copenhagen	13.4	8.6	2003-2004	Population based	1,211,000	Vind et al. 2006
Denmark (Northern)	16.7	8.5	1998-2002	Population based, male	490,000	Jakobsen et al. 2006
	17.0	10.7	1998-2002	Population based, female		
Iceland	16.5	5.5	1990-1994	Nationwide	260.000	Björnsson et al. 2000
Finland, Tampere	13.3	5.0	1986	Population based (> 15 yrs)	363,000	Manninen et al. 2010
	19.6	9.4	1999			
The Netherlands	8.5	4.8	1991-2002	Population based, male	579,000	Romberg-Camps et al. 2009
	6.8	7.6		Population based, female		
France (Northern)	4.2	5.2	1986-1990	Population based	5,790,000	Molinié et al. 2004
	3.5	6.4	1997-1999			
France	7.2	8.2	2000-2002	Nationwide	59,368,000	Nerich et al. 2006
France (Northern)	4.7	5.4	1988-1990	Population based	5,790,000	Chouraki et al. 2011
	3.4	6.7	2006-2007			
Italy	3.8	1.9	1978-1980	Population based	550,000	Trallori et al. 1996
	9.6	3.8	1990-1992			
United Kingdom	13.9	8.3	1990-1994	Population based	135,000	Rubin et al. 2000
United Kingdom	NA	10.6	1991-1992	Population based	468,000	Thompson et al. 1998
Germany	3.9	6.1	2004-2006	Population based	1,089,000	Ott et al. 2008
Austria	4.8	6.7	1997-2007	Population based	1,200,000	Petritch et al..2013
Hungary	1.7	0.4	1977	Population based	386,000	Lakatos et al. 2003
	11.0	4.7	2001		376,000	
Hungary	11.9	8.9	2002-2006	Population based	374,500	Lakatos et al. 2011
Croatia	4.3	7.0	2000-2004	Population based	305,500	Sincic et al. 2006

Table 1. (continued)

Location	Incidence UC	CD	Period	Case ascertainment	Population	Authors
Romania	0.97	0.5	2002-2003	Nationwide?		Gheorge et al. 2004
Spain	9.6	5.9	2001-2003	Population based	569,600	Arin et al. 2006
Spain	9.1	7.5	2000-2002	Population based	312,000	Rodrigo et al. 2004
Asia						
Israel	5.04	5.0	1987-1997	Population based	121,000	Niv et al..1999, 2000
Lebanon	4.1	1.4	2000-2004	Population based	15,000	Abdul-Baki et al. 2007
Korea, Seoul	1.7	0.5	1996-2000	Population based	1,069,000	Yang et al. 2008
	3.0	1.3	2001-2005			
India, North	6.0	NA	1999-2000	Population based	51,900	Sood et al..2003
China (Wuhan)	1.4	0.5	2010	Population based	6,085,800	Zhao et al. 2013
Asia	0.8	0.5	2011	Population based	30,192,000	Ng et al. 2013b
China (Guangzhou)	2.1	1.1	2011	Population based	1,400,000	Ng et al. 2013b
China (Hongkong)	1.3	1.3	2011	Population based	3,200,000	Ng et al. 2013b
Australia, New Zealand						
New Zealand	7.6	16.5	2004	Population based	460,000	Gearry et al. 2006
Australia	11.2	17.4	2007-2008	Population based	259,000	Wilson et al. 2010
Australia	7.5	14.6	2011	Population based	300,000	Ng et al. 2013b
Africa						
South Africa	0.9	0.5	1980-1985			Wright et al. 1986

Table 2. Prevalence rates of ulcerative colitis and Crohn's disease (per 100,000) in selected cohorts.

Location	Prevalence UC	CD	Period	Case ascertainment	Population	Authors
North America						
USA, Minnesota	229	133	1991	Population based	124,000	Loftus et al. 2004
USA, Minnesota	214	178	2001	Population based	124,000	Loftus et al. 2007
USA, California	156	96	2002	Medical care program	3,200,000	Herrinton et al. 2008
USA	191	129	1999-2001	Medical care program	1,800,000	Herrinton et al. 2007
USA	238	201	2003-2004	Medical care program (> 15 years)	8.998,000	Kappelman et al. 2007
Canada, Manitoba	170	190	1989-1994	Population based	1,100,000	Bernstein et al. 1999
Canada, Manitoba	241	270	1998-2000	Population based	1,100,000	Green et al. 2006
Canada	194	234	1998-2000	Population based	5,500,000	Bernstein et al. 2006
Canada, Quebec	NA	190	1998-2000	Population based	7,540,000	Lowe et al. 2009
Europe						
Sweden, Örebro	198	NA	1987	Population based	1,300,000	Tysk et al. 1992
Sweden, Stockholm,	NA	213	2001	Population based (> 15 yrs)	1,470,000	Lapidus et al. 2006
Norway	505	262	1990-1993	Population based	966,000	Bengtson et al. 2009
Denmark, Copenhagen	161	54	1987	Population based	550,000	Langholz et al. 1991
Denmark, Copenhagen	NA	54	1987	Population based	550,000	Munkholm et al. 1992
Denmark (Northern)	294	151	2002	Population based	490,000	Jakobsen et al. 2006
Iceland	318	33	1979	Nationwide	250.000	Björnsson et al.1989
Finland, Tampere	119	40	1986	Population based (> 15 yrs)	363,000	Manninen et al. 2010
	291	124	1999			
England	243	145	1994	Population based	135,000	Rubin et al. 2000
England	243	130	2002	Population based	86,800	Stone et al. 2003
Italy	121	40	1992	Population based	550,000	Trallori et al.1996
Spain	110	88	1997	Population based	462,000	Saro Gismera et al. 2003
Hungary	143	53	2001	Population based	376,000	Lakatos et al. 2003
Asia						
Israel	121	26	1987	Population based	121,000	Niv et al. 2000
	167	65	1997	Population based		Niv et al. 2000
India, North	44	NA	1999-2001	Population based	51,900	Sood et al. 2003
Lebanon	106	53	2000-2004	Population based	15.000	Abdul-Baki et al. 2006
Australia, New Zealand						
New Zealand	155	146	2004	Population based	460,000	Gerry et al. 2006

3 Diagnosis, clinical presentation and classification

No single specific test exists for diagnosing IBD. The diagnosis of IBD requires a multidisciplinary approach involving a team of specialists (e.g. gastroenterologists, pathologists and radiologists) (Magro et al. 2013). The diagnosis should be established by a combination of medical history, clinical evaluation, laboratory data (including negative stool examinations for infectious agents) and typical endoscopic, histologic and radiologic findings (Magro et al. 2013). UC and CD can most often be differentiated by their clinical characteristics. A patient is classified as having inflammatory bowel disease unclassified (IBDU), formerly termed indeterminate colitis (IC) if definitive distinction between UC, CD and other causes of colitis can be made after careful investigation (Silverberg et al. 2005, Satsangi et al. 2006). The diagnosis of IC should be made only after colectomy (Silverberg et al 2005, Satsangi et al. 2006). In some cases a correct diagnosis can only be made over time. In one-year follow-up as well as in five-year follow-up, change of diagnosis occurred in almost 10% of the patients originally classified as UC or CD (Moum et al. 1997, Henriksen et al. 2006).

3.1 Clinical presentation and classification

The most common symptoms of UC are loose stools or diarrhoea, which are almost invariably associated with rectal bleeding (Lennard-Jones and Shivananda 1997, Danese and Fiocchi 2011, Ordas et al. 2012). Patients with active disease also have rectal urgency, tenesmi, passage of mucopurulent exudates, crampy abdominal pain, and nocturnal and postprandial defecation. The onset is typically gradual, often followed by periods of spontaneous remission and subsequent relapses (Danese et al. 2011, Dignass et al. 2012a).

Clinical presentation and symptoms in CD depend on disease severity and location. Chronic diarrhoea and abdominal pain and weight loss are the most common presenting symptoms (Nikolaus and Schreiber 2007). Blood and/or mucus in the stool are seen in patients with Crohn's colitis, but less frequently than in ulcerative colitis (Van Assche et al. 2010a). Perianal fistulas may be present and may be the first presenting complaint. Systemic symptoms of malaise, anorexia, or elevated body temperature are common in CD patients (Van Assche et al. 2010a).

Extraintestinal manifestations (EIMs) are common in IBD, affecting up to 35% of patients and may precede intestinal symptoms (Van Assche et al. 2010b, Van Assche et al. 2013). The extraintestinal manifestations of IBD include arthropathies, oral aphthous ulcers, cutaneous, ocular and hepatobiliary manifestations. Between 1.4 and 7.5% of patients with IBD will develop primary sclerosing cholangitis (PSC) at some point during the course of their disease (Uko et al. 2012). Thromboembolism is more frequent in IBD than in general population and is generally associated with active disease (Grainge et al.2010, Kappelman et al. 2011). Low bone mass and osteoporosis are common in both male and female patients with UC (20%–50%) (Silvennoinen JA et al. 1995, Van Assche et al. 2010b, Van Assche et al. 2013).

UC affects the rectum and subsequently a variable extent of the colon in continuity; however, some patients with proctitis or left-sided colitis might have a caecal patch of inflammation (Dignass et al. 2012a). Infrequently backwash ileitis is seen in UC. The Montreal classification is now regarded as international standard for defining the

distribution of the disease (Table 3) (Dignass et al. 2012a, Silverberg et al. 2005, Satsangi et al. 2006). This is used to describe the maximal, macroscopic extent of disease at colonoscopy. The extent of UC influences the management and frequency of surveillance of patients (Cairns et al. 2010, Dignass et al. 2012b,Van Assche et al. 2012). However, the extent of the disease is not a fixed parameter and may change over time. Proximal extension of UC has been observed in up to 53% of patients with a left-sided UC or proctitis (Langholtz et al. 1996, Moum et al.1999, Lakatos et al. 2011).

Table 3. Montreal classification of the extent of ulcerative colitis (Silverberg et al. 2005).

Extend		*Anatomy*
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive colitis	Involvement extends proximal to the splenic flexure

CD may involve any part of the gastrointestinal tract, most often the ileum and the colon, however. Typical presentation includes discontinuous involvement of various parts of the gastrointestinal tract and development of disease complications such as strictures, fistules and abscesses (Van Assche et al. 2010a). The Montreal classification (Silverberg et al. 2005, Satsangi et al. 2006) is now regarded as the international standard of phenotype subtyping in Crohn's disease (Table 4). Whereas the anatomical location is mostly stable, behaviour of Crohn's disease classification varies substantially during the course of the disease (Van Asshe et al. 2010, Baumgart and Sandborn 2012). In a population-based study almost a fifth (19%) of patients progressed to a more aggressive phenotype at 90 days and more than half (51%) at 20 years after initial diagnosis (Thia et al. 2010).

Table 4. Montreal classification for Crohn`s disease (Silverberg et al. 2005).

Age at diagnosis	A1 below 16 y A2 between 17 and 40 y A3 above 40 y
Location	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifiifier#

*L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present
"p" is added to B1-B3 when concomitant perianal disease is present

3.2 Endoscopy

For suspected IBD, ileocolonoscopy and biopsies are first line procedures to establish a diagnosis of IBD. For a reliable diagnosis of CD and UC multiple biopsies from six segments (terminal ileum, ascending, transverse, descending, sigmoid and rectum) should be obtained (Annese et al. 2013). Multiple biopsies imply a minimum of two representative samples from each segment including macroscopically normal segments (Annese et al. 2013).
No endoscopic feature is specific to UC or CD (Annese et al. 2013). The most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement (Annese et al. 2013). The most useful endoscopic features in Crohn's disease are discontinuous lesions, presence of strictures and fistula and perianal involvement (Annese et al. 2013).
Upper GI endoscopy is routinely performed in the assessment of paediatric and adolescent IBD to accurately classify IBD (Annese et al. 2013) and is recommended for both adult CD and UC patients with upper gastrointestinal symptoms.
Small bowel wireless capsule (WCE) is a novel method of directly visualizing small bowel lesions in patients with IBD that may be missed by traditional endoscopic or radiological procedures (Annese et al. 2013). Double-balloon enteroscopy (DBE) is defined as endoluminal examination of the small bowel using a double-balloon endoscope. DBE is indicated in established Crohn's disease when direct visualization of the small intestine beyond the reach of ileocolonoscopy is necessary, in order to exclude an alternative diagnosis, or to undertake a therapeutic procedure (Bourreille´et al. 2009).

3.3 Imaging techniques

Radiological imaging techniques are complementary to endoscopic assessment in IBD. Cross-sectional imaging offers the opportunity to detect and stage inflammatory, obstructive and fistulizing CD (Panes et al. 2013). Radiological techniques are mainly used for the examination of the small bowel and extramural complications of IBD. Small bowel barium examinations with either enteroclysis or a small-bowel follow-through are long established for small bowel evaluation and in widespread use. Computed tomography (CT) and magnetic resonance imaging (MRI) are imaging techniques with the highest diagnostic accuracy for the detection of intestinal involvement and penetrating lesions in CD (Van Assche et al. 2010a). Radiation exposure should be considered when selecting techniques, especially in young patients, and techniques with radiation burden are not suitable for repeated use. Ultrasound is a useful additional technique for assessing bowel inflammation and extramural complication but it does not provide information on the extent of the disease and is operator dependent (Van Assche et al. 2010a).

3.4 Laboratory tests

Initial laboratory investigations of IBD should include a full blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), electrolytes, creatinine, and liver enzymes. Microbiological testing for infectious diarrhoea including clostridium difficile toxin is needed for differential diagnosis. Additional stool tests may be necessary for patients reportingrecent travel abroad. Anaemia and thrombocytosis are common in the full blood counts of patients with active IBD (Van Assche et al. 2010a, Dignass et al. 2012a).

In CD serum levels of CRP correlate well with disease activity but in UC CRP correlates less well with disease activity than in CD (Vermeire et al. 2004, Vermeire et al. 2006). Low serum protein or low serum albumin may be a consequence of protein loss from inflamed gut or may result from malabsorption or malnutrition secondary to inadequate protein intake (Nikolaus and Schreiber 2007). Faecal calprotectin can be used for monitoring disease activity, but is not specific to IBD (Vermeire et al. 2006, Sipponen et al. 2008).

3.5 Histopathology

In IBD histopathology is used for diagnosis, the assessment of disease activity and the identification of intraepithelial neoplasia (dysplasia). In the initial ileocolonoscopy examination, multiple mucosal biopsies should be taken from each segment of the colon (right, transverse, left, sigmoid colon and the rectum) and the ileum. Histology helps in distinguishing between UC and CD, and between IBD and other inflammatory disorders ofthe gastrointestinal tract (Van Assche et al. 2010a, Dignass et al. 2012a). Basal plasmacytosis at initial onset has a high predictive value for the diagnosis of IBD (Dignass et al. 2012a). Microscopic features used for the diagnosis of IBD are shown in Table 5 (Magro et al. 2013).

Table 5. Microscopic features used for the diagnosis of IBD (Magro et al. 2013).

	Ulcerative colitis	*Crohn`s disease*
Crypt architectural irregularity	Diffuse (continuous)	Focal (discontinuous)
Chronic inflammation	Diffuse (continuous) Decrease proximally	Focal (discontinuous) Variable
Patchiness	Uncommon	Common
Localization	Superficial Transmucosal Sometimes in submucosa	Transmural
Serositis	Absent except in fulminant colitis	Present
Lymphoid aggregates	Frequent in mucosa, submucosa	Common, transmural
Granulomas	Absent, except with ruptured crypts	Present
Acute inflammation	Diffuse (continuous)	Focal (discontinuous)
Crypt epithelial polymorphs	Diffuse (continuous)	Focal (discontinuous)
Crypt abscesses	Common	Uncommon
Mucin depletion	Present, pronounced	Uncommon, mild
Neuronal hyperplasia	Rare	Common
Muscular hypertrophy	Absent	Present
Paneth cell metaplasia	Present	Uncommon
Pyloric gland metaplasia	Rare	Present

4 Treatment

According to current consensus-based guidelines, the treatment of choice for patients with IBD should take into consideration the level of clinical activity (mild, moderate or severe) combined with the extent and site of disease and the course of the disease during follow-up, disease *behavior and patients' preferences (Dignass et al. 2012b, Van Assche et al. 2010b). In some CD patients with mild disease, no treatment is an option. Smoking increases the need for steroids, immunosuppressants and operations in patients with CD (Dignass et al. 2010). Smoking cessation is associated with a 65% reduction in the risk of a relapse compared to continued smokers, a magnitude similar to that obtained with immunosuppressive therapy (Johnson et al. 2005).
Medical therapy for IBD can be divided into induction and maintenance of remission.

4.1 Medical therapy

The medical therapy used in IBD is shown in Table 6.
The medical therapy for ulcerative colitis according to site of disease and disease activity is shown in Table 7 and the medical therapy for Crohn`s disease according to site of disease and disease activity is shown in Table 8.

