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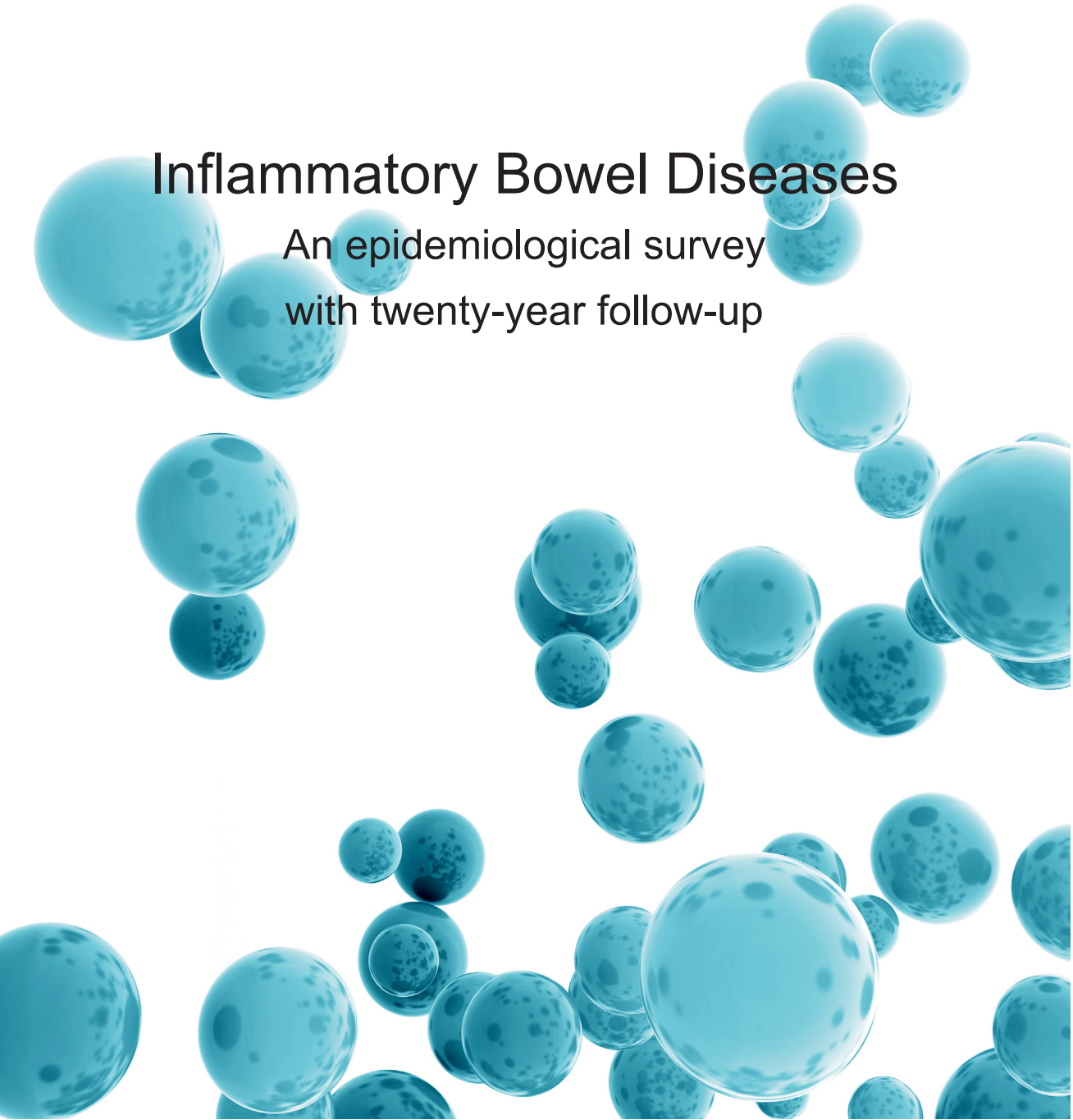
PIA MANNINEN

Inflammatory Bowel Diseases

An epidemiological survey with twenty-year follow-up



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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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Wonder is the beginning of wisdom.

Socrates

Contents

Abstract

Inflammatory bowel diseases (IBD) are chronic diseases of the gut with unknown aetiology. These diseases comprise ulcerative colitis (UC), Crohn's disease (CD) and IBD unspecified (IBDU), where a distinctive diagnosis between UC and CD cannot be set. According to the literature, the incidence of IBD has been increasing in Western countries and especially in Northern countries. The incidence of colorectal cancer in patients with IBD has previously been high but has recently shown a decline according to studies conducted in Denmark. The reports on mortality suggest a decrease in mortality from UC and an increase in mortality from CD.

Tampere University Hospital has maintained in its catchment area a registry of patients with IBD ≥15 years of age from 1986 to 2007. The registry included 1,915 patients with IBD in the study period; 1,253 with UC, 551 with CD and 111 patients with IBDU. The patients were on regular follow-up; after eight to 15 years from diagnosis surveillance colonoscopies were performed at one to three year intervals in order to prevent and detect colorectal cancer early at a curable state.

This summary comprises four separate studies. Study I evaluated the incidence and prevalence and described the clinical features of IBD in our area. Study II evaluated the risk of colorectal cancer in this cohort and the efficacy of endoscopic surveillance in cancer prevention. Study III estimated the risk of colorectal cancer and cholangiocarcinoma in a subgroup of patients with concomitant primary sclerosing cholangitis, which is an extra-intestinal manifestation of IBD. In Studies II and III the results were compared to the risk in general population, information supplied by Finnish Cancer Registry. Study IV assessed the overall and cause-specific mortality risk in the cohort and compared the results to the Finnish general population supplied by Statistics Finland.

In Study I, a high incidence of IBD was observed in the catchment area of Tampere University Hospital, the annual incidence of IBD was 29.2 per 100,000 patient-years in 1999. The incidence increased in both in UC and CD and placed Finland among the high-incidence countries. The prevalence increased in every subgroup of IBD. Study II

demonstrated an increased risk of colorectal cancer in IBD patients: standardized incidence ratio (SIR) was 1.83 (95% CI 1.13-2.79) for IBD altogether. In subgroup analysis, the relative risk was elevated in patients with young age at the time of diagnosis (SIR 8.89 95% CI 3.84-17.51), extensive disease (SIR 3.09, 95% CI 1.50-5.75), in UC altogether (SIR 1.99, 95% CI 1.14-3.25) and colonic disease in CD (SIR 3.62, 95% CI 2.00-11.87). Patients who developed colorectal cancer typically had additional risk factors for cancer; previous dysplasia, active inflammation or primary sclerosing cholangitis or they did not participate in the surveillance programme. Endoscopic surveillance was not particularly effective, in 67% of the patients with colorectal cancer the cancer was already at an invasive stage. Study III found a significant relative risk of colorectal cancer in patients with concomitant IBD and primary sclerosing cholangitis, SIR was 20.71 (95% CI 5.62-79.70) and a very high relative risk of cholangiocarcinoma, SIR 916.63 (95% CI 297.88-2140.99). Study IV found mortality in patients with IBD similar to that in general population, SMR being 0.97 (95% CI 0.80-1.31). Mortality was not elevated in UC (SMR 0.90, 95% CI 0.77-1.06) or CD (SMR 1.14, 95% CI 0.84-1.49). Mortality from mental and behavioural disorders due to alcohol (ICD-code F10) was significantly lower, SMR 0.00 (95% CI 0.00-0.36), its cause remained obscure.

To summarize, the study overall demonstrated a high and increasing incidence and prevalence of IBD in the area of Tampere University Hospital from 1986 to 1999. The follow-up to 2007 found no increased mortality but an increased risk of colorectal cancer in patients with IBD. The relative risk of colorectal cancer was increased in extensive disease and when the diagnosis had been set at young age. The patients who developed colorectal cancer frequently had other risk factors; previous dysplasia or active inflammation. Patients with concomitant primary sclerosing cholangitis were at particularly high risk of colorectal cancer or cholangicarcinoma. The surveillance of patients with IBD should be tailored individually; patients with high risk of developing colorectal cancer should be screened annually. Patients with low risk of colorectal cancer should be screened at five year intervals; this could take place in primary health care in the era of increasing prevalence. This recommendation of five year interval ensures that IBD remains in remission, although admittedly the risk of colorectal cancer remains low.

Tiivistelmä

Tulehdukselliset suolistosairaudet (IBD) ovat kroonisia suoliston sairauksia, joiden etiologia on tuntematon. Näihin sairauksiin kuuluvat haavainen paksusuolitulehdus (UC), Crohnin tauti sekä välimuotoinen koliitti (IBDU), jolloin tarkkaa diagnoosia haavaisen paksusuolitulehduksen ja Crohnin taudin välillä ei pystytä tekemään. Aiempien tutkimusten mukaan IBD:n ilmaantuvuus on lisääntynyt länsimaissa sekä erityisesti Pohjoismaissa. Paksusuolisyövän ilmaantuvuutta on aiemmin pidetty korkeana IBD-potilailla, mutta viimeaikaisissa tutkimuksissa Tanskasta sen ilmaantuvuus näyttää vähentyneen. IBD-potilaiden kuolleisuus näyttää aiempien tutkimusten mukaan olevan muuta väestöä pienempi haavaista paksusuolitulehdusta sairastavilla ja korkeampi Crohnin tautia sairastavilla.

Tampereen yliopistollisen sairaalan alueella on pidetty rekisteriä 15 vuotta täyttäneistä IBD:ta sairastavista potilaista vuodesta 1986 vuoteen 2007. IBD-rekisterissä oli yhteensä 1915 potilasta; 1253 potilaalla oli haavainen paksusuolitulehdus, 551 potilaalla Crohnin tauti ja 111 välimuotoinen koliitti. Potilaita seurattiin säännöllisesti, 8-15 vuoden kuluttua sairastumisesta aloitettiin paksusuolen tähystykset 1-3 vuoden välein paksusuolisyövän ehkäisemiseksi tai sen toteamiseksi riittävän ajoissa ennen taudin leviämistä.

Tämä yhteenveto sisältää neljä erillistä tutkimusta. Tutkimuksessa I arvioitiin IBD:n ilmaantuvuutta ja yleisyyttä Tampereen yliopistollisen sairaalan alueella sekä kuvattiin potilasryhmän yleisiä piirteitä. Tutkimuksessa II arvioitiin IBD:ta sairastavien potilaiden riskiä sairastua paksusuolisyöpään sekä tähystysseurannan tehokkuutta. Tutkimuksessa III arvioitiin samanaikaista IBD:ta ja primaari sklerosoivaa kolangiittia, yksi IBD:n suoliston ulkopuolisista manifestaatioista, sairastavien paksusuolisyöpä- sekä sappitiesyövän riskiä. Tutkimuksissa II ja III verrattiin syöpäriskiä Syöpärekisteriltä saatuun muun väestön syöpälukuihin. Tutkimuksessa IV arvioitiin IBD-potilaiden kuolleisuutta verrattuna muuhun väestöön. Vertailussa käytettiin Tilastokeskukselta saatuja kuolleisuustietoja.

Tutkimuksessa I havaittiin IBD:n ilmaantuvuuden olevan korkea Tampereen yliopistollisen sairaalan alueella, vuosittainen ilmaantuvuus oli vuonna 1999

29.2/100,000 potilasvuotta kohti. Ilmaantuvuus lisääntyi sekä haavaista paksusuolitulehdusta että Crohnin tautia sairastavilla tutkimusaikana ja Suomi kuului näin korkean ilmaantuvuuden maihin. Yleisyys lisääntyi kaikissa IBD:n alaluokissa. Tutkimuksessa II todettiin paksusuolisyövän riskin lisääntyneeksi IBD:ta sairastavilla, standardoitu ilmaantuvuus suhde (SIR) oli 1.83 (95 %:n luottamusväli (CI) 1.13 - 2.79) IBD:ta sairastavilla yhteensä. Alaluokka-analyyseissä suhteellinen riski oli lisääntynyt nuorella iällä sairastuneilla (SIR 8.89, 95 % CI 3.84 - 17.51), laaja-alaisessa taudissa (SIR 3.09, 95 % CI 1.50 - 5.75), haavaisessa paksusuolitulehdusta sairastavilla kokonaisuudessaan (SIR 1.99, 95 % CI 1.14 - 3.25) sekä Crohnin taudin koliittia sairastavilla (SIR 3.62, 95 % CI 2.00 - 11.87). Potilailla, jotka saivat seurannan aikana paksusuolisyövän, oli usein tyypillisesti muita riskitekijöitä syövälle; aikaisemmat dysplasiat, aktiivi tulehdus, primaari sklerosoiva kolangiitti tai he eivät olleet osallistuneet seurantaan. Tähystysseuranta oli tuloksiltaan epätyydyttävä, koska 67 %:lla syöpään sairastuneista se oli invasiivisessa vaiheessa löydettäessä. Tutkimuksessa III havaittiin potilailla, joilla oli samanaikainen IBD ja sklerosoiva kolangiitti, merkittävä paksusuolisyövän riski, SIR oli 20.71 (95 % CI 5.62 - 79.70) sekä erittäin korkea sappitiesyövän riski, SIR 916.63 (95 % CI 297.88 -2140.99). Tutkimuksessa IV ei havaittu kuolleisuudessa eroa IBD:ta sairastavilla muuhun väestöön verrattuna, standardoitu kuolleisuus suhde (SMR) oli 0.97 (95 % CI 0.80 - 1.31). Kuolleisuus ei ollut lisääntynyt ulseratiivista koliittia (SMR 0.90, 95 % CI 0.77 - 1.06) eikä myöskään Crohnin tautia sairastavilla (SMR 1.14, 95 % CI 0.84 - 1.49). IBD:ta sairastavien kuolleisuus alkoholinkäytön aiheuttamiin elimellisiin aivo-oireyhtymiin sekä käytöshäiriöihin (ICD-koodi F10) oli merkittävästi vähentynyt SMR 0.00 (95 % CI 0.00-0.36). Syytä tähän ei tiedetä.

Yhteenvetona, IBD:n ilmaantuvuuden ja yleisyyden havaittiin olevan korkea ja lisääntyneen merkittävästi Tampereen yliopistollisen sairaalan alueella vuodesta 1986 vuoteen 1999. Seurannassa vuoteen 2007 kuolleisuus ei eronnut muusta väestöstä, sen sijaan paksusuolisyövän ilmaantuvuus oli lisääntynyt IBD:ta sairastavilla. Paksusuolisyövän suhteellinen riski oli lisääntynyt niillä potilailla, joilla oli laaja-alainen tauti tai olivat sairastuneet nuorella iällä. Potilailla, joilla paksusuolisyöpä todettiin, oli lähes aina myös muita riskitekijöitä, kuten dysplasia tai aktiivinen tulehdus suolessa. Potilailla, joilla oli samanaikainen IBD ja primaari sklerosoiva kolangiitti, oli erityisen suuri suhteellinen riski saada paksusuolisyöpä tai sappitiesyöpä. Tutkimustulosten perusteella ehdotamme, että IBD:ta sairastavien potilaiden seuranta tulisi suunnitella yksilöllisesti riskitekijät huomioiden. Suuren riskin potilaille tulisi tehdä paksusuolen

tähystys vuosittain, kun taas matalan riskin potilaille voitaisiin paksusuolen tähystys tehdä viiden vuoden välein, jotta varmistetaan, että tauti pysyy inaktiivina. IBD:n jatkuvasti lisääntyessä matalan riskin potilaiden seuranta ja tähystykset voidaan siirtää perusterveydenhuollon piiriin.

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, referred to in the text by the Roman numerals I-IV:

I Manninen P, Karvonen AL, Huhtala H, Rasmussen M & Collin P. (2010) The epidemiology of inflammatory bowel diseases in Finland. Scand J Gastroenterol 45(9): 1063-1067.

II Manninen P, Karvonen AL, Huhtala H, Aitola P, Hyoty M, Nieminen I, Hemminki H & Collin P. (2013) The risk of colorectal cancer in patients with inflammatory bowel diseases in Finland: a follow-up of 20 years. J Crohns Colitis 7(11): e551-7.

III Manninen P, Karvonen AL, Laukkarinen J, Aitola P, Huhtala H & Collin P. (2015) Colorectal cancer and cholangiocarcinoma in patients with primary sclerosing cholangitis and inflammatory bowel disease. Scand J Gastroenterol 50(4): 423-428.

IV Manninen P, Karvonen AL, Huhtala H, Rasmussen M, Salo M, Mustaniemi L, Pirttiniemi I & Collin P. (2012) Mortality in ulcerative colitis and Crohn's disease. A population-based study in Finland. J Crohns Colitis 6(5): 524-528.

ABBREVIATIONS

AGA	the American Gastroenterological Association
5-ASA	5- amino salicylic acid
CA19-9	Carbohydrate 19-9
CARD9	Caspase recruitment domain-containing protein 9
CCA	cholangiocarcinoma
CD	Crohn's disease
CI	Confidence interval
CRP	C-reactive protein
CRC	Colorectal cancer
CT	Computed tomography
DNA	Deoxyribonucleic acid
ECCO	European Crohn's and Colitis Organisation
EIM	Extra intestinal manifestation
ERC	Endoscopic retrograde cholangiography
ESR	Erythrocyte sedimentation rate
GWAS	Genome-wide association scan
HLA	Human leucocyte antigen
HR	Hazard ratio

IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unspecified
IBS	Irritable bowel syndrome
ICD	International classification of diseases of the World Health Organization
IgA	Immunoglobulin A
IPAA	Ileal-anal pouch anastomosis
MAP	Mycobacterium avium subspecies paratuberculosis
MR	Magnetic resonance
MRC	Magnetic resonance cholangiography
NOD2	Nucleotide oligomerization domain 2
NSAID	Nonsteroidal anti-inflammatory drug
PUFA	Polyunsaturated fatty acid
PSC	Primary sclerosing cholangitis
PSC-IBD	Primary sclerosing cholangitis with concomitant inflammatory bowel disease
RNA	Ribonucleic acid
SES-CD	Simple endoscopic score for Crohn's disease
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio

Th17	Type 17 helper T cell
TNF-α	Tumour necrosis factor α
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity

Introduction

Inflammatory bowel diseases (IBD) are chronic diseases of the gut with unknown aetiology. Genetically susceptible individuals are thought to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation (Abraham and Cho 2009). IBD includes ulcerative colitis (UC), Crohn's disease (CD) and IBD unspecified (IBDU), which was formerly termed indeterminate colitis. The term IBDU is applied when no differential diagnosis between UC and CD can be made (Geboes and van Eyken 2008, Magro et al. 2013). These entities can be differentiated by their differences in genetic predisposition, risk factors and clinical, endoscopic and histological characteristics (Ordas et al. 2012). Environmental factors are considered to have a strong role in mediating the risk of IBD, although no single environmental factor has been proven to have a definite causative function (Bernstein 2012).

The diagnosis of IBD is established by a combination of medical history, clinical evaluation, laboratory data and typical endoscopic, histologic and radiological findings (van Assche et al 2010, Dignass et al. 2012). Clinical features of UC are bloody diarrhoea and chronic abdominal pain, in severe attack high temperature, tachycardia, weight loss, colonic tenderness, abdominal distension or reduced bowel sounds may also be present. Inflammation in UC is restricted to the mucosal surface, but may proceed deeper in severe course of the disease. Inflammation starts from the rectum and generally extends proximally in a continuous manner through the entire colon (Silverberg et al. 2005). CD is a lifelong disease characterized by various clinical symptoms including abdominal pain, diarrhoea, weight loss and fever. It is a chronic relapsing inflammatory disease potentially affecting any portion of the gastrointestinal tract from mouth to anus. CD is characterized by a discontinuous and ulcerous transmural inflammation often involving the terminal ileum (Van Assche et al. 2010).

The incidence of IBD varies considerably geographically. The incidence of IBD is highest in the westernized countries (Rubin et al. 2000, Bernstein et al. 2006, Vind et al. 2006, Loftus et al. 2007, Wilson et al. 2010, Jussila et al. 2012), but an increase in incidence has also been observed in previously low-incidence countries in the

Eastern Europe and Asia (Sincic et al. 2006, Yang et al. 2008). This increase has been associated with rapid socioeconomic development (Ng et al. 2013).

IBD can lead to life-threatening complications and result directly or indirectly in mortality. IBD, and especially UC, is associated with a risk of colorectal cancer (CRC) (Crohn and Rosenberg 1925). The increased risk of colorectal cancer in IBD is thought to be explained by a combination of genetic and acquired factors (Askling et al. 2001, Houlston et al. 2008). Chronic inflammation is an important factor in the pathogenesis of CRC (Gupta et al. 2007).

IBDs predominantly affect the gastrointestinal system but are associated with various extraintestinal manifestations. The most common manifestations include arthropathies, mucocutaneous and ophthalmological manifestations and conditions affecting the hepatobiliary system (Ott and Scholmercich 2013). Primary sclerosing cholangitis (PSC) is a chronic and progressive inflammatory disorder of unknown origin affecting the biliary tract, which leads to obliteration of the bile ducts and cholestasis (Ponsioen et al. 2002). PSC patients with IBD have a higher risk of developing colorectal cancer than IBD patients without PSC (Broome et al. 2006, Boonstra et al. 2013). PSC patients also have a high risk of cholangiocarcinoma (Boonstra et al. 2013).