At present, antibiotics are considered appropriate for septic complications, symptoms attributable to bacterial overgrowth or perineal disease in CD (Dignass et al. 2010). Some CD patients with colonic disease may respond to metronidazole but not as first-line therapy (Sutherland et al. 1991). Imidazoles are effective for the prevention of post-operative recurrence, but in clinical practice are rarely used due to side effects during long-term treatment (Van Assche et al. 2010b). Azathioprine combined with metronidazole can be used in selected patients in prevention of postoperative recurrence (D´Haens et al. 2008). Metronidazole and ciprofloxacin have been shown to be effective therapies for acute and/or chronic pouchitis but ciprofloxacin has been more effective than metronidazole in inducing remission (Van Assche et al. 2012). However, antibiotics are not effective in inducing or maintaining remission in UC (Dignass et al. 2012).
In recent years there has been increased interest in the use of probiotics in IBD due to the microbiome role in IBD pathogenesis. There are promising results for E. coli Nissle in inactive UC and the multispecies product VSL#3 in active UC and inactive pouch patients (Dignass et al. 2012b, Van Assche et al. 2013). So far, no evidence is available to support the use of probiotics in CD (Dignass et al. 2010).

4.2 Other therapies

Malnutrition in IBD is common and multi-factorial in origin and nutritional assessment including BMI is important. Nutritional supplementation is required especially in severe CD. The use of nutritional treatment as primary therapy in patients with CD is controversial and the results are less promising than those achieved using corticosteroid therapy in adult IBD patients, although there is some evidence of its usefulness in the maintenance of remission in adult CD patients (Dignass et al. 2010, Yamamoto et al. 2007). In contrast, nutritional therapy is considered to be a first-line therapy for active CD in children, causing mucosal healing and demonstrating an efficacy equal to that of steroids

(Van Assche et al. 2010b). Total parenteral nutrition is appropriateadjuvanttherapy in complex, fistulating disease (Dignass et al. 2010).

Because of the increased risk for osteoporosis, sufficient intake of calcium and vitamin D is necessary and patients receiving systemic steroid therapy should receive calcium and vitamin D for prophylaxis (Van Asshe et al. 2012). Anaemia is a common finding with IBD, and it should be treated by optimizing the therapy of active IBD, and by administering oral, or intravenous iron supplements (Van Asshe et al. 2012). Intravenous iron is more effective and better tolerated than oral iron supplements (Van Asshe et al. 2012). However, intravenous iron is more expensive than oral.

Table 6. Medical therapy for IBD.

Drug	Mechanism of action
The conventional medical therapy	
5-ASA (mesalazine, olsalazine) / sulfasalazine	Agonists of PPARγ[1] and many other mechanisms of actions
Corticosteroids	Various mechanisms of actions
Azatioprine /6-Mercaptopurine	Inhibition of purine synthesis
Methotrexate	Inhibition of dihydrofolate reductase
Ciclosporine, tacrolimus	Calcineurin inhibitors
Antibiotitics	Effect on the intestinal bacterial flora
Biological therapy	
Infliximab	Anti-TNFα antibody
Adalimumabi	Anti-TNFα antibody
Certolizumab[2]	Anti-TNFα antibody
Golimumab[2]	Anti-TNFα antibody
Ustekinumab[2]	Anti-IL-12/IL-23p40
Natalizumab[2]	Anti-α4 Integrin antibody
MLN002, Vedolizumab[2, 3]	Anti-α4β7 Integrin antibody
Tofacitinib[2]	Inhibitor of Janus kinases 1, 2, and 3
[1] PPAR= peroxisome proliferator-activated receptor [2] Not available in Finland	
*Based on the second ECCO consensus for CD and UC (Dignass et al. 2010, Dignass et al. 2012b), Sandborn et al. 2013a, Sandborn et al. 2013b	

Table 7. Medical therapy for ulcerative colitis. Treatment according to site of disease and disease activity.[a]	
Induction of remission	
Mildly active colitis	5-ASA topical therapy (proctitis, left sided colitis) or oral therapy 2-4.8 g/day (left sided colitis, extensive ulcerative colitis), combination of oral and topical therapy
Moderately active colitis	5-ASA topical therapy (proctitis, left sided colitis) or oral therapy 2-4.8 g/day (left sided colitis, extensive ulcerative colitis), combination of oral and topical therapy Corticosteroid topically (proctitis, left sided colitis) or oral therapy or combination of oral and topical therapy
Severely active colitis	Corticosteroids, oral or intravenous Ciclosporin 2 mg/kg, intravenous, 5-7 days, oral ciclosporin for 3-6 months for those who respond the treatment as a transition to thiopurines Infliximab 5 mg/kg, intravenous, 0, 2, 6 weeks Tacrolismus?
Maintenance of remission	
Mildly active colitis	5-ASA topical therapy (proctitis, left sided colitis) or oral therapy 2-4.8 g/day (left sided colitis, extensive ulcerative colitis), combination of oral and topical therapy
Moderately active colitis	5-ASA Corticosteroid resistant or dependent: azathioprine 2-2,5 mg/kg/day or mercaptopurine 1-1.,5 mg/kd/day
Severely active colitis	Azathioprine 2-2.5 mg/kg/day or mercaptopurine 1-1,5 mg/kd/day Infliximab 5 mg/kg every 8 weeks, intravenous, (for those who have responded to induction therapy) Adalimumab every 2 weeks, subcutaneously, (for those who have responded to induction therapy)
[a] Based on ECCO concensus (Dignass et al. 2012b).	

Table 8. Medical therapy for Crohn`s disease. Treatment according to site of disease and disease activity.[a]		
Site and severity of disease	First line treatment	Alternatives or additional therapy
Mildly active ileocecal CD	Budesonide 9mg/day at beginning.	No treatment?
Moderarately or severely active ileocecal CD	Budesonide 9mg/day at beginning.	Prednisolon 40-80 mg/day at beginning, oral Corticosteroid resistant or dependent: 1. Azathioprine 2-2.5 mg/kg/day or mercaptopurine 1-1.5 mg/kg/day 2. Methotrexate 15-25 mg/week, subcutaneous or intramuscular 3. Infliximab 5 mg/kg 0, 2 and 6 weeks, intravenous, and then every 8 weeks for those who have responded to induction therapy or adalimumab 160-80-40 mg every 2 weeks, subcutaneous,and then 40 mg every 2 weeks for those who have responded to induction therapy
Mildly active colonic CD	Sulfasalazine Mesalazine?	No treatment?
Moderarately or severely active colonic CD	Prednisolon 40-80 mg/day at beginning , oral.	Corticosteroid resistant or dependent: 1. Azathioprine 2-2.5 mg/kg/day or mercaptopurine 1-1.5 mg/kg/day 2. Methotrexate 15-25 mg/week, subcutaneous or intramuscular 3. Infliximab 5 mg/kg 0, 2 and 6 weeks, intravenous, and then every 8 weeks for those who have responded to induction therapy or adalimumab 160-80-40 mg every 2 weeks, subcutaneous,and then 40 mg every 2 weeks for those who have responded to induction therapy
Maintenance of remission	Azathioprine 2-2,5 mg/kg/day or mercaptopurine 1-1,5 mg/kg/day	1. Methotrexate 15-25 mg/week, subcutaneous or intramuscular 2. Infliximab 5 mg/kg every 8 weeks, intravenous, (for those who have responded to induction therapy) 3. Adalimumab every 2 weeks, subcutaneous, (for those who have responded to induction therapy)
[a] Based on ECCO consensus (Dignass et al. 2010)		

4.3 Surgical therapy

Up to 30% of patients will ultimately require colectomy for ulcerative colitis (Mowat et al. 2011). Indications for surgery in UC are severe acute colitis that does not respond to therapy, chronically active disease that causes steroid dependency, and dysplasia or cancer of the colon (Mowat et al. 2011). Nowadays restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the standard care in elective surgery for UC (Dignass et al. 2012b). Total colectomy with ileostomy is recommended for individuals with impaired sphincter function, advanced age, significant comorbidities or distal rectal cancer (Dignass et al. 2012b). Lifetime failure rates for IPAA will probably be in the region of 15% (Dignass et al. 2012). Up to 50% of patients who undergo ileal pouch surgery for ulcerative colitis suffer from pouchitis (Mowat et al.2011).

Despite continued advances in the medical management of Crohn's disease, up to 75% of patients will undergo an intestinal resection during their disease course (Mowat et al. 2011). During a 5-year follow-up in Norway, 28% of CD patients underwent surgery with intestinal resection (Henriksen et al. 2007). Furthermore, postoperative disease recurrence is common, with 70–90% of patients having endoscopic recurrence within 12 months of surgery (Olaison et al. 1992, Rutgeerts et al.1990). Surgical intervention in CD is governed by the extent of the disease, the response to medical treatment and the presence or absence of complications (Mowat et al. 2011). Fibrostenotic and fistulating intestinal disease in the presence of a limited ileocolic distribution surgery is a good therapeutic option. In more extensive disease, preservation of bowel length is crucial important. Limiting the resection to macroscopic disease and the use of strictureplasty have revolutionized surgery in this scenario. In perianal or rectovaginal disease surgery should be used in conjunction with best medical therapy (Mowat et al. 2011).

5 Malignancies

Immunosuppression and inflammation are the two main drivers of IBD related carcinogenesis (Beaugerie 2012). The difficulty is that these two mechanisms may be interlinked, particularly in the intestinal tissues. Patients with IBD with extensive long-standing colitis are at higher risk of CRC than individuals in general population (Ullman et al. 2012). Chronic inflammation of the colorectal mucosa, even at microscopic levels only (neutrophil infiltrate) in patients with clinically quiescent endoscopic and clinical disease, appears to be the major driver of these inflammation-related CRCs (Gupta et al. 2007, Beaugerie 2012) In addition to gastrointestinal malignancy, patients with IBD are also at increased risk of extra-intestinal malignancy, including lymphoma (Kandiel et al. 2005, Beaugerie et al. 2009) and non-melanoma skin cancer (NMSC) (Long et al. 2010, Peyrin-Biroulet et al. 2012, Long et al. 2012, Singh et al. 2011) among others.

5.1 Intestinal Cancer

5.1.1 Colorectal cancer

IBD is associated with an increased risk of CRC, which is thought to be primarily related to long-standing chronic inflammation (Rubin et al. 2013). Early studies from tertiary referral centrers have reported a high risk of CRC, but they tended to overestimate the risk (Jess et al. 2012a). In contrast, population-based studies covering defined geographical areas report a more conservative risk. However, these studies probably included patients with limited and less severe disease, and may have underestimated the risk (Jess et al. 2012a). In addition, geographical differences have been shown (Eaden et al. 2001).

5.1.1.1 Colorectal cancer in UC

A meta-analysis of cohort and case-controlled studies (Eaden 2001) on the risk of CRC in UC estimated an incidence rate of 3/1000 person years disease duration, an annual risk of 0.3% and a cumulative risk of 18.4% after 30 years of disease. More recent population-based studies have shown that the risk is lower than previously described or even similar to that of the general population (Table 9) (Rogler 2014).

Table 9. Risk of CRC in UC in population based studies.

	Publication year	Period	No. of patients	SIR (95% CI)	Cumulative incidence
Ekbom, Sweden	1990a	1922-1983	3117	5.5 (4,6-7.0)	
Stewenius, Sweden	1995	1958-1990	471	2.1 (1.01-4.1)	4% at 25 years
Palli, Italy	2000	1978-1997	689	1.79 (0.85-3.28)	
Wandall, Denmark	2000	1973-1998	801	1.67 (0.61-3.62)	10.1% at 25 years
Bernstein, Canada	2001	1984-1997	2,672	2.46 (1.82-3.25)	
Winther, Denmark	2004	1962-1997	1,160	1.05 (0.56-1.79)	2.1% at 30 years
Jess, USA	2006	1940-2001	378	1.1 (0.4-2.4)	2% at 25 years
Jess, Denmark	2007a	1962-2005	1575	1.1 (0.6-1.8)	
Söderlund, Sweden	2009	1954-2004	4,125	2.7 (2.3-3.2)	3% at 25 years
Jess, Denmark	2012a	1979-2008	32,911	1.07 (0.95-1.21), RR	
Manninen, Finland	2013	1985-2007	1254	1.99 (1.14-3.25)	
Kappelman, Denmark	2014	1978-2010	35,152	1.0 (0.9.-1.1)	

A recent meta-analysis of prospective population-based studies showed that the estimated standardized incidence ratio (SIR) was 2.39 (95% CI 2.1–2.7) (Jess et al. 2012b). A recent large nationwide study from Denmark demonstrated that a diagnosis of UC no longer seems to increase patients' risk of CRC, although subgroups of patients with UC remain at increased risk (Jess et al. 2012a).
Recent time-trend studies also demonstrate a decreasing risk of CRC in UC patients and in Denmark the relative risk (RR) decreased from 1.34 between 1979 and 1988 to 0.57 between 1999 and 2009 (Jess et al. 2012a). A follow-up study of IBD patients diagnosed in Sweden during the period 1954 –1989 and followed up until 2004 showed a substantial

decrease over time in mortality from CRC, whereas a 70% decrease in the incidence of CRC between 1960 and 1969 and 2000 and 2004 did not reach statistical significance (Söderlund et al. 2009).

5.1.1.2 Colorectal cancer in CD

The role of CD as a risk factor of CRC is controversial and, compared with UC, the risk is modest (Table 10). A meta-analysis of population-based studies in CD (Jess et al. 2005) estimated a pooled SIR for CRC at1.9 (95% CI 1.4–2.5). In another meta-analysis (Canavan et al. 2006) relative risk RR was 2.5 (95% CI 1.3–4.7) among all CD patients, with a higher risk for CD-colitis (RR 4.5 [95% CI 1.3–14.9)]. In recent Danish (Jess et al. 2012a) and Finnish (Manninen et al. 2013) studies the risk of CRC was not increased among patients with CD.

Table 10. Risk of CRC and small bowel adenocarcinoma in CD in population based studies.

Author, country	Publication year	Period	No. of patients	SIR CRC (95% CI)	SIR SBC (95% CI)
Fireman, Israel	1989	1970-1989	274	1.14 (0.03-6.33)	0 (-)
Ekbom, Sweden	1990b	1965-1983	1,469	2.2 (1.0-4.3)	3.4 (0.1-18.6)
Person, Sweden	1994	1955-1984	1,251	0.89 (0.29-2.07)	15.6 (4.3-40)
Bernstein, Canada	2001	1984-1997	2,857	2.11 (1.41-3.04)	17.4 (4.2-73)
Jess, Denmark	2004	1962-1997	373	1.14 (0.31-2.92)	66.7 (18.1-171)
Jess, USA	2005	1940-2002	313	1.87 (0.69-4.07)	41.1 (8.5-120)
Jess, Denmark	2007a	1962-2005	641	1.4 (0.5-3.1)	-
Jess, Denmark	2012a	1979-2008	14,463	0.85 (0.67-1.07), RR	-
Manninen, Finland	2013	1985-2007	550	1.92 (0.62-4.49)	-
Kappelman, Denmark	2014	1978-2010	13,756	0.9 (0.7-1.2)	8.4 (4.3-14.7)

5.1.1.3 Risk factors for colorectal cancer in patients with IBD

Reported risk factors for CRC include extensive disease (Eaden et al. 2001, Ekbom et al. 1990a, Jess et al. 2012a, Jess et al. 2012b), young age at diagnosis (Eaden et al. 2001, Jess et al. 2012a, Jess et al. 2012b), family history of CRC (Askling et al. 2001), co-existing primary sclerosing cholangitis (PSC) (Jayaram et al. 2001, Soetikno et al. 2002, Broome et al. 2006), persistent inflammation of the colon (Rutter et al. 2004, Gupta et al. 2007) and longstanding disease (Eaden 2001) (See figure 2).

In Crohn's colitis, the risk of CRC seems to be similar to that of UC if the extension and duration are comparable (Gillen et al. 1994, Choi et al. 1994, Kiran et al. 2010).
The gender-related risk of CRC in UC has been reportedly higher in men than in women in earlier studies (Jess et al. 2006, Bernstein et al. 2001). In a Swedish study (Söderlund et al. 2010) males had a 60% higher risk of CRC (compared with female gender) and a greater cumulative incidence after 40 years of disease. The effect of gender was limited to patients with more than 10 years of follow-up and to those aged <45 years at diagnosis.

PSC is a recognized risk factor for CRC in patients with UC, with a fourfold increase in risk compared with UC patients without PSC (Jess et al. 2012a, Soetikno et al. 2002, Leidenius et al. 1997). Dysplasia or CRC have also been found to appear soon after the diagnosis of both diseases in some patients (Thackeray et al. 2011). Current evidence emphasizes that the risk of CRC persists after liver transplantation (Hanouneh et al. 2012). Crohn's colitis patients with concomitant PSC also have an increased risk of CRC (Torres et al. 2012).