This thesis aims to evaluate the epidemiology and outcome of adult patients with inflammatory bowel diseases who were under surveillance from 1986 to 2007 in the catchment area of Tampere University Hospital, Finland. The specific aims are to evaluate the incidence and prevalence of IBD and to describe the clinical features of this cohort, to evaluate the risk of CRC and the efficacy of endoscopic surveillance in cancer prevention and to estimate the risk of CRC and CCA in a subgroup of patients with concomitant IBD and PSC and, finally, to evaluate the overall and cause-specific mortality risk in the cohort.

1 Definition of inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are diseases of the gut characterized by chronic inflammation of the gastrointestinal tract. The cause of IBD is unknown; genetically susceptible individuals are thought to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation. (Abraham and Cho 2009)

IBD comprises ulcerative colitis (UC), Crohn's disease (CD) and IBD unspecified (IBDU), which was formerly termed indeterminate colitis. The term IBDU is applied when the differential diagnosis between UC and CD cannot be set (Geboes and van Eyken 2008, Magro et al. 2013). These entities can be differentiated by differences in genetic predisposition, risk factors and clinical, endoscopic and histological characteristics (Ordas et al. 2012). The diagnosis of IBD is established by a combination of medical history, clinical evaluation, laboratory data, which includes negative stool examinations for infectious agents, and typical endoscopic, histologic and radiological findings (van Assche et al 2010, Dignass et al. 2012). Other non-infectious causes of diarrhoea should be ruled out before a diagnosis is made (Ordas et al. 2012).

UC and CD were recognized as definable entities in the late 19th century, before that time they appeared as isolated cases (Crohn and Rosenberg 1925, Kirsner 1988). Crohn's disease was first called terminal or regional ileitis and was later named after Dr Burril B. Crohn (Crohn, Ginzburg and Oppenhaimer 1932).

2 Aetiology and pathogenesis

2.1 Genetic factors

Through the use of genome-wide association scans (GWAS), 163 genetic risk loci have been demonstrated to contribute to the risk of ulcerative colitis, Crohn's disease or to both (Jostins et al. 2012). Analyses of the genes and genetic loci implicated in IBD show several pathways that are crucial for intestinal homeostasis, including barrier function, epithelial restitution, microbial defence, innate immune regulation, reactive oxygen species, autophagy, regulation of adaptive immunity, endoplasmic reticulum stress and metabolic pathways associated with cellular homeostasis (Khor et al. 2011). Prominent in these genetic findings are genomic regions containing nucleotide oligomerization domain 2 (NOD2), autophagy genes and components of the interleukin-23-type 17 helper T cell (Th17) pathway (Abraham and Cho 2009). These loci include mutations in autophagy genes promoting the elimination of bacteria, genes that are important in epithelial barrier integrity, T cell differentiation, modulating the inflammatory response and maintaining intestinal epithelial cell homeostasis (Khor et al. 2011, Scarpa et al. 2012). NOD2 mutations have been associated with stricturing ileal CD while DRB1*1502 has been associated with severe UC (Futami et al. 1995, Ahmad et al. 2002).

Despite distinct clinical features, approximately 30% of IBD-related genetic loci are shared between ulcerative colitis and Crohn's disease, indicating that these diseases have common pathways (Khor et al. 2011). The concordance rate in monozygotic twins of 30–35% in Crohn's disease compared with 10–15% in ulcerative colitis suggests that genetic factors may have a somewhat more important role in Crohn's disease than in ulcerative colitis (Spehlmann et al. 2008).

More than 50% of IBD susceptibility loci have also been associated with other inflammatory and autoimmune diseases (Khor et al. 2011). Three susceptibility loci, reticuloendotheliosis viral oncogene homolog, interleukin 2 and CARD9, are common to ulcerative colitis and primary sclerosing cholangitis (PSC) (Janse et al. 2011).

These indicate that genetic risk loci alone are not sufficient to trigger the disease and other risk factors must play a role in the pathogenesis. Among these potential factors are the diversity and composition of the gut microbiota, major environmental factors influencing gut homeostasis (Knights 2013). Recent analyses by the Immunochip consortium have revealed overlap between IBD risk loci and susceptibility to mycobacterial infection emphasizing the role of host-microbial interaction in disease pathogenesis (Ananthakrishnan and Xavier 2013).

2.2 Epigenetics

Epigenetics may be defined as mitotically heritable changes in gene function which cannot be explained by changes in the DNA sequence (Ventham et al. 2013). On a molecular level, DNA methylation, histone modifications and RNA interference are commonly regarded as the driving epigenetic mechanisms (Portela and Esteller 2010, Ventham et al. 2013).

The epigenome can be viewed as a system of chemical tags that attach to DNA and its associated histone proteins. These tags are retained through cell division to regulate the access and recruitment of proteins that switch genes off and on during development, cell differentiation and in disease. Epigenetic mechanisms allow the cell to adapt to the environment and adjust its phenotypic development accordingly. (Scarpa and Stylianou 2012) Epigenetic factors could mediate gene-environment interactions involved in pathogenesis of IBD. Epigenetic programming begins at fertilization and continues throughout life. (Ventham et al. 2013)

Studies on epigenetic markers in IBD have shown differential expression of microRNAs in the colon mucosa compared to mucosa samples of healthy controls (Wu et al. 2010), and analyses have identified microRNAs in peripheral blood which could distinguish the subtypes of IBD (Wu et al. 2011). Increased DNA methylation has been shown in dysplastic and the non-dysplastic surrounding colon tissues in patients with UC when compared with control subjects or patients with UC who do not have dysplastic changes in mucosa (Issa et al. 2001). DNA methylation changes in colonic epithelial cells normally due to aging are accelerated in IBD because of a high cell turnover in inflammation. Increased DNA methylation could lead to genetic instability and development of cancer in IBD. (Issa et al. 2001) It has been suggested that in the future epigenetic research may provide biomarkers for use in

the diagnosis of IBD, predicting disease course and response to therapy (Ventham et al. 2013).

2.3 Immune response

The intestinal epithelium at the interface between the intestinal microbiome and the gastrointestinal lymphoid tissue plays a critical role in shaping the mucosal immune response (Abraham and Cho 2009). An intact mucosal barrier depends on intercellular junctions, which help to seal the paracellular space and tight junctions. In IBD, the permeability of the paracellular space is increased and the regulation of tight junctions is defective (Turner 2006). In addition to providing a biophysical barrier, mucus forms a matrix enabling the retention of high concentrations of antimicrobial molecules, such as defensins and secretory IgA, close to the epithelial surface. Specialized epithelial cells, goblet cells and Paneth cells, are decreased in IBD, leading to reduced mucin secretion, which is one of the key factors of IBD (Maloy and Powrie 2011).

The hallmark of active inflammatory bowel disease is a pronounced infiltration of innate immune cells and adaptive immune cells into the lamina propria. Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α (TNF-α), interleukin-1β, interferon-γ and cytokines of the interleukin-23-Th17 pathway (Abraham and Cho 2009). A disruption of the immune balance where proinflammatory Th1 and Th17 cells and their corresponding proinflammatory cytokines outnumber the regulatory T cell responses can lead to inflammation (Heylen et al. 2014). In inflammatory bowel disease, the inflammatory response often results in continued epithelial damage, which causes erosions, ulcerations and a decrease in production of defensin (Abraham and Cho 2009).

A multihit model of IBD pathogenesis has been proposed where the induction and perpetuation of chronic intestinal pathology requires the convergence of many abnormalities that affect several overlapping layers of immune homeostasis in the intestine (Maloy and Powrie 2011). These layers include genetic susceptibility, barrier defects or bacterial handling, dysbiosis or infection, sustained innate immunity and defective regulation. Defects in one layer are unlikely to precipitate IBD in the absence of further pathogenic lesions. Defects in homeostatic modules (including autophagy, endoplasmic reticulum stress, antimicrobial peptides, microbiota, pattern recognition receptors, cytokine modules and regulatory T cells) may predispose to

the development of IBD by affecting several layers of immune homeostasis. (Maloy and Powrie 2011)

2.4 Microbiota

The human intestinal tract is colonized at birth by a complex microbiota consisting of altogether 10^{13} to 10^{14} microorganisms, including mainly bacteria, but also viruses, fungi and protozoa (Dupaul-Chicoine et al. 2013). The intestinal system has co-evolved with the microbiota, which is required for its normal development and function (Cader and Kaser 2013). The gut microbiota is essential in numerous physiological processes including metabolism, immunity and host defence. The interplay between the microbiota, intestinal epithelium and innate and adaptive immune cells at homeostasis favours the dominance of regulatory networks that prevent inflammation or immune-mediated disease. (Maynard et al. 2012)

In the pathogenesis of IBD, four hypotheses which include microbiota have been proposed. First, disease may be caused by a single, as yet unidentified pathogen. Infectious agents, such as Mycobacterium avium subspecies paratuberculosis (MAP) and adherent invasive E.coli, have been implicated as triggering agents of CD (Martinez-Medina et al. 2009, Mendoza et al. 2010, Comito and Romano 2012). The second hypothesis proposes that a normal balance between beneficial and harmful bacterial species in the mucosa-associated microbiota may be disturbed causing dysbiosis (Joossens et al. 2011, De Hertogh et al. 2012). A reduction of Firmicutes and a relative abundance of Enterobacteriacae were observed in IBD patients compared to controls (Sokol et al. 2008). A large study of new-onset CD in a multicentre paediatric cohort found an increased abundance in bacteria including Enterobacteriaceae, Pasteurellacaea, Veillonellaceae, and Fusobacteriaceae, and decreased abundance in Erysipelotrichales, Bacteroidales, and Clostridiales (Gevers et al. 2014.) The third hypothesis proposes that the mucosa may be abnormally permeable to bacteria or their products causing bacterial translocation (De Hertogh et al. 2012). Finally, the immune system may also react excessively to a normally composed bowel microbiota (Maynard et al. 2012).

Epidemiological observations suggest that early microbial exposure may be important in determining the risk of developing IBD. Respiratory infections and gastroenteritis in childhood may protect against IBD (Lopez-Serrano et al. 2010). However, in a hospital-based case-control study from Canada, childhood infections

between the age of 5 and 10 years seemed to increase the risk of CD in children (Amre et al. 2006). Helminths modulate immune response of their host by evoking Th2 immune response and experimental studies support the hypothesis that helminths suppress immune-mediated chronic inflammation in IBD (Heylen et al. 2014). There is insufficient evidence to draw firm conclusions regarding the efficacy and safety of helminths used to treat patients with IBD (Garg et al. 2014).

2.5 Environmental factors

2.5.1 Smoking

Environmental factors are considered to play a major role in mediating risk of IBD, although no single environmental factor has been proven to have a definite causative function (Bernstein 2012). Smoking has both positive and negative influences in IBD. It increases the risk of developing CD, but not UC (Calkins 1989, Mahid et al. 2006). Current smokers with CD were more likely to progress to stricturing or penetrating type CD than non-smoking patients (Louis et al. 2003). Patients with UC are more likely to flare if they stop smoking, whereas CD patients may show improvement in disease course along with smoking cessation (Beaugerie et al. 2001, Cosnes et al. 2001, Higuchi et al. 2012). However, low rates of IBD are reported in countries with high rates of smokers, such as China. Sweden is an example with low rate of smokers but high rates of IBD (Bernstein 2012). In Finland, daily smoking decreased among men from 58 to 28% from 1960 to 2000 but not among women, where the prevalence of daily smoking has remained at 20% since 1985 (Heloma et al. 2004). Yet the incidence of IBD in Finland has increased (Jussila et al. 2013a), which suggests that smoking alone cannot explain high rates of IBD.

2.5.2 Diet

Diet can influence gut inflammation through several mechanisms, including antigen presentation and alteration in the gut microbiota (Hou et al. 2011, De Filippo et al.

2010). Dietary n-3 polyunsaturated fatty acids (PUFAs) competitively inhibit the formation of proinflammatory prostaglandins and leukotrienes (Marion-Letellier et al. 2013). High dietary intakes of total fats, PUFAs, omega-6 fatty acids and meat are associated with an increased risk of UC and CD (Sakamoto et al. 2005, Amre et al. 2007, Jantchou et al. 2010) A high intake of trans-unsaturated fats may also be associated with an increased risk of CD, while a high intake of dietary long-chain n-3 PUFAs may be associated with a reduced risk of UC (Ananthakrishnan et al. 2014). High fibre and fruit intakes are associated with a decreased risk of CD (Sakamoto et al. 2005, Amre et al. 2007, Ananthakrishnan et al. 2013b), and a high vegetable intake with decreased risk of UC (Geerling et al. 2000, Sakamoto et al. 2005). High sugar intake is associated with the development of UC and CD (Sakamoto et al. 2005, Amre et al. 2007, Burisch et al. 2014).

2.5.3 Vitamin D

Vitamin D coordinates the activity of innate and adaptive immunity, and of the intestinal epithelium, in a manner that promotes barrier integrity, facilitates the clearance of translocated bacteria flora, and diverts CD4 T cell development away from inflammatory phenotypes (Palmer and Weaver 2013).

The vitamin D status in IBD patients has been estimated to be lower than in healthy controls (Silvennoinen 1996, El-Matary et al. 2011), but there are also contradictory studies (Harries et al. 1985, Tajika et al. 2004). Low vitamin D level is associated with an increased risk of CD (Ananthakrishnan et al. 2012a); a low vitamin D concentration may also correlate with the disease severity (Ulitsky et al. 2011). Lower levels of vitamin D associated with reduced solar ultraviolet radiation exposure could account for a north-south gradient, with increased incidence of IBD among populations in northern latitudes (Lim et al. 2005, Nerich et al. 2011, Jussila et al. 2013a). Oral supplementation with 1200 IE vitamin D3 may reduce the risk of relapse in CD (Jörgensen et al. 2010).

2.5.4 Medication

Several medications including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), postmenopausal hormone replacement and contraceptives may increase

the risk of IBD, although the mechanisms are poorly understood (Ananthakrishnan 2013c). Population-based studies have suggested an association between the use of antibiotics and risk of IBD. The use of antibiotics 2-5 years prior to the onset of IBD may induce changes on the gut microbiome that could trigger IBD. The effect of antibiotics is more profound in CD than in UC (Hviid et al. 2011, Shaw et al. 2011, Virta et al. 2012). The regular use of aspirin was associated with the onset of CD (Chan et al. 2011) and frequent use of NSAIDs seemed to be associated with increased incidence of UC and CD (Ananthakrishnan et al. 2012b). Hormone replacement therapy among post-menopausal women was associated with an increased risk of both UC and CD (Garcia Rodriguez et al. 2005, Khalili et al. 2012). The use of oral contraceptives was associated with risk of CD in two large prospective cohorts in the United States, but the association between oral contraceptives and UC was limited to women with a history of smoking (Khalili et al. 2013).

2.5.5 Appendectomy

A negative association between appendectomy and UC was reported in 1994 (Rutgeerts et al. 1994, Gent et al. 1994). Both a positive association (Gilat et al. 1987, Russel et al. 1997, Andersson et al. 2003) and a negative association (Radford et al. 2002) between appendectomy and CD have been reported. There are two theories on the positive association: first, patients undergoing appendectomy differ from those developing IBD in terms of genetic or environmental risk factors, and secondly, early appendectomy may modify the intestinal immune response to protect against the development of UC (Radford et al. 2002). Appendectomy before the age of 20 years and for inflammatory conditions such as appendicitis and lymphadenitis is suggested to have a protective effect against the development of UC (Andersson et al. 2001). Appendectomy before diagnosis of IBD may delay disease onset in both UC and CD and alleviate the phenotype of UC (Radford et al. 2002). Despite the reportedly protective role of appendectomy, negative results have also been published, a meta-analysis of 16 case-control studies and three cohort studies showed a significant risk of CD following appendectomy (RR 1.61, 95% CI 1.28-2.02) (Kaplan et al. 2008). The role of appendectomy remains uncertain.

2.5.6 Psychological stress

Stress has been suspected to play a role in the pathogenesis of IBD, and to induce disease flares (Ananthakrishnan 2013a), but there are insufficient data on severe life stress and subsequent development of IBD. The mechamisms of stress are unknown, possible effects are decreasing mucous secretion and increasing gut permeability, which have been demonstrated in murine studies (Collins 2001). Stressors may be either physical or psychological (LeResche and Dworkin 2002). In a large Danish registry study there was no elevation in risk of hospitalization for IBD in parents who lost a child compared to general population (Li et al. 2004). Results have remained inconsistent, prospective studies have supported the role of psychological stress in the course of UC and for depressive symptoms in the course of CD (Maunder 2005, Ananthakrishnan et al. 2013d). Mawdsley et al. (2006) showed in an experimental test that acute psychological stress induces systemic and mucosal proinflammatory responses, which may contribute to disease flares of UC. In a prospective study by Bitton et al. (2008) individuals with lower levels of stress and better coping mechanisms had a reduced risk of the disease flare. More randomized controlled clinical trials are needed to assess possible psychological interventions in lowering stress and reducing relapse rates (Martin et al. 2015).

2.5.7 The hygiene hypothesis

The hygiene hypothesis is derived from the idea that infections in childhood may protect against IBD. Gent et al found that CD was more common in subjects who had hot-water taps and separate bathrooms in their houses (Gent et al. 1994). In recent study from Spain, living in urban areas, high educational level and social status were risk factors for UC and CD, whereas childhood respiratory infections and gastroenteritis were protective factors (Lopez-Serrano et al. 2010). By contrast an earlier study from Canada found no support for the hygiene hypothesis (Amre et al. 2006). The recent biodiversity hypothesis suggests that reduced contact of people with natural environmental features and biodiversity may adversely affect the human commensal microbiota and its immunomodulatory capacity, and that the declining biodiversity may be a contributing factor to increasing the prevalence of allergies and other chronic inflammatory diseases among urban populations (Hanski et al. 2012).

3 Diagnosis and clinical presentation

3.1 Ulcerative colitis

UC is a chronic inflammatory condition causing mucosal inflammation of the colon without granulomas on biopsy, affecting the rectum and a variable extent of the colon, which is characterized by a relapsing and remitting course (Silverberg et al. 2005, Dignass et al. 2012a). Inflammation in UC is restricted to the mucosal surface, but may penetrate deeper in severe course of the disease. Inflammation starts form the rectum and generally extends proximally in a continuous manner through the entire colon (Silverberg et al. 2005). Some patients with proctitis or left-sided colitis have a cecal patch of inflammation (D'Haens et al. 1997).

3.1.1 Clinical features

Clinical features of UC consist of bloody diarrhoea and chronic abdominal pain. Patients with severe attacks suffer high temperature, tachycardia, weight loss, colonic tenderness, abdominal distension or reduced bowel sounds. Laboratory tests are no disease specific markers, but may help to assess disease activity and complications. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) reflect inflammatory processes, while iron deficiency anaemia and hypoalbuminemia are signs of malnutrition. (Diagnass et al. 2012a) Faecal calprotectin is a marker of colonic inflammation. (Sipponen and Kolho 2015) Patients with bloody diarrhoea ≥6/day and any signs of systemic toxicity e.g. tachycardia > 90 bpm, fever > 37.8 °C, haemoglobin < 10.5g/dL, or an ESR >30 mm/h, have severe colitis and should be admitted to hospital for intensive treatment (Truelove and Witts 1955, Dignass et al. 2012a).

3.1.2 Classification

The Montreal Classification (Table 1) is used to define the distribution of disease based on the maximal macroscopic extent of disease at colonoscopy. (Silverberg et al. 2005, Dignass et al. 2012a) The extent of UC should be assessed at the time of the diagnosis. The extent influences the patient's management and the treatment modality and determines if oral or topical therapy is used. It also influences the beginning and frequency of surveillance (Silverberg et al. 2005, Dignass et al. 2012a).

Table 1. Montreal Classification of ulcerative colitis (Dignass et al. 2012, Silverberg et al. 2005).

Term	Distribution	Description
E1	Proctitis	involvement limited to the rectum (i.e. proximal extent of inflammation is distal to rectosigmoid junction)
E2	Left-sided	involvement limited to the proportion of the colon distal to the splenic flexure
E3	Extensive	involvement extends proximal to the splenic flexure, including pancolitis

3.1.3 Endoscopic features

The endoscopic features of UC include the loss of vascular pattern, erythema, granularity, friability, erosions, ulcerations and spontaneous bleeding. The new validated Ulcerative Colitis Endoscopic Index of Severity (UCEIS) uses vascular pattern, bleeding and ulceration, each with three or four levels of severity, to capture the complete range of endoscopic severity (Table 2) (Dignass et al. 2012a, Travis et al. 2013). The UCEIS is used mainly in clinical trials. The endoscopic component of Mayo score (Schroeder et al. 1987), a stepwise four grade scale based on mucosal friability, can also be used in clinical practice.