Studies confirm that the severity of microscopic inflammation is an independent risk factor for developing advanced colorectal neoplasia among patients with long-standing UC (Rutter et al. 2004, Gupta et. al 2007). Although there is little doubt that chronic inflammation promotes colon cancer, the cellular and microbial mechanisms involved are not clear (Ullman et al. 2011). Colitis-associated cancers develop in chronically inflamed mucosa and are believed to develop in a sequence of no dysplasia–indefinite dysplasia–low-grade dysplasia–high-grade dysplasia–carcinoma (Ullman et al. 2011). Unlike sporadic CRC, which develops from dysplasia in one or two foci of the colon, cancer arising in colitic mucosa often develops from multifocal dysplasia.

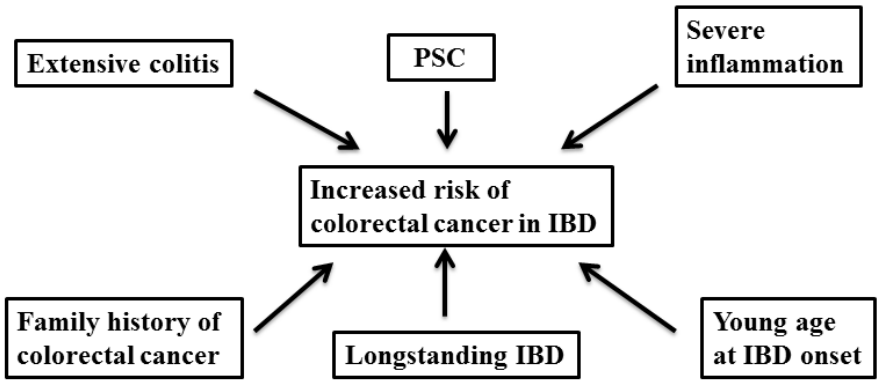

Figure 2. Risk factors for colorectal cancer in patients with IBD.

5.1.1.4 Chemoprevention of colorectal cancer in IBD

Earlier research has reported a chemopreventive effect of 5-aminosalicylic acid (5-ASA) drugs on colitis-associated CRC (Velayos et al. 2005) However, two more recent studies reported no effect of the use of 5-ASA on the risk of CRC (Terdiman et al. 2007, Bernstein et al. 2011). A recent Dutch study demonstrated thiopurine users to have a tenfold lower risk of developing either high-grade dysplasia or CRC (Van Schaik et al. 2011). The effect of 5-ASA therapy appeared to be less pronounced. In another Dutch study patients treated with thiopurines were less often diagnosed with CRC than those never treated (Baars et al, 2011). The recent reports from France and USA also suggest a decreased risk of CRC in patients taking thiopurines (Beaugerie et al. 2013, Rubin et al.2013).
Ursodeoxycholic acid UDCA therapy has previously been reported to reduce the relative risk for developing colorectal dysplasia or CRC to 0.26 (95% CI 0.06-0.92, P = 0.034) (Pardi et al. 2011). However, more recent studies have not found such an effect (Lindström et al. 2012). On the other hand, long-term use of high-dose UDCA (28–30 mg/kg/day) has been claimed to be associated with an increased risk of CRC in patients with UC and PSC (Eaton et al. 2011). In fact, after liver transplantation for PSC the risk of CRC is increased in UDCA (Jorgensen et al. 2012).

5.1.1.5 Surveillance of colorectal cancer in IBD

Because nearly all IBD-associated CRCs are believed to develop from dysplastic lesions, the current recommendation is to perform frequent colonoscopies to prevent carcinoma through early identification of precancerous lesions (Cairns 2010, Farraey 2011). The British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) updated the guidelines in 2010 (Cairns et al. 2010), and two other recent sets of guidelines are available; the American Gastroenterological Association (AGA) published US guidelines in 2010 and the European Crohn and Colitis Organisation the European guidelines in 2013 (Farraye et al. 2010, Annese et al. 2013). According to the present guidelines, patients with extensive colitis should have surveillance colonoscopies every 1–3 years, starting 7–10 years after onset of IBD, and UC patients with PSC yearly immediately after diagnosis (Table 11).

Table 11. Recent recommendations for colorectal cancer screenings in patients with inflammatory bowel disease [Edited version Manninen et al. 2013 (with permission P. Manninen)].

	AGA 2010 (Farraye et al.)	BSG 2010 (Cairns et al.)	ECCO 2013 (Annese et al. 2013)
First screening colonoscopy	8–10 years after onset of symptoms	8–10 years after onset of symptoms	8 years after onset of symptoms
Interval	1–3 years	Lower risk: 5 years Intermediate risk: 3 years Higher risk: 1 year	Low risk: 5 years Intermediate risk: 2-3 years High risk: 1 year
Crohn's disease	Same recommendation, if disease is involving at least one third of the length of the colon	Same recommendation	Same recommendation apart from those with Crohn's colitis involving only one segment of colorectum.
Extent of ulcerative colitis	Same recommendation for both left-sided and extensive colitis Proctitis and proctosigmoiditis excluded	Low risk recommendation for left-sided colitis Proctitis excluded	Same recommendation for both left-sided and extensive colitis Proctitis excluded

5.1.2 Anal cancer

Both fistula-associated anal adenocarcinoma and squamous cell carcinoma among patients with CD have been increasingly reported in the past 25 years (Iesalnieks et al. 2010, Frisch et al. 2000). Most reports consist of single cases or small series and both adenocarcinoma and squamous cell carcinoma (Iesalnieks et al. 2010). One study on 2,723 patients with CD (Frisch et al. 2000) found that the relative risk of anal squamous cell carcinoma was increased but this finding did not reach statistical significance. Most anal cancer patients have had long-standing perianal fistulae and present with perianal pain and clinical exacerbationof their CD. The majority of tumours are locally advanced mucin-producing adenocarcinomas. The outcome is poor following surgical treatment, especially if perirectal lymph nodes are involved (Iesalnieks et al. 2010). Anal squamous cell carcinoma is strongly associated with human papilloma virus infection (Egan et al. 2012).

5.1.3 Small bowel adenocarcinoma

Compared to general population CD markedly increases the risk of small intestine cancer (Table 10) (Canavan et al. 2006, Jess et al.2005, Kappelman et al. 2014). In earlier reports the risk was 15-66 times higher than in general population (Table10). In the most recent report from Denmark the risk was much lower than previously reported (Kappelman et al. 2014). However, it was still significantly increased (SIR 8.4, 95% CI: 4.3-14.7). The pathogenesis of small bowel adenocarcinoma (SBA) in CD is poorly defined. SBA is usually found in inflammatory areas, which suggests that the sequence inflammation–dysplasia–carcinoma is valid (Egan et al. 2014). In a recent report from France all small bowel adenocarcinomas detected were detected in patients with small bowel CD, within the inflamed area (Elriz et al. 2013).

5.2 Extra-intestinal cancer

A meta-analysis of population-based cohort studies demonstrated that patients with CD are at elevated risk of developing extra-intestinal cancers compared to UC patients, whose risk is similar to that of general population (Pedersen et al. 2010). Immunosuppressive therapy may, in a dose- and time dependent manner, facilitate the genesis of de novo malignancies, and, once the cancer has developed, accelerate tumor growth and metastasis (Beaugerie et al. 2012).

5.2.1 Lymphoproliferative disorders

The overall risk of lymphoma in IBD appears to be similar or slightly greater than in general population, whereas an increased risk of lymphoma has been observed among IBD patients taking thiopurines (Pedersen et al. 2010, Kandiel et al. 2005, Beaugerie et al. 2009a, Herrinton et al. 2011, Vos et al. 2011). Most of the cases of lymphomas observed in IBD patients treated with thiopurine have been associated with EBV (Ebstein Barr Virus) (Magro et al. 2014). Less than forty cases of hepatosplenic T Cell Lymphoma have been reported in IBD to date. The patients were all treated with thiopurines, either alone or in association with anti-TNF therapy (more that 50% of cases). The median duration of thiopurine exposure in these patients is around six years, patients are in most cases males (>90% of cases) with a young age (<35 years in >90% of cases). In a systematic review of registries and prospective observational studies of patients with rheumatoid arthritis, the pooled estimate for the risk of lymphoporiferative disease in patients exposed to anti-TNF therapy was not significantly increased (Magro et al. 2014). In the recent report from Denmark the risk of haematological malignancies was increased (Kappelman et al. 2013).

5.2.2 Skin cancers

Recent studies have shown an increased risk of NMSCs in IBD patients, and especially in those taking thiopurines (Long et al. 2010, Peyrin-Biroulet et al. 2011, Long et al. 2012, Singh et al. 2011). A study from the USA also demonstrated an increased incidence of melanoma (Long et al. 2012). Ongoing and past exposure to thiopurines significantly increases the risk of NMSC in patients with IBD (Peyrin-Biroulet et al. 2011). The risk of melanoma in patients taking thiopurines was not increased, whereas this risk was increased by the use of biologics (Long et al. 2012). However, in the most recent meta-analysis IBD was associated with an increased risk of melanoma independent of the use of biologic therapy (Singh et al. 2014). A recent nationwide study from Denmark demonstrated an increased risk of NMSC and also melanoma in both CD and UC (Kappelman et al. 2014).

5.2.3 Other extra-intestinal cancers

CD patients are moreover at increased risk of developing cancer of the upper gastrointestinal tract, lung or urinary bladder (Pedersen et al. 2010). A borderline significantly increased risk of cancer of the liver-biliary system has been observed, whereas no cancers have occurred with significantly reduced frequency in patients with CD. Patients with UC have a significantly increased risk of liver-biliary cancer and leaukemia, but a decreased risk of lung cancer (Pedersen et al. 2010).

6 Mortality

IBD can result in direct or indirect mortality. Most mortality data are from Europe and North America (Tables 12 and 13) and data from countries outside Europe and North America are scarce.

6.1 UC

6.1.1 All-cause mortality

Studies on overall mortality in UC are to some extent contradictory. Earlier population-based studies from Sweden (Ekbom et al. 1992, Stewenius et al, 1995, Person et al. 1999) and a study from Great Britain (Card et al. 2003) documented a slightly increased overall mortality for UC patients compared with general population, but most studies have reported no increased mortality risk (Table 12).

A meta-analysis of 10 population-based inception studies did not show increased allover mortality, SMR was 1.1 (95% CI: 0.9–1.2) (Jess et al. 2007c). A recent meta-analysis (Bewtra et al. 2013) of population-based studies and inception cohorts reported increased all-cause mortality in UC (SMR 1.16; 95% CI, 1.06–1.35). In line with this a recent nationwide Danish cohort study showed an increased overall mortality in UC (Hazard Ratio (HR) 1.25; 95% CI 1.22–1.28) (Jess et al. 2013a). Conversely recent population based studies from the Netherlands (Romberg-Camps et al. 2010) (SMR0.9; 95% CI 0.7-1.2), Finland (Manninen et al. 2012) (SMR 0.9; 95% CI 0.7-1.1) and Australia (Selinger et al. 2013) (SMR 0.8; 95% CI 0.7-1.0) did not reveal increased overall mortality in UC.

Jess et al. (2013a) showed that the overall risk of dying was high in the first year after UC diagnosis (HR, 2.43; 95% CI, 2.31–2.57) and then rapidly declined to a constant level around 1.1 after 2 years. Age at diagnosis has reportedly not affected SMR in earlier studies; however, in the Danish study mortality was higher among patients diagnosed at younger ages (Jess et al. 2013a). Patients diagnosed with UC in childhood or adolescence had a 2.15-fold higher relative mortality (95% CI, 1.67–2.76) than patients diagnosed with UC at age 60–79 years (Jess et al. 2013). In contrast to that, older age at diagnosis was associated with a significantly increased mortality risk (HR 9.4; 95% CI 3.2-77.3) in the Dutch study. The Danish study (Jess et al. 2013a) and the recent meta-analysis (Bewtra et al. 2013) showed a possible trend toward higher relative mortality in females.

The Danish study (Jess et al. 2013a) demonstrated that when comparing calendar periods of UC diagnosis, a gradual decrease in relative mortality was observed from patients diagnosed in 1982–1989 to patients diagnosed in 1990–1999 (HR, 0.96; 95% CI, 0.90 – 1.02) and in 2000–2010 (HR, 0.88; 95% CI, 0.82– 0.95). In contrast an Australian report did not reveal any difference in survival between patients diagnosed earlier (1971–1979) or later (1980–1992) (Selinger et al. 2013).

Table 12. Mortality in UC in selected studies.					
Author	Country	Year of publication	Period	Number of patients	SMR (95% CI)
Eason	New Zealand	1982	1969-1978	342	0.8 (0.4-1.1)
Ekbom	Sweden	1992	1965-1983	2,509	1.6 (1.4-1.5)
Probert	UK	1993	1972-1989	1,014	0.9 (0.8-1.1)
Stewenius	Sweden	1995	1958-1990	471	1.3 (1.0-1.5)
Person	Sweden	1996	1955-1990	1,547	1.4 (1.2-1.5)
Winther	Denmark	2003	1962-1997	1,160	1.1 (0.9-1.2-
Card	UK	2003	1987-	8301	1.4 (1.3-1.6)
Masala	Italy	2004	1978-2001	689	0.7 (0.6-0.9)
Jess	USA	2005	1940-2004	378	0.8 (0.6-1.0)
Hoie	EC-IBD study	2005	1991-2003	792	1.1 (0.9-1.4)
Hutfless	USA	2007	1992-2002	5238	1.0 (0.9-1.2)
Jess	Denmark	2007a	1962-2005	1575	1.1 (1.0-1.2)
Romberg-Camps	Netherlands	2010	1991-2005	630	0.9 (0.7-1.2)
Manninen	Finland	2012	1986-2007	1254	0.9 (0.7-1.1)
Jess	Denmark	2013a	1982-2010	36,080	1.2 (1.2-1.3), HR
Selinger	Australia	2013	1971-2010	401	0.8 (0.7-1.0)

6.1.2 Cause specific mortality

UC occurs more frequently in nonsmokers; therefore, smoking-related mortality, such as that from lung cancer (SMR: 0.3; 95% CI: 0.1–0.9; P= 0.04), is decreased (Jess et al. 2007).

A meta-analysis of earlier studies (Jess et al. 2007b) showed increased overall gastrointestinal disease mortality in UC, but after exclusion of direct disease-related deaths, statistical significance was not apparent (SMR: 1.7; 95% CI: 0.8–3.6). In recent reports from the Netherlands (Romberg-Camps et al. 2010) and Denmark (Jess et al. 2013a) increased mortality from gastrointestinal causes was shown (SMR 3.4, 95% CI: 1.4–7.0 in the Netherlands and HR 3.06; 95% CI 2.88–3.25 in Denmark). In a Finnish study (Manninen et al. 2012) SMR for gastrointestinal causes was increased only in males (SMR; 95% CI 2.77 1.13–5.77). In the research mortality directly related to UC has ranged from 11%–30% of all deaths in UC patients, mainly attributable to colorectal cancer and perioperative complications (Jess et al. 2007a, Romberg-Camps et al. 2010, Sellinger et al. 2013). In a recent Danish study (Jess et al. 2013a), about 40% of the gastrointestinal disease mortality was due UC and, after the exclusion of direct disease-related deaths, the HR remained elevated in UC (SMR 1.87; 95% CI 1.74-2.02). UC-related deaths occurred relatively early after diagnosis (Jess et al 2007a, Romberg-Camps et al. 2010, Jess et al. 2013a). Mortality from nonalcoholic liver diseases was also increased in the earlier meta-analysis (SMR 4.0; 95% CI: 2.5–6.5) (Jess et al. 2007a) and in a recent meta-analysis (SMR 2.26; 95% CI 1.14-4.49) (Bewtra et al. 2013). A Danish study (Jess et al.2013a) showed that mortality from gastrointestinal causes was significantly lower in the period 2000- 2010 than in 1982-1989.

Slightly increased mortality from respiratory disorders has also been reported in two meta-analyses (Jess et al. 2007b, Bewtra et al. 2013) and in a recent report from Denmark (Jess

et al. 2013a). This category not only included smoking-related diseases, but asthma and pneumonia as well.

An earlier meta-analysis (Jess et al. 2007b) showed that the overall malignancy mortality rate in UC was not increased, but SMR of CRC mortality was 1.9 (95% CI: 1.0–3.8). Risk of mortality for CRC was also elevated in the recent meta-analysis (SMR 2.82; 95% CI 1.68-4.74) (Bewtra et al. 2013). The nationwide Danish study (Jess et al. 2013a) reporteda slightly increased risk of overall malignancy mortality (HR 1.07; 95% CI 1.02-1.12) and (the) CRC mortality was also increased (HR1.58; 95% CI 1.45-1.74). These workers also showed that mortality from CRC was significantly lower in the period 2000- 2010 than in 1982-1989. An Australian study (Selinger et al. 2013) demonstrated that death from cholangiocarcinoma occurred nearly 15 times more often among patients with UC than in general population and CRC mortality was increased.