Table 2. Ulcerative colitis Endoscopic Index of Severity (UCEIS) (Travis et al. 2013)

Desciptor	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of endoscope or visible oozing from a haemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

3.1.4 Histopathological features

The histopathological features of UC can be classified into architectural features, epithelial abnormalities and inflammatory features. Architectural features include branching, crypt distortion and atrophy, and surface irregularity. Epithelial cell abnormalities are mucin depletion and Paneth cell metaplasia. Inflammatory features include increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates and lamina propria eosinophils. For a reliable diagnosis multiple biopsies from at least five sites around the colon (including the rectum) and the ileum should be obtained. (Dignass et al. 2012a, Magro et al. 2013)

3.2 Crohn's disease

CD is a chronic relapsing inflammatory bowel disease potentially affecting any portion of the gastrointestinal tract from mouth to anus. It is a heterogeneous entity comprising a variety of complex phenotypes in terms of age of onset, disease location and disease behavior. No single gold standard for diagnosis of CD is available. The diagnosis is based on patient's history, symptoms, clinical examination and supported by laboratory, serologic, endoscopic and histological findings. (Van Assche et al. 2010)

3.2.1 Clinical features

CD is a lifelong disease characterized by various clinical symptoms including abdominal pain, diarrhoea, weight loss and high temperature. Blood or mucus in the stool can be observed, though less frequently than in UC. Chronic non-specific symptoms mimicking irritable bowel disease (IBS), unexplained anaemia and growth failure in children may also be symptoms of CD. CD may present with extra-intestinal manifestations before the gastrointestinal symptoms become prominent. (Van Assche et al. 2010) Patients presenting at a young age and those with extensive disease needing initial treatment with steroids or with perianal disease at diagnosis can be considered to have a poor prognosis and this should be taken into account in the management (Dignass et al. 2010).

Laboratory findings in CD are not disease-specific. Anaemia and thrombocytosis represent the most common changes in the full blood count. CRP and ESR are standard laboratory surrogates of the acute phase response to inflammation (Van Assche et al. 2010). Estimations of faecal markers of inflammation correlate well with intestinal inflammation, particularly faecal calprotectin and lactoferrin (Sipponen et al. 2008). These markers can indicate active disease and may predict relapse in an asymptomatic patient, but are non-specific markers of inflammation (Sipponen 2013).

3.2.2 Classification

Patients with CD can be classified according to the Montreal Classification of CD regarding to age of onset, disease location, and behaviour (Table 3). CD is characterized by a discontinuous and ulcerous transmural inflammation often involving the terminal ileum. Ileocolonoscopy assesses the anatomical severity of CD colitis with a high specificity. Anatomical criteria of severity are defined as deep ulcerations eroding the muscle layer, or mucosal detachments or ulcerations limited to submucosa but extending to more than one third of a defined colonic segment (right, transverse and left colon) (Van Assche et al. 2010).

3.2.3 Endoscopic features

The first validated score for endoscopic findings in CD was the Crohn's Disease Endoscopic Index of Severity (CDEIS) (Mary and Modigliani 1989). It is mainly used in clinical studies. The simple endoscopic score for CD (SES-CD) can also be used in clinical practice (Sipponen et al. 2010). The SES-CD scores from 0 to 3 descibe four endoscopic varibles (presence and size of ulcers, extent of ulcerated surface, extent of affected surface and presence and type of narrowings) in the five segments of the ileocolon where higher scores indicate higher disease activity (Daperno et al. 2004).

Table 3. Montreal Classification of Crohn's disease (Silverberg et al. 2005, Laass et al. 2014)

Age at diagnosis (A)	A1 below 17 years [a]
	A2 between 17 and 40 years
	A3 above 40 years
Location (L)	L1 ileal
	L2 colonic
	L3 ileocolonic
	L4 isolated upper GI-disease [a]
Behaviour (B)	B1 non-stricturing, non-penetrating
	B2 stricturing
	B3 penetrating [b]
	p perianal disease modifier [c]

[a] L4 or respectively L4a/L4b is a modifier that is added to L1-L3 when concomitant upper gastrointestinal (GI) disease is present.

[b] Penetrating disease: bowel perforation, intra-abdominal fistulae, inflammatory masses and/or abscesses at any time in the course of the disease, and not secondary postoperative complication (excludes isolated perianal or rectovaginal fistulae).

[c] "p" is added to B1-B3 when concomitant perianal disease is present.

CD may affect the ileum beyond the reach of an endoscope, or involve more proximal small bowel. Additionally, at the time of diagnosis 15% of patients have penetrating lesions. CT and MR are the current standards for assessing the small intestine. Small bowel capsule endoscopy should be reserved for those patients with a high clinical suspicion of CD despite negative investigation by ileocolonscopy and other imaging modalities. (Van Assche et al. 2010)

3.2.4 Histopathological features

The histopathological features which warrant a diagnosis of CD in the colon are focal (discontinuous) chronic inflammation, focal crypt irregularity (discontinuous crypt distortion) and granulomas. The same features and, in addition, an irregular villous architecture, can be used for the analysis of endoscopic biopsy samples from the ileum. The presence of one single feature is not regarded as sufficient for a firm diagnosis. The presence of granulomas and at least one other feature establishes a diagnosis of CD. Granuloma in CD is defined as a collection of epithelioid histiocytes, while multinucleated giant cells are not characteristic in CD, (Magro et al. 2013) but granuloma is not a necessary find for a diagnosis of CD (van Assche et al. 2010).

3.3 Inflammatory bowel disease unspecified

The term indeterminate colitis was originally restricted to use as a pathological diagnosis applied to colectomy specimens for which a definite diagnosis of UC or CD of the colon was not possible. Since then, the term has been used for a form of colitis diagnosed by routine clinical tests but not meeting the criteria for either CD of the colon or UC (Tremaine 2012). Indeterminate colitis appears to be more common in children than in adults, a meta-analysis showed a frequency of 12.7% in children and 6.0% in adults (Prenzel and Uhlig 2009). Patients may eventually develop characteristic UC or CD, and in a nationwide study of IBD in children from 1984 to 1998 in Sweden the diagnosis changed from indeterminate colitis to UC or CD in 5% of the patients over the course of the study (Lindberg et al. 2000).

In 2005, a working party at the Montreal World Congress of Gastroenterology proposed that the term colonic inflammatory bowel disease unspecified (IBDU)

should be used for cases where there is chronic IBD with inflammation restricted to the colon and without small bowel involvement, endoscopy is inconclusive and in histopathology active patchy chronic inflammation with minimal or moderate architectural distortion and no diagnostic features for CD or UC. (Silverberg et al. 2005)

3.4 Concomitant primary sclerosing cholangitis and inflammatory bowel disease

IBDs predominantly affect the gastrointestinal system but are associated with various extraintestinal manifestations (EIM). The frequency of EIMs reported in the literature varies from 6.2% to 47% (Bernstein et al. 2001a, Ricart et al. 2003). The most common manifestations include arthropathies, mucocutaneous and ophthalmological manifestations and conditions affecting the hepatobiliary system (Ott and Scholmercich 2013). Primary sclerosing cholangitis (PSC) is a chronic and progressive inflammatory disorder of unknown origin affecting the biliary tract. PSC leads to obliteration of the bile ducts and cholestasis. (Ponsioen et al. 2002) Eight to 40% of patients need liver transplantation (Ponsioen et al. 2002, Tischendorf et al. 2007). Liver transplantation is the only proven therapy in advanced disease; no specific medical therapy has been proven to be efficacious in the treatment of PSC (Culver et al. 2011). There is a strong association with IBD, 50-80% of patients with PSC have IBD, notably UC (Ponsioen et al. 2002, Tischendorf et al. 2007, Boonstra et al. 2012). Conversely, the risk of developing PSC in a UC patient is reported to be 2-4% and 0.3-1.7% in a CD patient (Olsson et al. 1991, Bernstein et al. 2001a). PSC patients with IBD, especially UC, have a higher risk of developing colorectal cancer than UC patients without PSC (Broome et al. 2006, Boonstra et al. 2013). PSC patients also have a high risk of cholangiocarcinoma (CCA) (Boonstra et al. 2013).

3.4.1 Aetiology and pathogenesis

The pathogenesis of PSC is still largely unknown. The genetic predisposition is supported by a 100-fold increased risk of disease in first-degree relatives of patients with PSC (Bergquist et al. 2005). In a genome-wide association study the strongest association was detected for HLA-B*08 and DRB1 alleles *04, *04, *07 and *1301 in PSC (Karlsen et al. 2010). The leaky gut theory suggests that ongoing

inflammation causes disturbed gut barrier function in IBD patients which leads to increased intestinal permeability, lymphocyte activation and increased number of mononuclear cells in portal blood as well as translocation of bacteria and bacterial components and products (Pollheimer et al. 2011, Krones et al. 2012). The gut lymphocyte homing hypothesis proposes that memory T lymphocytes primed in the inflamed gut have the ability to bind both hepatic and mucosal epithelium and may persist as longlived memory cells capable of recirculation in the liver (Grant et al. 2002). The toxic bile theory is based in animal studies where genetically or chemically modified bile composition has been shown to induce sclerosing cholangitis and liver fibrosis (Pollheimer et al. 2011).

3.4.2 Diagnosis

A diagnosis of PSC is set when a patient has a cholestatic biochemical profile not otherwise explained, cholangiography shows typical findings and causes of secondary sclerosing cholangitis have been excluded. Typical bile duct changes include multifocal strictures and segmental dilatations in intra- and extrahepatic bile ducts. If high-quality magnetic resonance cholangiography (MRC) is uncertain, endoscopic retrograde cholangiography (ERC) may be considered. Patients presenting with clinical, biochemical and histological features compatible with PSC, but having normal cholangiography are classified as a small duct PSC and liver biopsy should be considered in these cases. (EASL 2009, Chapman et al. 2010, Karlsen et al. 2013) Periductal concentric fibrosis is a classic histopathological finding in PSC, although histological findings in the early stages are non-specific (EASL 2009, Chapman et al. 2010).

3.4.3 Phenotype

Concomitant PSC and IBD (PSC-IBD) represents a distinctive phenotype in that pancolitis is observed in 94% of patients with UC and 96% of CD patients have colonic involvement (Boonstra et al. 2012, O'Toole et al. 2012). Rectal sparing and ileal involvement are frequent (Loftus et al. 2005, Sinakos et al. 2013). If IBD precedes PSC diagnosis, pancolonic phenotype is frequent, while if PSC precedes IBD right-sided colitis may be more common (Schaeffer et al. 2013). The colitis in PSC-IBD patients is often mild and may show focal deep plasmacytosis and

occasional mild cryptitis. Active cryptitis and crypt abscesses, surface erosions and ulcerations are rare. (Schaeffer et al. 2013) Altogether, the bowel disease in PSC-IBD patients may have a more quiescent course (Loftus et al. 2005, Broome et al. 2006). The activity of IBD does not correlate with the severity of PSC, and PSC can be also diagnosed after total colectomy (Cangemi et al. 1989).