An increased risk of cardiovascular disease in IBD has been suggested and could be explained by mechanisms similar to those for the association between systemic inflammation and atherosclerosis (Jess et al. 2013a). The two meta-analyses did not show an increased overall mortality from cardiovascular disease in UC (Dorn et al. 2007, Bewtra et al. 2013). However, the Danish (Jess et al. 2013a) and Australian studies (Selinger et al. 2013) showed slightly increased mortality from cardiovascular disease.
The data on the risk of suicide in UC are contradictory (Jess et al. 2007a, Jess et al. 2013a) In the Danish study slightly increased mortality from suicide among patients with UC was observed (Jess et al. 2013a). However, a significant and reassuring relative reduction in mortality from suicide was observed over time. A Finnish population-based study showed reduced mortality from mental and alcohol-related behaevioral disorders when comparing IBD patients to general Finnish population (Manninen et al. 2012).

6.2 Mortality in CD

6.2.1 All-cause mortality

Overall mortality for patients with CD has reported in earlier studies to be increased (Table 13). Three meta-analyses have been published over the last seven years and have shown increased mortality in CD. Canavan et al. (2007) reported survival in population- or referral-based cohorts and SMR was 1.52 (95% CI 1.32–1.74). The second meta-analysis by Duricova et al. (2010) reported only population-based studies and SMR was 1.39 (95% CI: 1.30–1.49). The last meta-analysis (Bewtra et al. 2013) reported population based studies and inception cohorts and SMR was 1.38; (95% CI 1.23-1.55). The recent nationwide Danish cohort study also showed increased overall mortality in CD (HR 1.73 (95% CI 1.67-1.80) (Jess et al. 2013a). However, recent population based studies from the Netherlands (Romberg-Camps et al. 2010) (SMR1.1; 95% CI 0.7-1.6), Finland (Manninen et al. 2012) (SMR 1.1; 95% CI 0.8-1.5), Norway (Hovde et al. 2014) (SMR 1.3; 95% CI 0.9-1.9) and Australia (Selinger et al. 2013) (SMR 0.9; 95% CI 0.7-1.1) did not reveal increased overall mortality in CD.

Two earlier population-based studies found that SMR was increased in patients diagnosed with CD as teenagers (Wolters et al. 2006, Canavan et al. 2007) and Card et al (2007) reported that SMR in patients aged 20–39 had a higher SMR. Jess et al. (2013a) showed

that the overall mortality was markedly increased in the first year after CD diagnosis (HR 3.69; 95% CI, 3.41–3.99) and then rapidly declined to a level around 1.5 after 2 years. Relative mortality was 62% higher in patients diagnosed at age 0–19 years than in patients diagnosed with CD at age 60–79 years (HR, 1.62; 95% CI, 1.25–2.09) (Jess et al. 2013). In contrast to this Romberg et al. (2010) reported that age >40 years at diagnosis was associated with a significantly increased hazard ratio (HR 8.5; 95% CI: 2.2–32.4). The Danish study (Jess et al. 2013a) and two meta-analyses (Duricova et al. 2010, Bewtra et al. 2013) showed a trend toward higher relative mortality in females.

In contrast to UC, the Danish study (Jess et al. 2013a) demonstrated that mortality did not change at different time periods in CD. On this the Australian report revealed no difference in survival between CD patients diagnosed earlier (1971–1979) or later (1980–1992) (Selinger et al. 2013).

Table 13. Mortality in CD in selected studies.

Author	Country	Year of publication	Period	Number of patients	SMR (95% CI)
Probert	UK	1991	1972-1989	610	0.7 (0.5-1.1)
Ekbom	Sweden	1992	1965-1983	1469	1.6 (1.4-1.9)
Person	Sweden	1996	1955-1990	1251	1.5 (1.3-1.8)
Saro Gismera	Spain	1999	1954-1997	249	3.2 (0.4-11.0)
Jess	Denmark	2002	1962-1997	374	1.3 (1.0-1.6)
Card	UK	2003	1987-	5960	1.7 (1.5-1.9)
Masala	Italy	2004	1978-2001	231	1.5 (1.1-2.1)
Jess	USA	2006	1940-2004	314	1.2 (0.9-1.6)
Wolters	EC-IBD study	2006	1991-2004	380	1.8 (1.3-2.6)
Canavan	UK	2007	1934-1984	394	1.3 (1.1-1.5)
Hutfless	USA	2007	1996-2002	3241	1.4 (1.2-1.6)
Jess	Denmark	2007a	1962-2005	641	1.3 /1.1-1.6)
Romberg-Camps	Netherlands	2010	1991-2005	476	1.1 (0.7-1.6)
Manninen	Finland	2012	1986-2007	550	1.1 (0.8-1.5)
Jess	Denmark	2013a	1982-2010	15,361	1.7 (1.7-1.8), HR
Hovde	Norway	2013	1991-2002	237	1.3 (0.9-1.9), HR
Selinger	Australia	2013	1971-2010	373	0.9 (0.7-1.1)

6.2.2 Cause specific mortality

Smoking-related causes of death are a prominent feature in patients with CD. The meta-analysis by Duricova et al. demonstrated that lung cancer (SMR 2.72; 95% CI 1.35–5.45) and chronic obstructive pulmonary disease (SMR 2.55; 95% CI 1.19–5.47) are important causes of death a (Duricova et al. 2010). Arecent meta-analysis (Bewtra et al. 2013) revealed SMR 1.60 (95% CI 1.24-2.05) for pulmonary disease and in a Danish study (Jess et al. 2013) HR was 2.05 (95% CI 1.86-2.27). This category included non-smoking-related diseases such as asthma, pulmonary embolism, and pneumonia as well (Bewtra et al. 2013).

The overall cancer mortality was increased in a meta-analysis (Duricova et al. 2010), SMR was 1.50 (95% CI 1.18–1.92), and in the Danish report (Jess et al. 2013a),HR was 1.45 (95% CI 1.35–1.56). Two recent population-based studies from the Netherlands (Romberg-Clamps et al. 2010) and Norway showed no excess mortality from overall cancers. The two meta-analyses demonstrated a significantly increased risk of dying from CRC; in the earlier meta-analysis (Duricova et al.2010) SMR was 1.34 (95% CI: 0.54–3.33) and in the recent (Bewtra et al. 2013) SMR was 3.12 (95% CI 0.97-1.1). The nationwide study from Denmark showed also increased CRC mortality, HR was 2.26 (95% CI 1.97-2.60). Population based studies from Finland (Manninen et al. 2012), Norway (Hovde et al. 2014) and Australia (Selinger et al. 2013) did not demonstrate any increased CRC mortality among patients with CD.
Overall gastrointestinal disease mortality has increased significantly among patients with CD in most studies (Duricova et al. 2010, Jess et al. 2013a, Manninen et al. 2012, Romberg-Camps et al. 2010 and Selinger et al. 2013). A meta-analysis (Duricova et al. 2010) found SMR 6.76 (95% CI: 4.37–10.45). A population based study from Norway (Hovde et al. 2014) did not demonstrate increased mortality due to gastrointestinal causes. In a recent Danish study, about half of the gastrointestinal disease mortality in CD patients was due to CD and after the exclusion of direct disease-related deaths, theHR remained elevated in CD (HR 2.71; 95% CI 2.43-3.02 (Jess et al. 2013). In studies the number of deaths with a possible or certain relation to CD has ranged from 26%–50% of all deaths in CD patients (Duricova et al. 2010, Romberg-Camps et al. 2010, Selinger et al. 2013). CD-related deaths have occurred relatively early after diagnosis (Romberg-Camps et al. 2010, Jess et al. 2013). Increased mortality from nonalcoholic liver disease (SMR 2.82; 95% CI 1.52 5.21) was shown in the most recent meta-analysis (Bewtra et al. 2013).

Increased mortality from genitourinary tract disorders was observed in a meta-analysis (SMR 3.28; 95% CI 1.69–6.35) (Duricova et al. 2010) and in a Danish study (HR 1.60; 95% CI 1.21-2.09) (Jess et al. 2013a). Increased mortality from infections has been demonstrated in an earlier meta-analysis of older population-based cohort studies (SMR, 3.24; 95% CI, 0.99 –10.63) (Duricova et al. 2010), in a recent study from northern California (SMR, 4.1; 95% CI, 1.7– 8.5) (Hutfless et al. 2007) and in the recent Danish study (HR 3.23; 95% CI 2.64-3.94) (Jess et al. 2013a). Mortality from cardiovascular disease was not increased except in the Danish study and after ten years it was no longer significantly increased (Jess et al. 2013a).

AIMS OF THE STUDY

The general aims of the present study were to evaluate the overall burden of IBD, malignancies and mortality in Finland and to assess whether the degree of microscopic inflammation is a risk factor for developing advanced colorectal neoplasia in IBD.

More specifically the aims of the study were as follows:

1. To estimate the incidence of IBD in Finland between 2000 and 2007 by analysing the unique, comprehensive Finnish drug reimbursement database (I)
2. To estimate the nationwide prevalence of IBD, changes from 1993 to 2008 and further to test the North-South gradient of IBD in Finland by analy*zing the unique, comprehensive Finnish drug reimbursement database. In addition we had an opportunity to study the vitamin D levels in a health examination survey, the Health 2000 Survey conducted in Finland 2000-2001 to find out whether there is a geographical variation in vitamin D levels within the population of Finland (II).
3. To assess the long-term risks of malignant diseases among patients in Finland with IBD diagnosed 1987-1993 and 2000-2007 by using the comprehensive drug reimbursement database and the nationwide database of the Finnish Cancer Registry (III). Our specific aim was to assess the risk of CRC among patients with IBD and to study whether the degree of microscopic inflammation is a risk factor for developing dysplasia or CRC in IBD, and also to specify the risk for developing dysplasia in patients with no inflammation to better target surveillance in IBD in a retrospective case-control study (IV).
4. To assess overall and cause-specific mortality among patients in Finland with IBD diagnosed 1987-1993 and 2000-2007 by using the comprehensive drug reimbursement database and the national computerized Causes of Death Register maintained by Statistics Finland. In particular, we sought to determine the risk of cause-specific mortality related to CRC, gastrointestinal and cardiovascular diseases. (V).

PATIENTS AND METHODS

1 Study population

1.1 Incidence, prevalence, malignancy and mortality studies (Studies I, II, III and V)

In Finland all IBD patients, irrespective of the place of residence and the socioeconomic status of the family, are entitled to special refunds governed by the Social Insurance Institution of Finland (SII) to cover part of the medical costs and each Finnish resident has a unique personal identification code. SII processes drug reimbursements according to a written certificate describing the diagnostic criteria for IBD (ICD-10 code K50 or K51). These include endoscopy, histological verification, disease history and the type of medication started. As a rule, the diagnosis of IBD has to be assessed by a specialist in gastroenterology, internal medicine, paediatrics, digestive surgery or surgery. The certificates are checked by a medical examiner (physician) before SII grants the reimbursement.
Since 1986, the SII has recorded all decisions on entitlements to the special refunds paid to IBD patients in a nationwide register. In 1986-1993 CD and UC had separate reimbursement codes but in 1994-1999 CD and UC were recorded under the same reimbursement code, and the diagnosis codes of IBD subtypes were not registered. Since 2000, the ICD-10-codes K50 (CD) and K51 (UC) have been available to separately identify patients with CD and patients with UC (also including IBDU). Information on the date of approval for reimbursements, gender, date of birth and place of residence was obtained from the SII. The entire administrative process of certificate writing and decision-making by the SII generally takes only a couple of weeks. Therefore the date of the special refund decision was defined as the index date of diagnosis.

The population used in our incidence (Study I) and prevalence (Study II) as well as malignancy (Study III) and mortality (Study V) studies was based on the SII database, which includes information on all patients entitled to reimbursement for medication costs related to IBD.

The study population in the malignancy and mortality studies included 21,964 persons with IBD (16,649 with UC and 5,315 with CD) diagnosed during the periods 1987-1993 and 2000-2007 (Table 14).

1.2 The Vitamin D study (Study II)

Patients in the vitamin D study (II) were obtained from a comprehensive health survey, the Health 2000 Survey, conducted in Finland in 2000–2001. A stratified two-stage cluster sample (N=8,028) representative of the Finnish population aged 30 years or over was drawn from the population registry. Those aged 80 years or over were oversampled (2:1) relative to their proportion in the population. The study population of the present study consisted of the 6,134 participants for whom serum vitamin D status was available.

Table 14. Characteristics of the 21,964 persons with inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn´s disease (CD) from the registry of the Social Insurance Institution of Finland diagnosed in two periods between 1987-1993 and 2000-2007 diagnosed in two periods between 1987-1993 and 2000-2007.

		Men		Women		All	
	Age	N	Person years	N	Person years	N	Person years
CD	0-14	194	648	138	493	332	1,141
	15-29	818	5,824	884	5,786	1702	11,610
	30-44	768	8,631	672	8,819	1,440	17,450
	45-59	534	7,083	585	6,963	1,119	14,046
	60-74	265	3,219	291	3,557	556	6,776
	Over 75	55	695	111	1,299	166	1,994
	Total	2,634	26,100	2,681	26,917	5,315	53,017
UC	0-14	345	1,219	317	1,233	662	2,452
	15-29	2,364	14,497	2,220	13,273	4,584	27,770
	30-44	2,858	31,049	2,269	28,468	5,127	59,517
	45-59	2,102	30,637	1,447	22,669	3,549	53,306
	60-74	1,252	17,577	885	12,003	2,137	29,580
	Over 75	255	4,640	335	5,847	590	10,487
	Total	9,176	99,619	7,473	83,493	16,649	183,112
IBD	0-14	539	1,867	455	1,726	994	3,593
	15-29	3,182	20,321	3,104	19,059	6,286	39,380
	30-44	3,626	39,680	2,941	37,287	6,567	76,967
	45-59	2,636	37,720	2,032	29,632	4,668	67,352
	60-74	1,517	20,796	1,176	15,560	2,693	36,356
	Over 75	310	5,335	446	7,146	756	12,481
	Total	11,810	125,719	10,154	110,410	21,964	236,129

Age of person (N columns) columns refers to the age at the beginning of follow-up. Age in the person-years columns refers to the age attained at follow-up.

1.3 Histological inflammation as a risk factor for colorectal dysplasia or colorectal cancer (Study IV)

Patients for the study "Histological inflammation as a risk factor for colorectal dysplasia or CRC" (Study IV) were identified from the database of the Department of Pathology (QPATI) electronic database and the patient registry of HUCH for the period 1996-2008. First, all patients with UC or CD as a study indication were selected from QPATI, and all colonoscopy biopsy samples of these patients served as a raw database (31,231 pathology reports). Second, all patients with an IBD diagnosis (ICD-10; K50 or K51) from the Departments of Medicine and Surgery at the Meilahti, Jorvi, and Peijas Hospitals were selected (8,737 patients). These two files were combined to find colonoscopy samples (n=24,758) of patients treated at HUCH during this period. Samples with dysplasia or carcinoma in the histopathology report were then identified. Samples with adenoma or undefined for dysplasia were excluded. Three hundred and seven samples with epithelial dysplasia and 132 with CRC were found. In the next stage, we identified individual patients and excluded patients resident outside the HUCH catchment area. Finally, we recognized sample duplicates and identified the first sample of each patient with dysplasia or carcinoma as the index sample (n=183). All samples with severe dysplasia and most with mild dysplasia were confirmed by an independent pathologist, and most of them were also re-evaluated together with pathologists and clinicians.

2 Methods

2.1 Incidence and prevalence and studies (Studies I and II)

Prevalence and incidence rates were expressed per 100,000 persons. Population sizes for the calculation of rates were obtained from from Statistics Finland.
In the incidence study (Study I) all patients who between 1January 2000 and 31 December 2007 were for the first time in their lives granted the special refund for medication costs for CD or UC were retrieved from the SII register. We ensured that the decision to grant a special refund was in fact the first one; all certificates for these patients were checked back, starting from the year 1986. The mean annual incidence rates were calculated by dividing the number of newly diagnosed IBD patients over an eight-year period (2000–2007) by the population at risk (per 100,000 persons). The group at risk consisted of the mean total population in the whole of Finland during the years 2000–2007.

In Study II the prevalence rates were calculated by dividing the number of IBD patients at the end of the year by the population at risk (per 100,000 persons). The group at risk comprised the total population of Finland in 1993 (5.0 million) and 2008 (5.3 million). The prevalence rates for spatial geographical study were based on patietns' places of residence at IBD diagnosis.

2.2 Malignancy and mortality studies (Studies III and V)

In Study III the study cohort (Table 14) was linked with the nationwide Finnish Cancer Registry. The Finnish Cancer Registry includes >99% of incident cancer cases diagnosed in Finland since 1953 and has been shown to be a valuable source of information as the data are of good quality (Teppo et al. 1994, Korhonen et al. 2002)

In Study V the dates of death were taken from the national Population Register System. The causes of death were coded according to ICD-9 (1987-1995) and ICD-10 (1996+). The causes of death of those suffering from IBD, UC and CD (Table 14) were identified by collating the personal identity codes with the death certificate files held by Statistics Finland, which cover virtually all causes of death in our country. The causes of death were coded according to ICD-9 (1987-1995) and ICD-10 (1996+).

2.3 The vitamin D study (Study II)

S-25(OH)D concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN, USA). The intra-assay coefficient of variation (CV) was 3.5%, and the inter assay CV was 6.9% at the concentration of 36 nmol/l. The limit of detection was 3.8nmol/l. The serum specimens were stored frozen (at −70 °C) until analyszed, and protected from light when processed. For evaluation of the seasonal variation in S-25(OH)D, the period August–October represented autumn, and the period November–March, winter.

2.4 Histological inflammation as a risk factor for colorectal dysplasia or colorectal cancer (Study IV)

The study "Histological inflammation as a risk factor for colorectal dysplasia or CRC" (Study IV) was a case-control study. The control group was collected from the registry of patients with IBD (IBD registry) of the Meilahti Hospital. The controls were matched for IBD diagnosis (K50 or K51), gender, age at time of diagnosis (grouped for both CU and CD consistent with the Montreal classification for CD; <17, 17-40, >40 years), and disease extent: E1, E2 and E3 for UC; L1, L2 and L3 for CD according to the Montreal classification (28). Any colon resection, except ileo-coecal resection in CD, and histological dysplasia served as exclusion criteria for controls. We assigned two controls for each index patient with dysplasia or CRC (N=370). Among the controls we had five equally matched controls for each CRC patient. The following clinical parameters were collected from the hospital electronic database: gender, year of birth, year of IBD diagnosis, concomitant PSC, date of dysplasia for index patients and date of latest colonoscopy for control patients, histological activity of IBD at that examination, and medication used prior to that date. Histological activity of IBD of index patients reported at the corresponding endoscopy or operative sample was graded according to the previous classification reported by Gupta et al. (2007): 0 = no activity, 1 = mild to moderate activity and 2 = severe activity. The sample at the latest colonoscopy examination of the control patients served as the control. From the demographic data, age at IBD diagnosis, disease duration, and age at time of sample were compiled for both index patients and controls. Use of 5-aminosalicylic acid (5-ASA) or thiopurines for IBD and ursodeoxycholic acid (UDCA) for PSC was recorded, and any missing data were collected from patients' hospital files.

3 Statistics

3.1 Incidence and prevalence and studies (Studies I and II)

The 95% confidence intervals (95% CI) for the incidence rates were calculated assuming a Poisson distribution. Poisson regression models were used to adjust the rates for gender or age (categorized as 0–6, 7–14, 15–24, 25–34, 35–44, 45–54, 55–64, and >64years). The statistical significance of the relationships of incident cases based on gender or 2-year periods was quantified by calculating the incidence rate ratio (IRR) with 95% CI. Statistical computation was performed using Stata v. 10.1 (StataCorp, College Station, TX).

The 95% confidence intervals (95% CI) for the prevalence rates were calculated assuming a Poisson distribution. The areal comparisons were made between the five University Hospital districts in Finland and between three geographical regions: Southern Finland (Helsinki and Turku University Hospital districts), Central Finland (Tampere and Kuopio) and Northern Finland (Oulu) in prevalence rates, and the linear trends over three geographical regions were tested by Poisson regression models (adjusted for gender and age groups). A Poisson regression model was also used to quantify the statistical significance between annual (2008 vs. 1993) prevalence of IBD by calculating the prevalence rate ratio (PRR) with a 95% CI (adjusted for gender and age groups). Statistical computation was performed using Stata v. 10.1 (StataCorp, College Station, TX).

3.2 Malignancy and mortality studies (Studies III and V)

Follow-up for cancer started on the date of the diagnosis of IBD and ended at death or on 31 December 2010. The numbers of observed cases and person-years at risk among the IBD patients were calculated separately for two follow-up periods (< 3 years and ≥ 3 years after the diagnosis of IBD), by gender and 5-year age groups. Analyses were performed separately for CD and UC. The expected numbers of cases for total cancer and for specific cancer sites were calculated by multiplying the person-years of follow-up by the incidence rate of each malignant disease in the respective sex, age and calendar period in the Finnish population. To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. The 95% confidence intervals (CIs) were based on the assumption that the number of observed cases followed a Poisson distribution. *P* values <0.05 were considered statistically significant.

For mortality analysis, the number of person-years followed up was calculated starting at the date of the diagnosis of IBD and ending at death or on 31 December 2010. The numbers of observed deaths and person-years at risk were counted by gender, calendar period (1987-1992, 1993-1998, 1999-2004, 2005-2010) and 5-year age group separately for three follow-up periods (<3 years after the diagnosis of IBD, 3-9.99 years after the diagnosis of IBD, ≥10 years after the diagnosis of IBD. The numbers of observed deaths and person-years at risk for all-cause mortality were also counted yearly after the diagnosis of IBD. Analyses were also performed separately for CD and UC. All-cause mortality was also compared between the two cohorts 1987–1993 and 2000–2007 during the first three years after the IBD diagnosis was set. The expected number of deaths was calculated by multiplying the sex-, age- and calendar period-specific numbers of person-years by the

respective mortality rates in the Finnish population obtained from Statistics Finland. SMR was calculated as the ratio of observed to expected number of deaths, for all-cause mortality and the 53 specific cause-of-death categories included in the selection of categories of the longitudinal time series of Statistics Finland. The reference mortality rates were obtained from Statistics Finland. The corresponding 95% confidence intervals (CIs) were defined assuming a Poisson distribution of the observed number of deaths. *P* values <0.05 were considered statistically significant.

3.3 The vitamin D study (Study II)

Regional trends in levels ofvitamin D were tested by general linear models [adjusted for age and seasons of blood sampling (September–October, November–December or January–February)]. Statistical analyses were performed using the SAS system for Windows (version 9.2 SAS Institute Inc., Cary, NC, USA)

3.4 Histological inflammation as a risk factor for colorectal dysplasia or colorectal cancer (Study IV)

In the study "Histological inflammation as a risk factor for colorectal dysplasia or CRC" (Study IV) results are presented as mean (SD) or median (range) or numbers of patients and percentages. The data were analysed using SPSS v 20.0 (IBM Corporation, Somers, NY) or Logexact v 5.0 (Cytel Software Corporation, Cambridge, MA) software. Pearson's exact chi-square test was used to compare categorical data between the groups. The nonparametric Mann-Whitney test was used to compare continuous data between the groups. Multivariate stratified logistic regression was used toidentify factors affecting the risk of histological dysplasia or CRC. Risk factors between cases and controls with univariate $P < 0.1$ were included in the logistic regression models in addition to PSC. Odds ratios (ORs) were presented with 95% confidence intervals (CIs). Interaction terms were considered, but they were not significant. McNemar-Bowker test was used to compare ordered categorical data in related samples. Jonckheere-Terpstra test was used to ascertain significant trends between continuous and ordered categorical variables. Statistical significance was set at $P < 0.05$. Bonferroni correction was used in multiple comparisons by adjusting local significance level by the number of comparisons performed.

4 Ethical considerations

The IBD study protocol was approved by the Ethics Committee of the Hospital District of South Ostrobothnia. No informed consent was required in accordance with Finnish regulations for registry-based studies involving no contact with the study subjects. The Health 2000 Survey study was approved by the Ethics Committee for Epidemiology and Public Health in the hospital district of Helsinki and Uusimaa, Finland.

RESULTS

1 Incidence

During the period 1988-2008 the number of IBD patients increased from 5,686 to 31,703. Between 1 January 2000 and 31 December 2007 14,214 IBD patients (7,600 males and 6,614 females) were diagnosed and 73% of them had UC. 83% of the patients with newly diagnosed IBD were of working age (16–64 years) and 6% were children.

In the period 2000-2007 the nationwide mean annual incidence of IBD was 34.0 (95% CI 33.4–34.6) per 100,000, the incidence of UC was 24.8 (95% CI 24.5–25.2) and that of CD was 9.2 (95% CI 8.9–9.5). UC was more common in males than in females (incidence 27.8; 95% CI 27.1–28.5 among males and 21.9; 95% CI 21.2–22.5 in females). In CD there were no gender difference (incidence 9.4; 95% CI 9.0-9.8) among males and 9.1; 95% CI 8.7-9.5 in females).

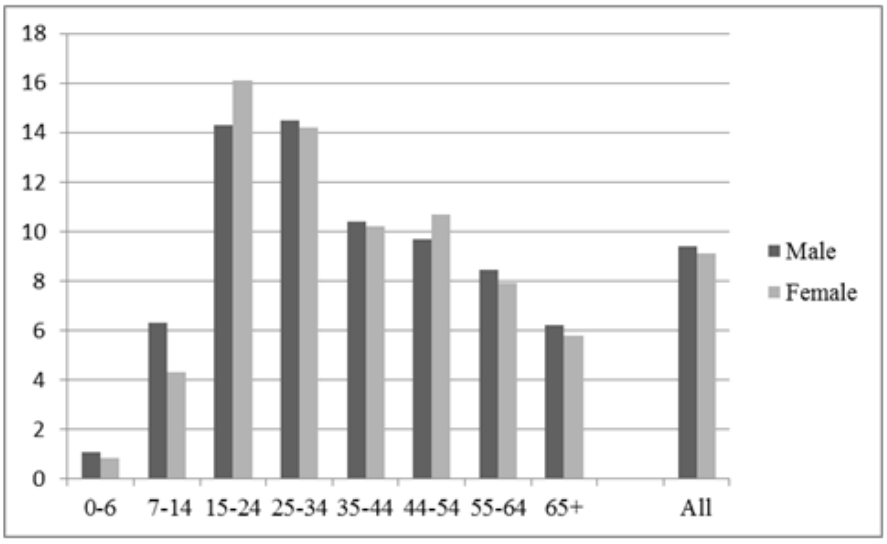

Figure 3. Annual incidence of CD by age group 2000–2007 in Finland per 100,000.

The peak incidence of CD was seen in females aged 21 years (22.6 per 100,000), and in males aged 17 years (18.4) (Figure 3) and in UC the highest annual incidence was seen in females aged 25 years (53.0) and in males aged 27 years (48.7) (Figure 4). The incidence rate of UC was significantly higher in males than in females in persons aged 35 years and older, with a gender IRR of 1.39 (1.20–1.61), $p < 0.001$, after adjusting for age (Figure 4). In CD there were no significant differences between genders in any age group (Figure 3).

The incidence of UC increased from 22.1 (95% CI: 21.2–23.0) in 2000–2001 to 27.4 (95% CI: 26.4–28.4) in 2006–2007 while the incidence of CD increased only slightly, from 8.7 (95% CI: 8.12–9.26) to 9.4 (95% CI: 8.78–9.95) (Figure 5).

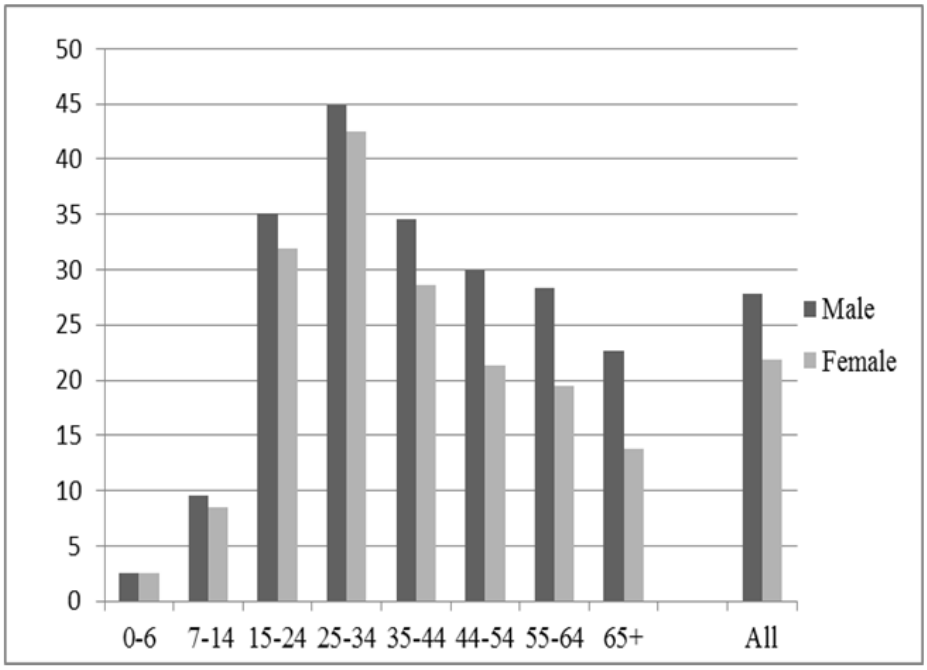

Figure 4. Annual incidence of UC by age group 2000–2007 in Finland per 100,000.

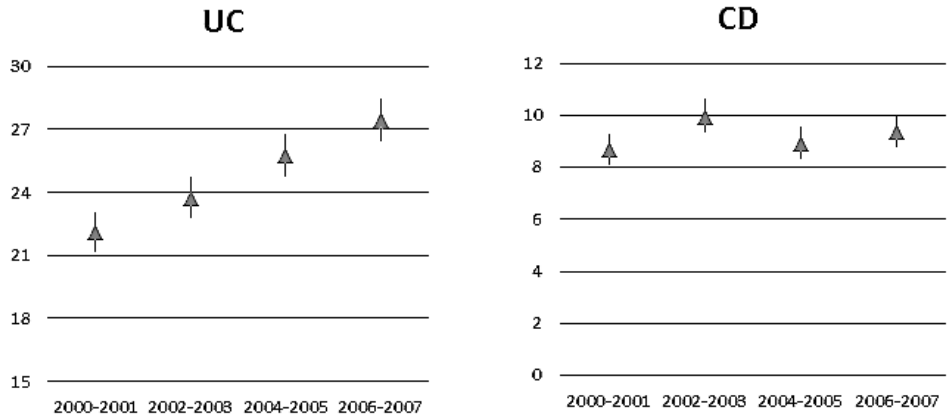

Figure 5. Age-adjusted incidence with 95% CI of UC and CD (per 100,000) in 2-year periods 2000–2007 in Finland.

2 Prevalence

The prevalence of IBD in Finland increased fivefold from 1988 to 2008 (Jussila et al. unpublished data) and nearly threefold from 1993 to 2008 (Table 14). In December 1988 the nationwide point prevalence of IBD was 115 per 100,000 inhabitants, in December 1993 it was 216 and in December 2008 it was 595 (Table 15). The prevalence rate for UC (177) was fourfold higher than the prevalence rate for CD (38) in 1993.

Table 15. The crude prevalence of IBD (as absolute numbers and as rates per 100.000 persons) in Finland in 1988, 1993 and 2008.

Year		**All**	**Prevalence rate (95% CI)**	**Male**	**Prevalence rate (95% CI)**	**Female**	**Prevalence rate (95% CI)**
		N		N		N	
1988[1]	IBD	5.686	115	3135	131	2551	100
1993	CD	1,945	38 (37-40)	956	39 (36-41)	989	38 (36-40)
1993	UC	9,013	177 (174-181)	4,982	202 (196-207)	4,031	155 (150-159)
1993	IBD	10,958	216 (212-220)	5,938	240 (234-247)	5,020	192 (187-198)
2008	IBD	31,703	595 (589-602)	16,680	639 (629-648)	15,023	553 (545-562)

[1]Jussila et al. Unpublished data

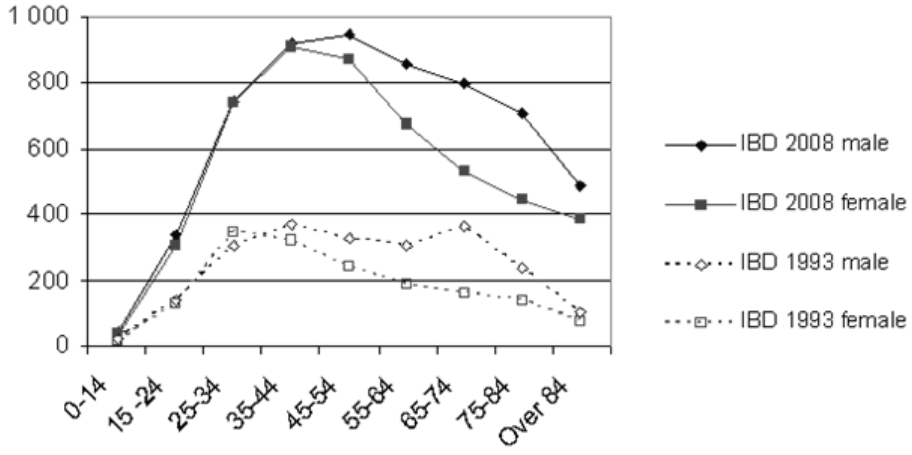

Figure 6. Age-specific prevalences of IBD in 1993 and 2008 calculated per 100,000 persons in Finland.

The highest prevalence rate of IBD, 914 in both genders, was seen in 2008 in patients aged 35–44, after which the prevalence decreased with age in both genders (Figure 6). The IBD prevalence in 1993 and in 2008 and the prevalence of UC in 1993 were notably higher in

males than in females (Table 15), especially in the age group over 44 years (Figure 6). In CD there was no gender difference.