4 Management of inflammatory bowel diseases

4.1 Goals

Treatment goals have changed over time from the treatment of symptoms and induction of clinical remission to steroid-free remission, prevention of hospital admission and surgery, mucosal healing, improved quality of life and avoidance of disability (Peyrin-Biroulet et al. 2011). Current therapeutic goals are to induce remission both clinically and endoscopically, and mucosal healing is a target in UC. In CD there is no validated cut-off value for mucosal healing and the current definition of mucosal healing is disappearance of mucosal alterations (Armuzzi et al. 2012). Mucosal healing may change the course of the disease and is associated with lower relapse rates, lower hospitalization rates, reduced need for surgery in IBD and lower risk of colorectal cancer (CRC) in UC (Peyrin-Biroulet et al. 2011). The term deep remission has been proposed in clinical remission associated with complete mucosal healing (Allen and Peyrin-Biroulet 2013).

4.2 Medical therapy

4.2.1 Induction therapy in ulcerative colitis

Medical therapy should be tailored individually depending on the diagnosis, extent and severity of the disease. The age at onset and the disease duration are important factors in making decisions (Dignass et al. 2012b). Treatment success is dependent on the correct indication, induction or maintenance, optimization of the dose, and maximization of drug adherence (Ordas et al. 2012).

5-aminosalicylic acids (5-ASAs) are recommended for inducing and maintaining remission for patients with mild to moderate UC (Dignass et al. 2012b). In proctitis topical 5-ASAs are effective. Intravenous corticosteroid is the mainstay of conventional induction therapy in severe colitis. In steroid-refractory disease the therapeutic alternatives should be considered as early as on day three of

corticosteroid therapy; these alternatives include ciclosporin, infliximab and tacrolimus. If there is no improvement within 4-7 days of salvage therapy, colectomy is recommended. (Dignass et al. 2012b)

4.2.2 Maintenance therapy in ulcerative colitis

Maintenance treatment is recommended for all patients with UC. Oral 5-ASAs are the first line treatment in patients responding to 5-ASAs or corticosteroids. Sulphasalazine is equally effective, but with more side effects. Azathiopurine or mercaptopurine is recommended for patients who have early frequent relapses when taking the optimal dose of 5-ASA, who are intolerant of 5-ASA, steroid-dependent and for patients responding to ciclosporin or tacrolimus for induction of remission. In patients responding to anti-TNF therapy, both maintaining remission with thiopurines and continuing anti-TNF therapy with or without thiopurines are appropriate. (Dignass et al. 2012b) A new anti-α4-integrin, vedolizumab, may be effective in the treatment of moderate to severe UC (Bickston et al. 2014).

4.2.3 Induction therapy in Crohn's disease

In mildly active ileocaecal CD budesonide is recommended (Sandborn and Feagan 2003, Dignass et al. 2010). Mildly active colonic CD may be treated with sulphasalazine. In moderately active CD, budesonide or systemic corticosteroids should be preferred and antibiotics added if septic complications are suspected. In severe active CD systemic corticosteroids is the initial treatment. Patients with extensive small bowel disease should be treated with systemic corticosteroids and thiopurines or methotrexate. For relapsed patients, restarting corticosteroids with azathiopurine, mercaptopurine, methotrexate or anti-TNF therapy should be considered (Dignass et al. 2010). The Cochrane review to determine the efficacy and safety of vedolizumab in maintaining and inducing remission in CD is still ongoing (The Cochrane Library 2015).

4.2.4 Maintenance therapy in Crohn's disease

The efficacy of 5-ASAs in active or maintenance treatment is insufficient in CD (Bergman and Parkes 2006, Lim and Hanauer 2010, Dignass et al. 2010). For some patients with mild symptoms no treatment is an option. Patients who have clinical features suggesting a poor prognosis are best suited for early induction of thiopurines, methotrexate or anti-TNF therapy. Corticosteroids are not effective and should not be used to maintain remission. (Dignass et al. 2010)

4.3 Surgical treatment

Indications for surgery in UC are acute severe disease, chronic refractory UC and dysplasia or colorectal cancer. When no improvement is seen in acute severe UC with medical therapy, early colectomy is recommended to avoid further increase in surgical morbidity and mortality (Maser et al. 2008, Randall et al. 2010, Oresland et al. 2015). The standard treatment of care is ileal-anal pouch anastomosis (IPAA) and colectomy (Bordeianou and Maguire 2013). Colectomy is also recommended for patients with a non-visible high grade dysplasia, as it may be associated with synchronous concomitant colorectal cancer (CRC) or it may progress to CRC in follow-up (Bernstein et al. 1994, Rutter et al. 2006). In recent studies the rate of colectomy at ten years from diagnosis is 10% in countries with high incidence and 3-4% in countries with lower incidence (Park et al. 2007, Solberg et al. 2009, Bernstein et al. 2013).

Even though intestinal surgery in CD is not curative, it can achieve long-term remission (Silverstein et al. 1999). Terminal ileal location, structuring disease, penetrating behaviour and < 40 years of age at diagnosis are independent indicators for surgery (Solberg et al. 2007). In a population-based study from United Kingdom the cumulative probability of surgery was 19% and 25% at one and five years, respectively (Ramadas et al. 2010). The rate of surgery seems to be lower than in the pre-biological therapy era (Ramadas et al. 2010).

5 Epidemiology of inflammatory bowel diseases

5.1 Incidence

5.1.1 Ulcerative colitis

The incidence of IBD varies considerably geographically. In UC the high-incidence countries include those in Northern Europe (Vind et al. 2006, Rönnblom et al. 2010, Jussila et al. 2012), the United Kingdom (Rubin et al. 2000), North America (Bernstein et al. 2006, Loftus et al. 2007) and Australia (Wilson et al. 2010). The highest incidence of UC reported, 31.5 per 100,000, is in the Faroe Islands (Burisch et al. 2014). In the United States and Canada the incidence seems to have reached a plateau (Bernstein et al. 2006, Loftus et al. 2007), but in Northern Europe the incidence is still increasing (Rönnblom et al. 2010, Jussila et al. 2012). In previously low-incidence countries in Eastern Europe and Asia, e.g. Croatia and South Korea, an increase in incidence has been observed (Sincic et al. 2006, Yang et al. 2008). This increase has been associated with rapid socioeconomic development (Ng et al. 2013). A north-south gradient in incidence of IBD has been demonstrated in studies from North America and Europe (Shivananda et al. 1996, Blanchard et al. 2001, Sonnenberg 2009, Nerich et al. 2010). IBD is more common in urban than in rural regions (Blanchard et al. 2001, Klement et al. 2008, Sonnenberg 2009). The earlier research has often been hospital-based studies while more recent studies are often population-based. The diagnostic facilities may also have changed over time.

In Finland, the first report of incidence of UC in 1971 is from a hospital-based study by Linden and Moller with a low incidence of 4.8 per 100,000 (Linden and Moller 1971). In a recent population-based study by Jussila et al. the incidence of UC was one of the highest reported, 24.8 per 100,000 (Jussila et al. 2012). The annual incidence of UC in different countries is shown in Table 4.

The peak age for UC occurrence is 25-34 years of age (Shivananda et al. 1996, Rubin et al. 2000, Lakatos et al. 2011, Jussila et al. 2012). Some studies have reported a second peak of incidence in UC at the age of 60-70 years (Bernstein et al. 2006, Sincic et al. 2006, Vind et al. 2006).

Table 4. Annual incidence of ulcerative colitis in selected countries.

First author	Publication year	Country	Study period	Annual incidence /100,000	Number of patients
Wilson J	2010	Australia	2007-2008	11.2	29
Bernstein CN	1999	Canada	1989-1994	14.3	977
Bernstein CN	2006		1998-2000	11.8	ND
Vucelic B	1991	Croatia	1980-1989	1.5	173
Sincic BM	2006		2000-2004	4.3	70
Fonager K	1997	Denmark	1981-1992	13.2	8,125
Vind I	2006		2003-2005	13.4	326
Salupere R	2001	Estonia	1993-1998	1.7	16
Berner J	1986	Faroe Islands	1964-1983	7.5	72
Roin F	1989		1981-1988	20.3	66
Linden G	1971	Finland	1967	4.8	223
Jussila A	2012		2000-2007	24.8	10,352
Colombel JF	1989	France	1988	4.6	207
Nerich V	2006		2000-2002	7.1	12,452
Lakatos L	2004	Hungary	1977-2001	5.89	560
Lakatos L	2011		2002-2006	11.9	220
Bjornsson S	1998	Iceland	1980-1989	11.7	282
Bjornsson S	2000		1990-1993	16.5	215
Eason RJ	1982	New Zealand	1969-1978	5.4	456
Gearry RB	2006		2004-2005	7.6	668
Haug K	1988	Norway	1984-1985	14.8	239
Moum B	1996		1990-1993	13.6	525

Yang SK	2008	South Korea	1986-1990	1.34	18
			2001-2005	3.08	177
Stewenius J	1995	Sweden	1958-1982	8.3	354
Rönnblom A	2010		1945-1963	2.0	220
			2005-2007	19.2	165
Devlin HB	1980	United Kingdom	1971-1977	15.1	212
Rubin GP	2000		1991-1994	13.9	334
Loftus EV	2000	United States	1940-1993	7.6	278
Loftus CG	2007		1980-1989	8.9	ND
			1990-2000	8.8	ND

ND = no data

UC is slightly more common in men than in women, especially in the age groups after peak incidence (Shivananda et al. 1996, Rubin et al. 2000, Loftus et al. 2007, Jussila et al. 2012).

5.1.2 Crohn's disease

The incidence of CD is highest in westernized countries. The highest incidence of CD, 20.2 per 100,000, is that reported in Quebec, Canada (Lowe et al. 2009). Other high-incidence countries are Australia (Wilson et al. 2010) and New Zealand (Gearry et al. 2006). The incidence rates are generally lower than in UC, in European countries the annual incidence varies from five to ten per 100,000 (Table 5). In previously low-incidence countries the increase in incidence of CD has been even more prominent than in UC (Sincic et al. 2006, Yang et al. 2008). In Finland, the first report is a hospital-based study from Helsinki metropolitan area reporting CD incidence of 2.3 per 100,000 (Halme et al. 1989). In a recent population-based study from Finland the incidence was reported to be 9.2 per 100,000 (Jussila et al. 2012).

Table 5. Annual incidence of Crohn's disease in selected countries.