2.1 The North-South gradient of prevalence

The prevalence rates of IBD in Finland varied in three geographical regions (Table 16). In both 1993 and 2008 the prevalence of IBD increased from South to North. In 2008 the highest prevalence was seen in North Finland (702) and the lowest in South Finland (561). In the prevalence of IBD and UC, a statistically highly significant increasing linear trend ($p<0.001$) from South to North was seen (Table 16) but in CD there was no significant North-South difference.

Table 16. Prevalence rates of IBD in three geographical regions in Finland in 1993 and 2008.

	CD 1993	UC 1993	IBD 1993	IBD 2008
	Prevalence rate (95% CI)	Prevalence rate (95% CI)	Prevalence rate (95% CI)	Prevalence rate (95% CI)
Southern Finland	39 (36-41)	154 (149-159)	193 (187-199)	561 (552-571)
Central Finland	37 (35-40)	187 (182-193)	219 (208-230)	594 (584-605)
Northern Finland	38 (34-43)	225 (218-231)	257 (246-269)	702 (683-721)
P for value[1] linear trend	0.631	< 0,001	< 0,001	< 0,001
[1]adjusted for gender and age groups				

3 Serum vitamin D levels

Serum vitamin D levels in both genders were higher in Southern (46 nmol/L) than Northern Finland (44 nmol/L) in the Health 2000 Survey and a statistically significant linear trend ($p< 0.05$) in vitamin D levels over three regions was observed.

4 Malignancies and mortality in IBD

Overall, 21,964 patients with IBD were followed up for 236,129 person-years. The mean follow-up was 11.0 years in UC and 10.0 in CD.

4.1 Malignancies

A total of 1,316 cancers were identified while the expected number was 1,185. In addition there were 345 cases of basal cell carcinoma of the skin that were not included in the total number of cancers. The cancer risk was increased among UC patients (SIR 1.08; 1.02-1.14) and among CD patients (SIR 1.28; 95% CI 1.08-1.50) and especially so in males (Tables 17 and 18) and in young patients (SIR 2.21; 95% CI 1.40-3.31 in UC in ages 15-29 and SIR 1.91; 95% CI 1.35-1.2.63 in CD in ages 30-44).

Table 17. Observed (Obs) numbers of intestinal and most common extra-intestinal malignancies and standardized incidence ratios (SIR) among patients with ulcerative colitis during the follow-up period.

Site (ICD 10)	*Male*			*Female*			*All*		
	Obs	*SIR*	*95% CI*	*Obs*	*SIR*	*95% CI*	*Obs*	*SIR*	*95% CI*
All cancers[a]	642	1.11[c]	1.02-1.19	404	1.05	0.95-1.15	1,046	1.08[c]	1.02-1.14
Colon C18	53	1.73[d]	1.30-2.26	42	1.92[d]	1.38-2.59	95	1.81[d]	1.46-2.21
Rectum (C19-21)	39	1.65[d]	1.18-2.26	24	1.96[c]	1.26-2.91	63	1.76[e]	1.35-2.25
Biliary tract (C22.1,C23, C24)[b]	14	8.81[e]	4.82-14.8	5	4.86[d]	1.58-11.3	19	7.26[e]	4.37-11.1
Lung, trachea (C33-34)	58	0.74[c]	0.56-0.95	18	1.01	0.60-1.59	76	0.79[c]	0.62-0.98
Hodgkin lymphoma (C81)	8	2.45[c]	1.06-4.81	2	1.04	0.13-3.74	10	1.92	0.92-3.53
Non-Hodgkin lymphoma (C82-85, C96)	33	1.40	0.96-1.96	15	1.03	0.57-1.69	48	1.26	0.93-1.66
Prostate (C61)	150	0.85[c]	0.72-0.99						
Thyroid (C73)	10	2.47[c]	1.18-4.54	18	1.73[c]	1.02-2.72	28	1.93[d]	1.28-2.79
Skin, basal cell carcinoma	148	1.20[c]	1.02-1.40	116	1.22[c]	1.01-1.45	264	1.21[d]	1.07-1.36

[a] Skin, basal cell carcinoma (345 cases) not included, [b]Histologically confirmed diagnosis, [c]p<0.05, [d]p<0.01, [e]p<0.00.

Table 18. Observed (Obs) numbers of intestinal and most common extra-intestinal malignancies and standardized incidence ratios (SIR) among patients with Crohn´s disease during the follow-up period.

Site (ICD 10)	*Male*			*Female*			*All*		
	Obs	*SIR*	*95% CI*	*Obs*	*SIR*	*95% CI*	*Obs*	*SIR*	*95% CI*
All cancers[a]	140	1.28[d]	1.08-1.50	130	1.18	0.99-1.39	270	1.23[d]	1.09-1.38
Small intestine (C17)	3	6.83[c]	1.41-19.9	5	13.8[e]	4.46-32.1	8	9.97[e]	4.30-19.6
Colon (C18)	10	1.75	0.84-3.20	8	1.36	0.59-2.67	18	1.55	0.92-2.44
Rectum (C19-21)	8	1.81	0.78-3.56	6	1.79	0.66-3.90	14	1.80	0.99-3.02
Gastric (C16)	4	1.17	0.32-2.99	7	2.80[d]	1.13-5.57	11	1.86	0.93-3.32
Biliary tract (C22.1, C23, C24)[b]	1	3.15	0.08-17.6	2	6.86	0.83-24.8	3	4.93[c]	1.02-14.4
Lung, trachea (C33-34)	13	0.97	0.52-1.65	8	1.60	0.69-3.14	21	1.14	0.71-1.74
Kidney (C64-65)	9	2.24[c]	1.02-4.24	2	0.71	0.09-2.55	11	1.61	0.80-2.87
Myeloma (C90)	5	3.84[c]	1.25-8.95	2	1.72	0.21-6.22	7	2.84[c]	1.14-5.85
Non Hodgkin lymphoma (C82-85, C96)	10	2.09[c]	1.00-3.48	3	0.73	0.15-2.12	13	1.46	0.78-2.49
Melanoma (C43)	10	2.33[c]	1.12-4.28	3	0.74	0.15-2.15	13	1.55	0.83-2.65
Skin, basal cell carcinoma	39	1.68[d]	1.19-2.29	42	1.60[d]	1.15-2.15	81	1.63[e]	1.30-2.03

[a] Skin, basal cell carcinoma (345 cases) not included, [b]Histologically confirmed diagnosis, [c]p<0.05, [d]p<0.01, [e]p<0.00.

4.1.1 Colorectal cancer and dysplasia

An increased rate of both colon cancers (SIR 1.73; 95% CI 1.30-2.26 in males and SIR 1.92; 95% CI 1.38-2.59 in females) and rectal cancers (SIR 1.65; 95% CI 1.18-2.26 among males and SIR 1.96; 95% CI 1.26-2.91 among females) was found in both genders in UC (Table 17). In contrast to UC, neither the risk of colon nor of rectal cancer was increased among CD patients (Table 18).
The risk of CRC was highest among the youngest UC patients. In total, 52% (82/158) of CRCs were diagnosed in patients under 60 years old and 20% (32/158) in patients under 45 years old. The risk of colon cancer was most significantly increased in ages 30-44 (SIR 10.1; 95% CI 5.21-17.6 in males and SIR 6.21; 95% CI 2.68-12.2 in females; $p<0.001$) and the risk of rectal cancer in ages 44 (SIR 4.97; 95% CI 2.00-10.2) and in ages 45-59 (SIR 3.19; 95% CI 2.08-4.66). Although there was no excess CRC in CD, the risk of rectal cancer was increased in ages 30-44 in both genders (SIR 21.7; 95% CI 5.93-55.7 in males and 13.5 95% CI 2.78-39.5 in females) and of colon cancer in males in ages 30-44 (SIR 9.25 95% CI 1.91-27.0).

4.1.1.1 Risk factors for advanced colorectal neoplasia in IBD

By combining the hospital patient registry and the pathology database of HUCH between 1996 and 2008, 183 IBD patients with dysplasia or CRC were identified. Of these 152 were epithelial dysplasia (144 had UC and 8 CD) and 31 were CRC (24 had UC and 7 CD). Detailed characteristics of patients and controls are presented in Table 19. Most dysplasias (51.1%) were detected within the first ten years after diagnosis. Severe dysplasia was detected in eleven patients, all with UC. In CRC the disease duration was longer (15.7 vs. 10.4 years; $P = 0.010$) and their mean age at the time of sampling was higher than that of the controls (52.9 vs. 45.6 years; $P = 0.032$). High inflammatory activity in the histological analysis was detected in 41.4% of the dysplasia patients and in 24.1% of the CRC patients, but in only 4.3% of the controls (Table 20). The risk of dysplasia and CRC was strongly associated with the degree of inflammation and disease duration, showing an additive effect in the risk of CRC. Patients with a high inflammation grade had an OR 31.8 (95% CI 15.6-64.9, $P < 0.001$) for dysplasia or carcinoma relative to patients with no inflammation (Table 21).
Moreover, patients with mild to moderate inflammation had an OR of 2.6 (95% CI 1.6-4.1, $P = 0.0001$). However, there was no inflammation activity in 19.0% of the dysplasias and in 48.3% of the CRC patients (Table 20). Disease duration increased the annual risk of dysplasia or CRC by 4.5%, but unexpectedly co-existing PSC did not add to the risk (OR = 0.92, 95% CI 0.51-1.67). Use of thiopurines protected against the development of dysplasia or CRC (OR = 0.31, 95% CI 0.19-0.51, $P <0.0001$) (Table 21).

Table 19. Clinical characteristics of colorectal cancer and dysplasia patients and controls.

		Dysplasia (n=152)		Cancer (n=31)		Controls (n=370)		P [1]
Gender	F	60	39.5%	9	29.0%	143	38.6%	
	M	92	60.5%	22	71.0%	227	61.4%	0.853
UC		144		24		338		
	E1	0	0.0%	1	4.2%	2	0.6%	
	E2	13	9.0%	3	12.5%	28	8.3%	
	E3	131	91.0%	20	83.3%	308	91.1%	0.883
CD		8		7		32		
	A1	1	14.3%	0	0.0%	2	6.3%	
	A2	3	42.9%	2	28.6%	12	37.5%	
	A3	3	42.9%	5	71.4%	18	56.3%	0.956
	L1	0	0.0%	2	28.6%	8	25.0%	
	L2	3	37.5%	4	57.1%	7	21.9%	
	L3	5	62.5%	1	14.3%	17	53.1%	0.219
	B1	3	42.9%	2	28.6%	7	21.9%	
	B2	2	28.6%	3	42.9%	14	43.8%	
	B3	2	28.6%	2	28.6%	9	28.1%	0.654
	Perianal	3	37.5%	3	42.9%	4	12.9%	0.047
	Upper GI	0	0.0%	0	0.0%	4	12.5%	0.298
5-ASA[2]		145	97.3%	25	83.3%	363	98.1%	0.056
Thiopurines[2]		51	34.5%	4	13.3%	197	53.2%	<0.001
PSC		28	18.4%	1	3.2%	60	16.2%	1.0

Table 20. Inflammation grades in controls and patients with epithelial dysplasia or colorectal carcinoma (CRC). [The distribution of inflammation between the groups differed significantly (P < 0.001). For post-hoc comparisons, local significance level was reduced to P = 0.025.]

	No activity	Mild to moderate activity	High activity	P (vs. all controls)
Controls (n=370)	195 52.7%	159 43.0%	16 4.3%	
Dysplasia (n=147)	28 19.0%	58 39.5%	61 41.5%	P< 0.001
CRC (n=29)	14 48.3%	8 7.6%	7 24.1%	P< 0.001

Table 21. Odds ratios for clinical variables for epithelial dysplasia and carcinoma.

	Odds ratio for epithelial dysplasia and carcinoma		Odds ratio for carcinoma	
		P		P
	Odds Ratio	2*1-Sided	Odds Ratio	2*1-Sided
Mild to moderate inflammation activity vs. No inflammation	2.6	0.0001	0.89	0.839
High inflammation activity vs. No inflammation	31.8	< 0.0001	8.48	0.018
Disease duration per year	1.045	0.0003	1.12	0.0013
PSC	0.92	0.786	0.11	0.0617
Use of 5-ASA	0.46	0.215	0.17	0.051
Use of thiopurines	0.31	< 0.0001	0.085	0.0003

4.1.2 Non-colorectal intestinal cancer

CD patients had a 10-fold increased risk of small bowel cancer (SIR 6.83; 95% CI 1.41-19.9 for male and 13.7; 95% CI 4.46-32.1 for female) (Table 18). The incidence of anal cancer was increased among males in CD (SIR 24.6; 95% CI 5.07-71.9).

4.1.3 Extra-intestinal cancer

The risk of histologically confirmed biliary tract cancer was significantly increased among patients with UC (SIR 7.26; 95% CI 4.37-11.13) and was higher in males than in females (SIR 8.81, 95% CI 4.82-14.8 in males and 4.86; 95% CI 1.58-11.3 in females). In CD the risk of histologically confirmed biliary tract cancer was also slightly increased (SIR 4.93; 95% CI 1.02-14.4).
A slightly increased risk of Hodgkin lymphomas was observed among male UC patients (SIR 2.45; 95% CI 1.06-4.81) (Table 17) and the incidence of non-Hodgkin lymphomas (SIR 2.09; 95% CI 1.00-3.48) and myeloma (SIR 3.84: 95% CI 1.25-8.95) was slightly increased among males with CD (Table 18).

The number of thyroid cancers was increased in both genders (SIR 2.47; 95% CI 1.18-4.54 in males and 1.73; 95% CI 95% CI 1.02-2.72 in females) among patients with UC (Table 16). The risk of gastric cancer was slightly elevated among female CD patients (SIR 4.93; 95% CI 1.02-14.4) and kidney cancer (SIR 2.24; 95% CI 1.02-4.24) among males with CD (Table 18).

The risk of basal cell carcinoma of the skin was elevated in both genders among patients with CD (Table 18) and also slightly elevated in both genders among patients with UC (Table 17). Excess of basal cell carcinoma of the skin was seen most pronounced in ages 30-44 over three years after the diagnosis of IBD (SIR 3.12; 95% CI 1.64-5.54 in males and SIR 2.07; 95% CI 1.04- 3.71 in females) among patients with UC and among males with CD (SIR 3.84; 95% CI 1.05-9.83). Among females with CD the risk was most prominent at ages 45-59 (SIR 2.90; 95% CI 1.59- 4.86). Male CD patients had also a slightly increased risk of melanoma (SIR 2.33 95% CI 1.12-4.28). A reduced frequency of lung and tracheal cancer and prostate cancer was observed among male UC patients (Table 17).

4.2 Mortality

The observed number of deaths among patients with IBD was 2,244 whereas 1,966 deaths were expected (SMR 1.14; 95% CI 1.09-1.18). Overall mortality was slightly increased both among patients with CD (SMR 1.33, 95% confidence interval 1.21-1.46) and UC (SMR 1.10, 95% CI 1.05-1.15). The SMR for overall mortality remained constantly above 1.0. In CD the SMR for overall mortality was significantly elevated in both genders in patients diagnosed 1987-1993 (SMR 1.68; 95% CI 1.05-2.53 in males and 2.04; 95% CI 1.21-3.22 in females) and only slightly elevated in those diagnosed 2000-2007 (SMR 1.32; 95% CI 1.06-1.63).

4.2.1 Cause-specific mortality

The most common causes of death were cardiovascular diseases (42% in UC and 32% in CD) and malignancies (23% in UC and 24% in CD).

Overall gastrointestinal disease mortality was increased in UC (SMR 2.81; 95% CI 2.32-3.33) and significantly increased in CD (SMR 6.53; 95% CI 4.91-8.52) (Table 22). The gastrointestinal disease mortality remained markedly elevated in CD (SMR 2.68; 95% CI 1.68-4.06 and slightly elevated in UC (SMR 1.42; 95% CI 1.08-1.83) after exclusion of directly disease-related deaths (Table 22). However, in UC it was elevated only among males (SMR 1.54; 95% CI 1.07-2.14 in males, SMR 1.27; 95% CI 0.80-1.90 among females). In total, 50% of gastrointestinal mortality was directly disease-related in UC and 45% of direct disease-related deaths occurred within the first three years after IBD diagnosis. Respectively 59% of the gastrointestinal mortality was directly related to CD and 50% of direct disease-related deaths occurred within the first three years after IBD diagnosis. Among patients with UC the SMR for primary sclerosing cholangitis (PSC) was significantly increased (Table 22).

Overall cancer-specific mortality was slightly increased in CD (SMR 1.32; 95% CI 1.08-1.58) (Table 22), especially in males (SMR 1.36; 95% CI 1.04-1.76 among males) but not in UC. In UC the risk of mortality for colon (SMR 1.90; 95% CI 1.38-2.55) and rectal cancer (SMR 1.79; 95% CI 1.14-2.69), and especially for intrahepatic biliary tract cancer (SMR 5.65; 95% CI 3.54-8.54) was increased (Table 22). In CD mortality ofdue to intrahepatic biliary tract cancer (SMR 4.51; 95% CI 1.23-11.54) and malignant neoplasm of lymphoid and hemaetopoietic tissue (SMR 2.95; 95% CI 1.85-4.45) was increased (Table 22).