First author	Publication year	Country	Study period	Annual incidence /100,000	Number of patients
Wilson J	2010	Australia	2007-2008	17.4	45
Vucelic B	1991	Croatia	1980-1989	0.7	77
Sincic BM	2006		2000-2004	7.0	100
Bernstein CN	1999	Canada	1984-1995	14.6	997
Bernstein CN	2006		1998-2000	13.4	ND
Fonager K	1997	Denmark	1981-1992	4.6	2,806
Vind I	2006		2003-2005	8.6	209
Salupere R	2001	Estonia	1993-1998	1.4	13
Halme L	1989	Finland	1975-1985	2.3	193
Jussila A	2012		2000-2007	9.2	3,862
Colombel JF	1989	France	1988	6.3	281
Nerich V	2006		2000-2002	8.1	14,213
Lakatos L	2004	Hungary	1977-2001	2.23	212
Lakatos L	2011		2002-2006	8.9	163
Bjornsson S	1998	Iceland	1980-1989	3.1	75
Bjornsson S	2000		1990-1994	5.5	72
Eason RJ	1982	New Zealand	1969-1978	1.75	137
Gearry RB	2006		2004-2005	16.5	715
Haug K	1989	Norway	1984-1985	5.3	86
Moum B	1996		1990-1993	5.8	225

Yang SK	2008	South Korea	1986-1990	0.05	3
			2001-2005	0.34	81
Lapidus A	1997	Sweden	1955-1989	3.7	1,936
Lapidus A	2006		1990-2001	8.3	1,389
Devlin HB	1980	United Kingdom	1971-1977	5.3	73
Rubin GP	2000		1991-1994	8.3	200
Loftus EV	1998	United States	1940-1993	5.8	225
Loftus CG	2007		1980-1989	6.8	ND
			1990-2000	7.9	ND

ND = no data

The peak incidence in CD is earlier than in UC in the age group 15-24 years (Shivananda et al. 1996, Lapidus et al. 1997, Bernstein et al. 2006, Jussila et al. 2012). While some studies show a slight female preponderance (Bernstein et al. 2006), there seems to be no obvious sex difference in CD (Shivananda et al. 1996, Loftus et al. 2007, Jussila et al. 2012).

5.2 Prevalence

5.2.1 Ulcerative colitis

The prevalence of UC in Europe varies from 2.4 cases per 100,000 in Romania (Gheorghe et al. 2004) to 505 in Norway (Bengtson et al. 2009); the highest prevalence occuring in the Northern Europe (Tysk et al. 1987, Jakobsen et al. 2006, Bengtson et al. 2009, Jussila et al. 2013a) and United Kingdom (Stone et al. 2003). High-prevalence countries outside Europe are Canada, United States and New Zealand (Loftus et al. 2000, Bernstein et al. 2006, Gearry et al. 2006) (Table 6). In Finland, a north-south gradient of prevalence has been reported (Jussila et al. 2013a). Extrapolating prevalence figures from European studies for the total European population, there may be up to 2.1 million persons with UC in Europe (Burisch et al. 2013).

5.2.2 Crohn's disease

The highest reported prevalence of CD is 279 per 100,000 in Canada (Bernstein et al. 2006). In Europe, the prevalence of CD varies from 1.51 in Croatia (Gheorghe et al. 2004) to 262 per 100,000 in Norway (Bengtson et al. 2009) (Table 6). Extrapolating numbers for the total European population there may be as many as 1.6 million persons with CD and a total overall of 3.7 million persons with IBD in Europe. The prevalence of IBD is likely to continue to increase due to early age of onset and low mortality in IBD and increasing or stable incidence in westernized countries and increasing incidence in some previously low-incidence countries (Burisch et al. 2013).

Table 6. Prevalence of ulcerative colitis and Crohn's disease in selected countries.

First author	Publication year	Country	Prevalence year	Prevalence of ulcerative colitis /100,000	Prevalence of Crohn's disease /100,000
Bernstein CN	1999	Canada	1994	170	199
Bernstein CN	2006		2000	194	279
Vucelic N	1991	Croatia	1989	21	8
Binder V	1982	Denmark	1978	117	34
Jakobsen BA	2006		2002	294	151
Berner J	1986	Faroe Islands	1983	157	32
Jussila A	2013	Finland	1993	177	38
Lakatos L	2004	Hungary	1991	59	17
			2001	143	53
Bjornsson S	1989	Iceland	1979	122	38
Gearry RB	2006	New Zealand	2005	145	155
Haug K	1988	Norway	1985	92	ND
Bengtson MB	2009		1993	505	262
Gheorghe C	2004	Romania	2003	2.42	1.51
Yang SK	2000	South Korea	1997	8	ND
Yang SK	2008		2005	31	11
Tysk C	1992	Sweden	1987	234	ND

Lindberg E	1991		1987	ND	146
Lapidus A	2006		2001	ND	213
Rubin GP	2000	United Kingdom	1994	243	145
Stone MA	2003		2002	243	130
Loftus EV	2000	United States	2000	229	ND
Loftus EV	1998		1991	ND	133
Loftus CG	2007		2001	214	174

ND = no data

5.3 Paediatric inflammatory bowel disease

According to population-based studies the paediatric IBD accounts for 7% to 20% of all cases, (Auvin et al. 2005, Jakobsen et al. 2011, Lehtinen et al. 2011) Paediatric IBD shows an increase in incidence similar to that in adult IBD. This increase has been reported in both in Canada, France and Northern Europe (Auvin et al. 2005, Perminow et al. 2009, Jakobsen et al. 2011, Benchimol et al. 2014) and in Czech Republic and Hungary (Kolek et al. 2004, Muller et al. 2013). Recent data indicate higher rates of paediatric CD than UC, except in Finland, Sweden and Northern California, where the incidence of paediatric UC is higher than that of paediatric CD (Abramson et al. 2010, Lehtinen et al. 2011, Malmborg et al. 2013). (Table 7).

Table 7. Annual incidence of paediatric IBD per 100,000 in selected countries.

First author	Publication year	Country	Study period	IBD	UC	CD
Benchimol EI	2014	Canada	1994	9.4	3.9	5.2
			2009	13.2	4.1	7.9
Wang X	2013	China	2000-2010	5.5	2.9	2.5
Kolek A	2004	Czech Republic	1990-2001	2.24	1.12	0.97
Jakobsen C	2011	Denmark	2007-2009	6.4	3.2	3.1
Vind I	2006		2003-2004	ND	4.4	5.0
Lehtinen P	2011	Finland	1987-2003	9.6	ND	ND
			1987	4.8	4.1	2.0
			2003	15.0	9.1	5.0
Auvin S	2005	France	1988-1999	3.1	0.8	2.3
Muller KE	2013	Hungary	2007-2009	7.48	2.32	4.72
Yap J	2008	New Zealand	2002-2003	2.9	0.5	1.9
Perminow G	2009	Norway	2005-2007	10.9	3.6	6.8
Malmborg P	2013	Sweden	2002-2007	12.8	9.2	2.8
Henderson P	2012	United Kingdom	2003-2008	7.82	2.06	4.75
Malaty HM	2010	United States	1991-1996	1.10	0.34	0.66
			1997-2002	2.44	0.45	1.33
Abramson O	2010	United States	1996-2006	ND	3.2	2.7

ND = no data

5.4 Primary sclerosing cholangitis

The true incidence of PSC is unknown, but recent studies have estimated the yearly incidence of PSC to range from 0.90 to 1.22 per 100,000 (Table 8). The incidence is highest in Northern Europe (Boberg et al. 1998, Lindkvist et al. 2010). The prevalence varies from 0.95 per 100,000 in Japan (Tanaka et al. 2013) to 16.2 in Sweden, (Lindkvist et al. 2010). The population-based study from Sweden reported a rising trend in the incidence of PSC in the period 1992-2005 in IBD associated PSC, large duct PSC in women, PSC without IBD and small duct PSC in men (Lindkvist et al. 2010). PSC is generally more common in men than in women (Banbha et al. 2003, Lindkvist et al. 2010, Boonstra et al. 2013,). The typical age at onset is 30-40 years, but it may be diagnosed at any age (Bambha et al. 2003, Lindkvist et al. 2010, Boonstra et al. 2013).

Table 8. Annual incidence and prevalence per 100, 000 in primary sclerosing cholangitis (PSC).

First author	Year	Country	Study period	Incidence	Prevalence	Number of patients
Kaplan GG	2007	Canada	2000-2005	0.92	ND	49
Tanaka A	2012	Japan	2007	ND	0.95	415
Boberg KM	1998	Norway	1986-1995	1.30	8.5	17
Lindkvist B	2010	Sweden	1992-2005	1.22	16.2	199
Kingham J	2004	United Kingdom	1984-2003	0.91	12.7	46
Card TR	2008	United Kingdom	1987-2002	0.41	3.85	149
Bambha K	2003	United States	1976-2000	0.90	13.6	22

ND = no data

6 Colorectal cancer and cholangiocarcinoma

6.1 Colorectal cancer in ulcerative colitis

The association of colorectal cancer and UC has been known for almost a century since the time of Crohn and Rosenberg (Crohn and Rosenberg 1925). It is estimated that colorectal cancer accounts for 10% to 15% of deaths in patients with IBD (Munkholm 2003). The increased risk of colorectal cancer in IBD is thought to be explained by a combination of genetic and acquired factors (Askling et al. 2001, Houlston et al. 2008). Chronic inflammation is an important factor in the pathogenesis of CRC. Gupta et al. (2007) estimated the degree of inflammation in colon biopsies in a prospective cohort study and noted that in patients with UC chronic inflammation even at microscopic levels is an independent risk factor for developing CRC. The severity of histologic inflammation in UC patients was directly related to the likelihood of developing neoplasia (Gupta et al. 2007). Other risk factors for developing CRC include extensive disease, long duration of the disease, young age at diagnosis, family history of CRC, postinflammatory polyps and strictures and concurrent PSC (Rutter et al. 2004, Sebastian et al. 2014).

CRC is believed to develop through a chronic inflammation-dysplasia-carcinoma pathway (Okayasu 2012). Yet cells from colonic mucosa in patients with colitis may bear the molecular signs of dysplasia and cancer, including aneuploidy, aberrant DNA methylation and p53 mutations even before there is any histologic evidence of dysplasia or cancer; this phenomenon is called the field effect (Sebastian et al. 2014).

Data on the incidence of CRC in UC are variable geographically and in terms of study designs. In a meta-analysis by Eaden et al. (2001) the overall incidence of CRC in UC was 5/1000 person-years in the United States, 4/1000 in the United Kingdom and 2/1000 in Scandinavia. In a recent meta-analysis by Castano-Milla et al. (2014), the incidence rate was 1.24/1000 person-years according to population-based studies while it was 1.9/1000 in referral centre studies. A decreasing trend in the incidence rate has been seen in recent decades, with incidence rate decreasing from 4.29/1000 person-years in the 1950s to 1.21/1000 in studies from the last decade (Castano-Milla et al. 2014).

Table 9. Incidence of colorectal cancer in ulcerative colitis.