An excess of deaths due to cardiovascular disease was observed in UC (SMR 1.14; 95% CI 1.06-1.22) (Table 22) and also among female patients with CD (SMR 1.35; 95% CI 1.06-1.69 in females), mainly due to mortality from ischaemic heart disease (IHD). In UC both SMR for whole cardiovascular disease and IHD remained elevated for ten years after UC diagnosis (Table 23). In CD excess mortality from pulmonary embolism was observed among females (SMR 5.29; 95% CI 1.55-14.57). Significantly elevated SMR 2.01 (95% CI 1.39-2.80) for pulmonary disease was seen in CD and a slightly elevated SMR of 1.24 (95% CI 1-02-1.45) also in UC. Mortality from infectious diseases was increased (SMR 4.27; 95% CI 2.13-7.63) in CD and remained elevated for ten years after CD diagnosis (Table 23). In UC the risk of dying of infectious diseases was increased in the first three years after UC diagnosis (Table 23).

Reduced mortality from alcohol related deaths was observed in UC among males (SMR 0.52; 95% CI 0.37-0.72). The mortality from accidents and violence excluding accidental alcohol poisoning was also decreased among males with UC (SMR 0.82; 95% CI 0.66-0.98).

Table 22. Most common causes of death observed (Obs) numbers of deaths and standardized mortality ratios (SMR) with 95% confidence intervals (CI) among patients with ulcerative colitis (UC) and Crohn´s disease (CD) during the whole of the follow-up time.

Cause of death	*UC*			*CD*		
	Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	1805	1.10 [b]	1.05-1.15	439	1.33 [c]	1.21-1.46
All diseases	1667	1.13[C]	1.08-1.18	398	1.37[c]	1.24-1.51
Infections A00-B99	16	1.28	0.73-2.08	11	4.27 [c]	2.13-7.63
Malign neoplasm C00-C97	420	1.10	0.99-1.20	104	1.32 [b]	1.08-1.58
Colon C18, C19	44	1.90 [c]	1.38-2.55	7	1.46	0.59-3.01
Rectum C20, C21	23	1.79 [a]	1.14-2.69	4	1.55	0.42-3.97
Biliary tract (intra hepatic) C22.1	22	5.65[c]	3.54-8.54	4	4.51 [a]	1.23-11.5
Lung, trachea, larynx C32-C34	67	0.80	0.62-1.02	14	0.91	0.50-1.52
Lymphoid and hematopoietic tissue C81- C96				22	2.95[c]	1.85-4.45
Cardiovascular diseases I00-I99	760	1.14 [b]	1.06-1.22	139	1.13	0.95-1.32
Ischemic heart disease I20-I25	489	1.21 [b]	1.10-1.31	82	1.13	0.90-1.39
Cerebrovascular disease I60-I69	142	1.00	0.84-1.16	29	1.07	0.72-1.54
Pulmonary embolism, I26	11	1.84	0.92-3.28	4	3.29	0.90-14.6
Respiratory diseases J00-J99	120	1.24 [a]	1.02-1.46	34	2.01[b]	1.39-2.80
Pneumonia J12-J18	57	1.29	0.98-1.67	16	2.16[b]	1.24-3.51
Bronchitis, emphysema J40-J44, J47	46	1.18	0.87-1.57	14	2.06[a]	1.13-3.45
Gastrointestinal diseases K00-K291, K293-K67,K71-K85, K861-K93	116	2.81 [b]	2.32-3.34	54	6.53 [c]	4.91-8.52
Primary sclerosing cholangitis K83.0	6	23.6[c]	8.64-51.3	0	0.05	0.00-67.9
Gastrointestinal diseases excluding UC/CD	58	1.42[b]	1.08-1.83	22	2.68[c]	1.68-4.06
Genitourinary tract diseases N00-N99	17	1.34	0.78-2.14	4	1.68	0.46-4.30
Alcohol- related diseases and accidents F10, G312, G4051,G621, G721, I426,K292, K70, K860,K8600, 0354, P043,X45	45	0.54 [b]	0.39-0.71	15	0.74	0.41-1.22
Accidents and violence excl. accidental poisoning by alcohol V01-X44, X46-Y89	132	0.84 [a]	0.70-0.98	41	1.07	0.77-1.45
Suicides X60-X84, Y87.0	55	1.03	0.77-1.33	20	1.44	0.88-2.21

[a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$

Table 23. Standardized mortality ratios (SMR) with 95% confidence intervals for cause-specific mortality according to duration of ulcerative colitis (UC) and Crohn´s disease (CD).

	UC			CD		
Cause of death	SMR (95% CI)			SMR (95% CI)		
	< 3 years	3-9.9 years	≥10 years	< 3 years	3-9.9 years	≥10 years
All causes	1.15 (1.04-1.26)	1.12 (1.04-1.19)	1.06 (0.98-1.14)	1.44 (1.20-1.70)	1.31 (1.14-1.50)	1.26 (1.04-1.50)
All diseases	1.22 (1.10-1.34)	1.13 (1.04-1.21)	1.09 (1.00-1.17)	1.52 (1.26-1.80)	1.33 (1.14-1.53)	1.30 (1.06-1.55)
Infections A00-B99	3.05 (1.32-6.01)	1.40 (0.56-2.87)	0.21 (0.01-1.14)	5.81 (1.58-14.9)	5.90 (2.37-12.2)	0.00 (0.00-5.23)
Malign neoplasm C00-C97	1.24 (1.01-1.48)	1.07 (0.91-1.24)	1.04 (0.89-1.21)	1.54 (1.05-2.16)	1.26 (0.92-1.69)	1.22 (0.81-1.75)
Colon C18, C19	2.11 (1.01-3.88)	1.86 (1.08-2.98)	1.84 (1.07-2.94)	3.20 (0.87-8.19)	0.00 (0.00-1.72)	2.14 (0.44-6.26)
Rectum C20, C21	0.74 (0.09-2.67)	1.57 (0.68-3.08)	2.59 (1.38-4.43)	1.47 (0.04-8.18)	0.00 (0.00-3.23)	3.96 (0.82-11.56)
Biliary tract (inthepatic) C22.1	5.10 (1.39-13.1)	4.71 (1.89-9.69)	6.76 (3.38-12.10)	0.00 (0.00-16.6)	7.73 (1.59-22.6)	3.63 (0.09-20.2)
Cardiovascular disease I00-I99	1.23 (1.06-1.42)	1.16 (1.03-1.29)	1.08 (0.96-1.21)	0.00 (0.00-0.80)	0.76 (0.31-1.57)	2.12 (1.02-3.90)
Ischeamic heart disease I20-I25	1.24 (1.02-1.48)	1.28 (1.12-1.46)	1.11 (0.95-1.28)	1.25 (0.90-1.68)	1.19 (0.92-1.50)	0.91 (0.62-1.30)
Respiratory diseases J00-J99	1.05 (0.65-1.60)	1.26 (0.93-1.65)	1.31 (0.97-1.73)	5.93 (0.72-21.4)	3.64 (0.44-13.1)	0.00 (0.00-11.3)
Pneumonia J12-J18	0.86 (0.37-1.68)	0.86 (0.37-1.68)	1.88 (1.27-2.68)	1.22 (0.45-2.65)	2.52 (1.52-9.93)	2.00 (0.92-3.80)
Bronchitis, emphysema J40-J44, J47	1.41 (0.70-2.51)	1.43 (0.90-2.16)	0.83 (0.44-1.41)	0.85 (1.10-3.05)	2.45 (1.06-4.82)	3.40 (1.25-7.40)
Gastrointestinal diseases K00-K291, K293-K67, K71-K85, K861-K93	4.31 (3.02-5.96)	2.68 (1.95-3.59)	2.18 (1.53-3.02)	1.66 (0.34-4.83)	2.99 (1.37-5.66)	1.02 (0.12-3.66)
Primary sclerosing cholangitis K83.0	0.00 (0.00-91.6)	22.2 (2.68-80.1)	32.2 (8.76-82.3)	12.3 (8.09-17.9)	4.78(2.83-7.54)	3.92 (1.79-7.44)
Gastrointestinal diseases excluding UC/CD	1.21 (0.58-2.22)	1.78 (1.19-2.56)	1.16 (0.70-1.82)	5.02 (2.51-8.99)	2.67 (1.28-4.90)	0.44 (0.01-2.44)
Alcohol related diseases and accidents	0.61 (0.31-1.09)	0.52 (0.30-0.82)	0.52 (0.30-0.82)	0.61 (0.13-1.79)	0.58 (0.19-1.35)	1.03 (0.42-2.13)
Accidents and violence excl. accidental poisoning by alcohol	0.65 (0.43-0.95)	1.01 (0.78-1.28)	0.75 (0.53-1.02)	0.92 (0.44-1.68)	1.21 (0.75-1.85)	0.99 (0.47-1.81)
Suicides X60-X84, Y87.0	0.88 (0.47-1.51)	1.28 (0.87-1.83)	0.77 (0.40-1.34)	1.23 (0.40-2.87)	1.89 (0.98-3.30)	0.85 (0.18-2.48)

[a]p<0.05, [b]p<0.01, [c]p<0.001

DISCUSSION

1 Incidence and prevalence

In recent years IBD has risen to become one of the major challenges in gastroenterology. This increase in worldwide trends is evident in both adult (Molodecky et al. 2012) and paediatric-onset IBD patients (Benchimol et al. 2011). Our studies showed high and increasing incidence and prevalence rates of IBD in Finland during the study periods. In fact, 0.6% of the Finnish population had IBD in 2008, and in the age group 35–54 almost 1% were suffering from IBD. The incidence of IBD and UC in Finland and the prevalence of IBD are among the highest ever reported (Molodecky et al. 2012). The incidence figures of CD are as high as those in Sweden and Denmark (Lapidus 2006, Vind et al. 2006, Jacobsen et al. 2006). Similar to the other Northern European countries (e.g. Sweden, Norway, Denmark and Iceland) (Molodecky et al. 2012), we also observed a predominance of UC over CD. UC was almost three times more common than CD. An outstanding finding of our study was that the incidence of UC increased by 24% in the period 2000 - 2007 while the incidence of CD increased only slightly. The continually increasing incidence of UC in high prevalence areas, when the incidence of CD remains fairly stable 2000-2007, differs from the findings of earlier reports (Vind et al. 2006, Jacobsen et al. 2006, Chouraki et al. 2012).

Over 80% of the patients with newly diagnosed IBD were of working age (16–64 years) and 6% were children (< 16 years). Paediatric IBD accounted for 7% to 20% of all IBD cases, based on varying results from population-based studies (age range 0-19) (Cosnes et al. 2011, Benchimol et al. 2011). As seen universally, incidence rates for both CD and UC in Finland, too, were highest in the second to the fourth decade of life (Ekbom et al. 1991, Moum et al.1996a, Vind et al. 2006, Shivananda et al. 1996, Nerich et al. 2006, Petrisch et al. 2013, Sjöberg et al, 2013). Thus IBD affects individuals in their most hectic and productive years, resulting in long-term morbidy for the patient and long-term costs for the patient, the healthcare system and society.

The reasons for these rising figures in the incidence and prevalence of IBD and especially the incidence of UC are uncertain. Some of the increase might be explained by better awareness of the disease and better diagnostic tools and the availability of endoscopy. This, however, cannot explain everything and the tools for diagnosing UC, i.e. blood in stools and sigmoideoscopy, have been available for several decades. The changing epidemiology of IBD across time and geographically suggests that environmental factors play a major role in modifying disease expression (Ng et al. 2013a). Disease emergence in developing nations suggests that epidemiological evolution is related to westernization of lifestyle and industrialization (Ng et al. 2013a). The strongest environmental association identified is cigarette smoking, although it cannot alone explains the variation in the incidence of IBD worldwide. Urbanization of societies, associated with changes in diet, antibiotic use, hygiene status, microbial exposures and pollution have been implicated as potential environmental risk factors for IBD (Ng et al. 2013a). Diet has been hypothesized to play an important role in the pathogenesis of inflammatory IBD (Gruber at. al 2012). Major changes in diet and smoking habits have also occurred in Finland (Vartiainen et al. 2010, www.lihatiedotus.fi/ 2010). Tobacco smoking in Finland has decreased among males from 50% to 30% since the 1970s (Vartiainen et al. 2010). The role of epigenetic factors in the aetiology and pathogenesis of IBD is unknown, but they could mediate gene-environment interactions involved in pathogenesis (Ventham et al. 2013) et al. 2013).

The study population was based on the SII database, which includes information on all patients entitled to reimbursement for medication costs related to IBD. All patients diagnosed with IBD taking medication for it at some point of the disease course are entitled to reimbursement as a part of the comprehensive national health insurance. Therefore the SII database provides comprehensive information on all IBD patients treated in Finland and it is likely that the coverage of patients taking maintenance medication for IBD is high; e.g. for paediatric IBD the coverage was 94%.
We believe that the true incidence of IBD in Finland does not significantly differ from our estimate. However, studies of IBD may over- or underestimate the incidence and also prevalence. The incidence rates obtained from the health insurance registry may be higher than those measured by the population based registry. The diagnostic criteria applied by the health insurance system may be different, less stringent, than those used by population based registries. In some registries, patients who have been in remission for years are registered as incident cases when in relapse; and have been removed from the system during_long-term remission. It has also been claimed that the data lack sufficient clinical detail to confirm each case, resulting in diagnostic misclassification. The key issue is the validity of the written SII certificates. In Finland administrative databases concerning IBD haven not so far been validated against medical chart reviews in adult patients. Possible misclassification of non-IBD cases and prevalent IBD cases may have occurred, and misclassification error may in part contribute to some of the findings. However, in a recent Finnish study on paediatric IBD patients between the years 1987–2003, 50 reimbursement reports were randomly selected from the two hospital districts with the highest incidence to assess the consistency of the diagnostic criteria. Only one of the 50 diagnoses was questionable (Lehtinen et al. 2011). Our register-based figures concerning the classification of IBD are also in line with the results from a Finnish population-based prospective study from the Tampere area (Manninen et al. 2010). In addition in the region of Southern Ostrobothnia, Finland, the prevalence rate of IBD in a retrospective analysis (based on patients' records and checked by two gastroenterologists) was similar to the Social Insurance Institution of Finland numbers at the end of 2000 (Jussila et al. unpublished data).

1.1 North–South gradient

We found a clear North-South gradient for prevalence of IBD in 1993 and 2008, and for UC in 1993. The prevalence rates of IBD and UC were higher in the northern than the southern part of Finland. A North–South gradient has been reported for IBD in Europe and North America and also in several countries including the USA, UK and France (Shivananda et al. 1996, Sonnenberg et al. 1991, Kappelman et al. 2007, Armitage et al. 2004, Nerich et al. 2006, Sonnenberg et al. 2012). The North–South gradient in the prevalence of IBD in Finland was seen in 1993 and also in 2008, indicating a constant difference. Unfortunately we did not analyse North-South gradient in the incidence study. We found that vitamin D levels in both genders were slightly higher in Southern Finland than in Northern Finland in the Health 2000 Survey of the general population. Low D vitamin levels before illness has been associated with increased risk of IBD (Ananthakrishnan et al. 2012a). In a large prospective cohort of US women, the Nurses' Health Study, there was a 6% relative risk reduction for CD for each 1 ng/mL increase in the plasma level of 25(OH)D (Ananthakrishnan et al. 2012a). An inverse association between UV light exposure and incidence of CD has also been shown (Nerich et al. 2006). Although we do not know the vitamin D levels in IBD patients, especially before they

have contracted the disease, the unselected population-based vitamin D data gives a good estimate of differences in vitamin levels between South and North in the Finnish population. In our study the plasma levels of 25(OH)D both in Southern (46 nmol/L) and in Northern Finland (44 nmol/L) indicate vitamin D deficiency. It is uncertain whether the slightly lower vitamin D levels in Northern Finland, 2 nmol/L (0.8ng/mL) observed in general population have any impact on the observed higher prevalence of IBD there. There are several possible explanations for regional variations in IBD risk, such as living in an urban society, level of education, different environmental factors, genetics or disparate patient access to healthcare (Soon et al. 2012, Armitage et al. 2004, Green et al. 2006, Blanchard et al. 2001). A Norwegian study demonstrated that the prevalence of UC was associated with summer temperatures (Aamodt et al. 2013).

2 Malignancies and mortality in IBD

2.1 Malignancies

Our population-based nationwide study demonstrated that patients with UC had a 10% increased overall cancer risk and patients with CD had a 30% increased overall cancer risk and that the risk was highest in the younger IBD patients. Our findings are in line with the recent nationwide study from Denmark (Kappelman et al. 2014). In a recent Danish population based study (Jess et al. 2013b) a 55% increased risk of cancer overall was found among patients with CD but not among patients with UC.

2.1.1 Colorectal cancer and other intestinal cancer

There is a general consensus that the risk of CRC is increased in IBD (Ullman et al. 2011). The well known risk factors for the development of CRC are young age at diagnosis, patients with a diagnosis of PSC, and those with extensive long-standing colitis (Rogler 2014, Jess et al. 2012a, Ullman et al. 2011). The exact magnitude of the risk is controversial, ranging from a cumulative probability of CRC in ulcerative colitis from only 2% and 3% by 25 years (Winther et al. 2004, Söderlund et al. 2009) to 18% by 30 years (Eaden et al. 2001). Two Danish nationwide studies have demonstrated a marked reduction in CRC risk in recent decades (Jess et al. 2012a, Kappelman et al. 2014). In our study UC patients had an increased risk of CRC in both genders (80% increased risk) in line with the most recent meta-analysis (Jess et al. 2012a) and a recent Finnish study (Manninen et al. 2013) but in contrast to the recent Danish studies (Jess et al. 2012b, Jess et al. 2013b, Kappelman et al. 2014). The results regarding the risk of CRC in CD are to some extent contradictory. Earlier meta-analyses (Jess et al. 2005, Canavan et al. 2006) and the most recent Danish report (Jess et al. 2013a) revealed an increased risk of CRC, but two nationwide studies from Denmark (Jess et al. 2012b, Kappelman et al. 2014) and a Finnish population-based study did not show an increased risk of CRC. In our study the risk of colon or rectal cancer was likewise not increased among CD patients. A very important finding in our study is the increased relative risk of CRC in younger patients with IBD, both UC and CD, as shown in some other studies (Karlen et al. 1999, Winther et al. 2004, Kappelman et al. 2014). Patients with UC at ages 30-44 had a 6 to10-fold increased relative risk of colon cancer and patients with UC at ages 45-59 had a 3-4-fold increased relative risk of rectal cancer compared to same aged general population. Although patients

with CD overall had no excess risk of CRC, patients aged 30-44 had a 13-20-fold increased risk of rectal cancer and male CD patients aged 30-44 a 9-fold increased risk of colon cancer. In our case control study, perianal CD seems to be associated with increased dysplasia or CRC among CD patients.

In our study colon cancers were staged using TMN staging to localized or non-localized. An important finding is that colon cancers were non-localized in 69% of patients with CD and in 57% of patients with UC, indicating either failure in CRC dysplasia surveillance or non-adherence to the surveillance programme.

Even only microscopic chronic inflammation of colorectal mucosa (neutrophil infiltrate) in patients with clinically quiescent endoscopic and clinical disease has been shown to be a significant risk factor for CRC in UC (Rutter et al. 2004, Gupta et al. 2007, Beaugerie 2011). We demonstrated in our retrospective case-control study that the risk of dysplasia and CRC in CD and UC was strongly associated with the degree of inflammation and disease duration, showing an additive effect in the risk of CRC, but unexpectedly PSC did not increase the risk for colonic dysplasia or CRC. We also demonstrated that taking thiopurines reduced the risk for both dysplasia and CRC. The recent study by Rubin et al. (2013) confirmed the significance of inflammation as a risk factor for colorectal neoplasia. They observed that increased inflammation was associated with colorectal neoplasia in patients with UC and, similar to our study, taking immune modulators reduced the risk of colorectal neoplasia. Two Dutch (Baars et al. 2011, van Schaik et al. 2011) and a recent French study (Beaugerie et al. 2013) have also suggested a decreased risk of CRC in patients taking thiopurines. The reduced risk for colorectal neoplasia in patients taking thiopurines may be a consequence of decreased inflammation activity.

Because nearly all IBD-associated CRCs are believed to develop from dysplastic lesions, the current recommendation is to perform frequent colonoscopies to prevent carcinoma through early identification of precancerous lesions (Cairns et al. 2010, Farraye 2010). According to the present guidelines, patients with extensive colitis should have surveillance colonoscopies every 1–3 years, starting 7–10 years after the onset of IBD, and UC patients with PSC should have colonoscopies yearly immediately after diagnosis (Farraye et al. 2010, Cairns et al, 2010, Annese et al. 2013). Extensive colitis, long disease duration, young age at diagnosis of IBD, family history of CRC under 50 years and multiple post-inflammatory polyps are also well known risk factors for CRC (Cairns et al. 2010, Ullman et al. 2011, Jess et al. 2012a, Beaugerie et al. 2013 Annese et al. 2013). In our study as well in the study by Kappelman et al. (2014) cancer risk was increased in earlier life probably due to young age at diagnosis. Peadiatric UC patients may have more extensive disease and more severe disease course than adult UC patients (Jakobsen et al. 2011). Although in our study PSC did not increase the risk of colorectal neoplasia, the elevated risk of CRC among patients with IBD and PSC has been very well demonstrated (Ullman et al. 2011, Jess et al. 2012a).

The surveillance programme used in Finland is laborious and not particularly effective. According to our study and the recent study by Rutter et al. 2013, the intensive endoscopy surveillance ought to be targeted at patients with chronic, especially high grade inflammation according to the guidelines British Society of Gastroenterology as well as the recent ECCO guidelines for CRC surveillance in IBD (Cairns et al. 2010, Annese et al. 2013). In contrast surveillance of patients without inflammation or other risk factors should have their next surveillance colonoscopy scheduled for longer intervals.

The risk of small bowel adenocarcinoma was increased among patients with CD and of anal cancer among males with CD. The risk of small intestine cancer in CD was about 10-fold increased in line with a recent Danish nationwide study (about 8-fold increased risk) (Kappelman et al. 2014) but lower than reported in earlier studies (Jess et al. 2005, Canavan et al. 2006). The absolute risk, however, is small.

2.1.2 Extraintestinal cancer

Patients with UC and to some extent patients with CD were found to be at increased risk of cancer of the liver and biliary system, as shown in a recent meta-analysis (Pedersen et al. 2010) and in a recent Danish study (Kappelman et al. 2014). The increased risk of cancer of the biliary tract is very likely associated with PSC (Cleassen et al. 2009). Kappelman et al. (2014) reported that the risk of cancer of liver and biliary system in IBD with cholangitis was highly elevated (SIR 80-129). It is a clear limitation of the presentstudy that no data on the incidence of PSC was available due to nature of the study.

We observed higher risks of melanoma in CD among males and basal cell carcinoma of the skin in patients with both CD and UC. The increased risk of basal carcinoma of the skin in both UC and CD could reflect enhanced screening in this patient group. However, earlier studies have shown a significantly increased risk of NMSC in IBD patients with ongoing and past exposure to thiopurines IBD (Long et al. 2010, Peyrin-Biroulet et al. 2011, Singh et al. 2011, Long et al. 2012). The potential explanation for the excess of basal cell carcinoma of the skin in our study may also be the use of thiopurines, especially as the risk is increased in patients over three years after the diagnosis of IBD. Unfortunately we do not have any data on IBD-related medication.

2.2 Mortality

Our study demonstrated slightly increased overall mortality both among patients with CD and UC as shown in the most recent meta-analyses (Canavan et al.2007, Duricova et al. 2010, Bewtra et al. 2013) and a recent nationwide Danish study (Jess et al. 2013). By contrast recent reports from the Netherlands, Finland (Manninen et al. 2012), Australia (Selinger et al. 2013) and Norway (Hovde et al. 2014) did not reveal increased overall mortality in UC or CD. Some mild IBD cases may not require any medication and they may have been omitted from the SII database and the exclusion of patients with very mild disease may have led to an overestimation of the mortality risk in IBD. This is highly unlikely due to the chronic and relapsing disease course of IBD and the financial burden of the disease medication for the patient.

The most common causes of death both in CD and UC were cardiovascular disease and malignancies as seen in general population in Finland.

The mortality risk for gastrointestinal diseases was increased both in UC and CD as seen in many studies (Jess et a.2007, Romberg-Camps et al. 2010; Jess et al. 2013, Bewtra et al. 2013, Duricova et al. 2010) and remained elevated in CD and slightly elevated in UC, also after the exclusion of direct disease-related deaths. About half of the gastrointestinal disease mortality was due to IBD-related causes and occurred relatively soon after diagnosis of IBD, as shown in the recent Danish and Dutch studies (Jess et al. 2013, Romberg –Camps et al. 2010). In UC increased risk of dyingfromPSC was observed in line

with two meta-analyses showing that patients with UC are at increased risk of dying of non-alcoholic liver diseases (Jess et al. 2007, Bewtra et al. 2013).

We observed that the mortality risk from cardiovascular diseases was increased in UC and among females in CD, mainly due to IHD, similar to the recent Danish and Australian studies (Jess et al. 2012, Selinger et al. 2013). Increased risk of IHD among patients with IBD was also observed in a population-based study from Denmark and a tendency towards a lower risk of IHD was seen among patients treated with 5-ASA, thiopurines and TNFα antagonists and also among patients with CD who had undergone surgery (Rungoe et al. 2012). These observations suggest that lowering the inflammatory burden may reduce the risk of IHD in IBD.

The overall malignancy mortality rate was slightly increased in CD but not increased in UC. An excess of deaths due to colorectal and biliary tract cancer was observed in UC and cancers of the biliary tract and lymphoid and haematopoietic tissue in CD. Increased CRC mortality rates in UC have been observed in meta-analyses (Jess et al. 2007b, Bewtra et al. 2013) and in recent studies from Denmark, Australia and the USA (Jess et al.2013, Selinger et al. 2013, Herrinton et al. 2012). The excess mortality in biliary tract cancers among CD and UC patients found in our study was also reported in a recent Australian study (Selinger et al. 2013) and is very likely associated with concomitant PSC.

A recent Finnish population-based study (Manninen et al. 2012) demonstrated that deaths related to mental and behaevioral disorders due to alcohol consumption were significantly less common in IBD than in general population. We observed reduced mortality due to alcohol-related deaths as well as mortality due to accidents and violence excluding accidental alcohol poisoning especially among male UC patients but not in CD. The reduced SMR for alcohol-related deaths may be a consequence of avoiding heavy drinking, but the mortality from accidents and violence excluding accidental alcohol poisoning was also reduced. Alcohol consumption has been associated with more symptoms in IBD (Swanson et al. 2010, Cohen et al. 2013) and high alcohol intake with an increased risk of relapse (Jowett et al. 2004).We do not know if some psychological factors such as predisposing personality have some influence on the reduced mortality from alcohol related deaths as well as the reduced mortality from accidents and violence excluding accidental alcohol poisoning.

Overall, the excess mortality of 14% in IBD is mainly due to deaths related to inflammation in the gut and interventions to reduce inflammation in the gut can potentially decrease the mortality risk in IBD.

CONCLUSIONS

The incidence and prevalence of IBD are increasing in Finland as in other regions around the world. The incidence of IBD and especially that of UC as well as the prevalence of IBD are among the highest ever reported. UC is almost three times more common than CD in Finland. The incidence of UC increased by 24% during the study period 2000-2007 while the incidence of CD increased only slightly. Incidence rates for both CD and UC were highest among the second to the fourth decade of life, thus IBD affects individuals in their most hectic and productive years.The increase of prevalence is mainly a consequence of rising incidence. 0.6% of the Finnish population and at age 35-54 nearly 1% of population has IBD, which is a disease of emerging significance to public health.

A clear North–South gradient was observed in IBD and in UC but not in CD. The prevalence rates of IBD and UC were significantly higher in the northern than the southern part of Finland.

Patients with UC and CD had only slightly increased overall cancer risk but the risk was highest in the younger IBD patients. The risk of inflammation-related cancers, CRC in UC, small bowel adenocarcinoma and anal cancer in CD, was increased. In addition the risk of cholangiocarcinoma was significantly elevated in UC. The risk of cancers related to immunosuppressive therapy, non-Hodgkin lymphoma among male CD patients and basal cell carcinoma of the skin in both CD and UC was increased. Unfortunately there were no data about IBD-related medication due to the nature of the study.

The risk of dysplasia and CRC in IBD was strongly associated with the degree of inflammation and disease duration, showing an additive effect in the risk of CRC but unexpectedly PSC did not increase the risk for colonic dysplasia or CRC. Use of thiopurines reduced the risk for both dysplasia and CRC. Patients with UC and also CD, although the overall risk for CRC in CD was not increased, were at higher risk of CRCs occurring earlier in life, reinforcing the importance of initiating proper surveillance early in the course of the disease.

A slightly increased overall mortality was observed in both CD and UC. The excess mortality of 14% in IBD is mainly due to deaths related to inflammation in the gut; gastrointestinal diseases in both UC and CD and CRC and cardiovascular diseases in UC.

Surveillance strategies should be targeted at those at real risk of CRC and intensive surveillance should be considered for patients with longstanding active severe inflammation. The therapeutic goal should be sustained control of inflammation in the gut. Interventions to reduce inflammation, not forgetting surgery, may decrease the inflammation-related cancers and also potentially the mortality risk in IBD. Although the use of immunosuppressive agents may on the other hand predispose to non-Hodgkin lymphoma and skin cancer, patients and clinicians should be aware that the absolute rates of these malignancies remain low and weigh these risks carefully against the significant potential benefits offered by these medications.

FINNISH SUMMARY

Yhteenveto

Tausta

Tulehdukselliset suolistosairaudet, Crohnin tauti ja haavainen paksusuolitulehdus, ovat kroonisia, uusiutuvia tulehduksellisia sairauksia. Tulehduksellisten suolistosairauksien esiintyminen on kehittyneissä maissa huomattavasti tavallisempaa kuin kehittyvissä maissa ja näyttää edelleen lisääntyvän. Tulehduksellisiin suolistosairauksiin, etenkin haavaiseen paksusuolitulehdukseen, on liittynyt selvästi lisääntynyt paksuolisyöpäriski. Crohn-potilaiden kuolleisuus on hiukan lisääntynyt.

Potilaat ja menetelmät

Väitöskirjatyö koostui viidestä osatyötä (I-V). Kelan erityiskorvattavien lääkkeiden rekisteristä saatiin tiedot vuosina 2000-2007 myönnetyistä uusista lääkekorvauksista haavaiseen paksusuolitulehdukseen ja Crohnin tautiin sekä vuosina 1993 ja 2008 tiedot voimassa olevista lääkekorvauksista tulehduksellisiin suolistosairauksiin. Tulehduksellisten suolistosairauksien ilmaantuvuus sekä ilmaantuvuuden muutokset selvitettiin 2000–2007 sekä esiintyvyys ja esiintyyden muutokset 1993 sekä 2008. Vuosina 1987-1993 sekä 2000-2007 Crohnin tautiin sekä haavaiseen paksusuolitulehdukseen erityislääkekorvauksen saaneiden kuolleisuuus ja kuolinsyyt sekä todetut syövät selvitettiin Tilastokeskuksesta ja Syöpärekisteristä. Lisäksi tapaus-verrokkitutkimuksessa selvitettiin takautuvasti vuosina 1996–2008 HUS:ssa tulehduksellisia suolistosairauksia sairastavilla todetut paksusuolisyövät ja dysplasiat sekä selvitettiin syöpäriskiä lisääviä ja siltä suojaavia tekijöitä.

Tulokset

Haavainen paksusuolitulehdus lisääntyi 25 %:lla vuosina 2000-2007 ja oli yleisempi miehillä kuin naisilla, ja sen ilmaantuvuus oli lähes kolme kertaa suurempi kuin Crohnin taudin. Tulehdukselisten suolistosairauksien esiintyvyys kolminkertaistui vuosien 1993-2008 välillä. Vuonna 2008 Suomessa 0,6 %:lla väestöstä oli tulehduksellinen suolistosairaus. Paksusuolisyöpäriski oli lisääntynyt haavaista paksusuolitulehdusta sairastavilla. Vaikea mikroskooppinen tulehdus ja pitkäkestoinen tauti lisäsivät syöpäriskiä, sen sijaan tiopuriinien käyttö vähensi sitä. Ihon tyvisolusyöpäriski oli hiukan lisääntynyt sekä haavaista paksusuolitulehdusta että Crohnin tautia sairastavilla. Tulehduksellisiin suolistosairauksiin liittyi noin 14% lisääntynyt kuolleisuus. Tämä johtui lisääntyneestä kuolleisuudesta ruuansulatuskanavan sairauksiin, sappitie- ja paksusuolisyöpään sekä sydän- ja verisuonisairauksiin.

Päätelmät

Tulehdukselliset suolistosairaudet ovat lisääntyneet Suomessa merkittävästi viimeisen parinkymmenen vuoden aikana, ja niiden esiintyvyys ja ilmaantuvuus ovat korkeimpia maailmassa. Voimakkaimmin on lisääntynyt haavaisen paksusuolitulehduksen esiintyvyys. Hoidon tavoitteena tulehduksellisia suolistosairauksia sairastavilla tulee olla suolen limakalvon tulehduksen tehokas hoito. Näin voidaan todennäköisesti vähentää riskiä sairastua paksusuolisyöpään samoin kuin kuolleisuutta sekä ruuansulatuskanavan sairauksiin että sydän- ja verisuonisairauksiin.

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