First author	Year	Country	Study period	SIR	95% CI	Number of patients
Bernstein CN	2001	Canada	1984-1997	2.75 * RR	1.91-3.97	2,672
Mellemkjaer I	1995	Denmark	1977-1989	1.8 RR	1.3-2.4	5,546
Jess T	2012	Denmark	1979-2008	1.07 RR	0.95-1.21	32,911
			1979-1988	1.34 RR	1.13-1.58	
			1999-2008	0.57 RR	0.41-0.80	
Kappelman MD	2014	Denmark	1978-2010	1.0	0.9-1.1	35,152
Jussila A	2013	Finland	1987-1993, 2000-2007	1.81 *	1.46-2.21	16,649
Beaugerie L	2013	France	2004-2005	1.94	1.15-3.07	7,727
Lakatos L	2006	Hungary	1974-	1.74	1.01-3.0	723
Palli D	1998	Italy	1978-1997	1.79	0.85-3.28	689
Karlen P	1999	Sweden	1955-1984	4.1	2.7-5.8	1,547
Hemminki K	2008	Sweden	1964-2004	2.51 *	2.20-2.85	27,606
Soderlund S	2009	Sweden	1954-1989	2.7	2.3-3.2	4,125
Goldacre MJ	2008	United Kingdom	1963-1999	2.22 * RR	1.71-2.38	6,990
Jess T	2006	Unites States	1940-2001	1.1	0.4-2.4	378

SIR = standardized incidence ratio, RR = relative risk, * incidence separately for colon cancer

In a population-based study from Denmark with a follow-up of 30 years, the overall risk of CRC in UC patients was equal to that in general population, relative risk being 1.07 (95% CI 0.95-1.21) (Jess et al. 2012a). In the subgroups diagnosed at a young age (RR 43.8, 95% CI 27.2-70.7) or with long duration of UC (RR 1.34, 95% CI 1.13-1.58) the risk was increased (Jess et al. 2012a).

In a Finnish population-based study SIR 1.81 (95% CI 1.46-2.2) was observed for colon cancer in UC patients and SIR 1.76 (95% CI 1.35-2.25) for rectal cancer. The colon cancer risk was highest among patients with young age at diagnosis. (Jussila et al. 2013b) The incidence of CRC in UC in different studies is presented in Table 9.

6.2 Colorectal cancer in Crohn's disease

Studies on the risk of CRC in CD report even greater variability than those on UC. A meta-analysis by Jess et al. (2005) which included six population-based studies from North America, Scandinavia and Israel, reported SIR ranging from 0.9 to 2.2 and pooled SIR for CRC 1.9 (95% CI 1.4-2.5). In a meta-analysis by Canavan et al. (2006) the majority (9/13) of the studies were hospital or referral centre based and the overall relative risk of CRC was 2.5 (95% CI 1.3-4.7), 4.5 (1.3-14.9) for patients with colonic disease and 1.1 (0.8-1.5) for ileal disease. In a subgroup analysis patients in Scandinavia had a significantly lower risk (RR 1.4, 95% CI 0.9-2.2) of CRC than patients in the United Kingdom (3.9, 2.4-6.2) and North America (8.5, 2.9-24.7). A recent meta-analysis including CD by Lutgens et al. (2012) reported a pooled SIR of 1.7 (95% CI 1.01-2.5) for CRC in CD in population-based studies and 4.4 in referral centre studies. In CD patients with only colonic involvement, the pooled SIR was 1.7 (0.9-2.6) and with only small bowel disease, the pooled SIR was 1.04 (0.1-2.0) in population-based studies. In subgroup analysis the risk was increased (pooled SIR 8.2, 95% CI 1.8-14.6) in patients less than 30 years at the time of diagnosis of CD and in patients with disease duration over 20 years (pooled SIR 4.2, 95% CI 1.3-13.8). In Finland in a study by Jussila et al. (2013b) the risk of colon cancer (SIR 1.55, 95% CI 0.92-2.44) or rectal cancer (SIR 1.80, 0.99-3.02) was not increased in CD patients. Data on time trends in the risk of CRC in CD are scarce; one study by Soderlund et al. (2009) has reported a decreasing incidence of CRC in CD patients in Sweden. The incidence of CRC in CD in different studies is presented in Table 10.

Table 10. Incidence of colorectal cancer in Crohn's disease.

First author	Year	Country	Study period	SIR	95% CI	Number of patients
Bernstein CN	2001	Canada	1984-1997	2.64 * RR	1.69-4.12	2,857
Jess T	2012	Denmark	1979-2008	0.85	0.67-1.07	14,463
Kappelman MD	2014	Denmark	1978-2010	0.9	0.7-1.2	13,756
Jussila A	2013	Finland	1987-1993, 2000-2007	1.55 *	0.92-2.44	5,315
Beaugerie L	2013	France	2004-2005	2.44	1.47-3.82	11,759
Lakatos PL	2011	Hungary	1977-2008	0.99	0.41-2.39	506
Palli D	1998	Italy	1978-1997	1.43	0.16-5.26	231
Yano Y	2013	Japan	1985-2010	2.79	1.28-5.29	770
Hemminki K	2008	Sweden	1964-2004	1.64 *	1.33-2.00	21,788
Soderlund S	2009	Sweden	1954-1989	2.1	1.2-3.4	3,482
Goldacre MJ	2008	United Kingdom	1963-1999	1.64 * RR	1.09-2.,39	5,127
Jess T	2006	Unites States	1940-2001	1.9	0.7-4.1	314

SIR = standardized incidence ratio, RR = relative risk, * incidence separately for colon cancer

6.3 Colorectal cancer and cholangiocarcinoma in patients with concomitant primary sclerosing cholangitis and inflammatory bowel disease

Patients with concomitant IBD and PSC are at higher risk of CRC than patients without PSC (Ekbom et al. 1990, Broome et al. 1995, Leidenius et al. 1997, Aitola et al. 2000). A meta-analysis by Soetikno et al. (2002) consisted of 11 studies with 16,844 patients with UC and a total of 564 PSC-IBD patients. Overall, 21% of PSC-IBD patients developed CRC compared to 4% to those without PSC, the OR (Odds Ratio) being 4.8 (95% CI 3.6-6.4). The risk of CRC was also increased in PSC patients with CD. In a prospective population-based study from Canada 45 PSC-IBD patients underwent surveillance colonscopies between 2000 and 2005, one colorectal cancer in a CD patient and four low-grade dysplasia or lesion-associated lesions or masses in UC patients were detected (Kaplan et al. 2007). In a recent cohort study by Ananthakrishnan et al. (2014) from the United States, with 224 PSC-IBD patients, the OR for CRC was 5.00 (95% CI 2.80-8.95). PSC-IBD patients developing CRC were younger (Brackmann et al. 2009) and there were more cancers on the right side of the colon than in IBD patients without PSC (Lindberg et al. 2001).

PSC-IBD patients carry also a high risk of cholangiocarcinoma (CCA) (Broome et al. 1995). The number of PSC patients who develop CCA varies depending upon patient selection and length of follow-up (Boberg and Lind 2011). In a Swedish population-based cohort of 604 PSC patients (79% with IBD) SIR for hepatobiliary cancers (CCA, hepatocellular and gallbladder) was 160.6 (95% CI 120.3-210.1) (Bergquist et al. 2002). In the study by Ananthakrishnan et al. (2014) the OR for cholangiocarcinoma was 55.31 (95% CI 22.20-137.80). Suggested risk factors for CCA in PSC include elevated serum bilirubin, variceal bleeding, proctocolectomy, smoking, alcohol consumption, longer duration of IBD, coexisting ulcerative colitis with colorectal neoplasia and polymorphisms of the NKG2D gene encoding a protein involved in NK cell activity (Chapman et al. 2010, Bergquist et al. 2002, Boberg et al. 2002, Melum et al. 2008). A large proportion of CCA (50%) is diagnosed within the first year after diagnosis of PSC (Boberg et al. 2002). Mortality is increased significantly in PSC-IBD patients with OR of 3.51 reported in a study from the United States among 224 PSC-IBD patients (95% CI 2.30-5.36) (Ananthakrishnan et al. 2014). In Minnesota, USA, the estimated ten-year survival among PSC patients was 65% while the expected survival was 94% ($P<0.001$) (Bambha et al. 2003).

6.4 Chemoprevention of cancer

Medical therapy may reduce colorectal cancer in IBD through primary chemoprevention by reducing inflammation over time or by altering the molecular pathways to dysplasia development or by secondary prevention, where treatment results in healed bowel and allows more accurate neoplasia detection in endoscopy and histological examination (Chapman and Rubin 2014).

The 5-aminosalicylic acid (5-ASA) derivatives are the first-line therapy in UC. A meta-analysis in 2005 of nine studies and 1,932 patients found a protective association between 5-ASA use and CRC, OR 0.51 (95% CI 0.37-0.69) (Velayos et al. 2005). In more recent meta-analysis focusing on non-referral studies the authors found no protective benefit, with a pooled adjusted OR of 0.95 (95% CI 0.66-1.38) (Nguyen et al. 2012). The American Gastroenterological Association (AGA) and the European Crohn's and Colitis Organization (ECCO) have suggested that despite the lack of good quality prospective randomised trials there is moderate certainty that aminosalicylates are chemopreventive against CRC and recommend the use of 5-ASAs for chemoprevention of CRC (Farraye et al. 2010, Sebastian et al. 2014).

Rubin et al. (2013) found thiopurine exposure to be protective against CRC (adjusted OR 0.25, 95% CI 0.08-0.73). There are also contradictory studies; a recent meta-analysis by Jess et al. (2014) found no significant protective effect of treatment with thiopurines on the risk of CRC in IBD. There are no current recommendations for the use of thiopurines in chemoprevention.

Ursodeoxycholic acid (UCDA) is a 7-β-epimer of chenodeoxycoli acid used in patients with PSC due to its beneficial effects on cholestatic parameters. The first studies on the chemoprotective action of UCDA showed protective effects (Tung et al. 2001, Pardi et al. 2003) in patients with UC and PSC. In a subsequent study the risk of developing CRC was higher (HR 4.44 (95% CI 1.30-20.10) in patients receiving high-dose UDCA (28-30 mg/kg/day) than those receiving placebo (Eaton et al. 2011). The role of UDCA as a chemoprotective agent, especially in high doses, is still controversial and UDCA is not recommended for chemoprotective use alone (Sebastian et al. 2014, Chapman et al. 2014).

6.5 Monitoring

Regular monitoring of patients with IBD has been recommended since the association between IBD and CRC has been recognized (Crohn 1925). The goal of endoscopic surveillance in IBD is to reduce morbidity and mortality from CRC, by either detecting and resecting dysplasia or detecting CRC early, at a potentially curable stage (Shergill et al. 2014). The recommendations have been variable, in previous recommendations in the 1980s surveillance endoscopies were offered eight years after diagnosis to patients with extensive colitis and after 15 years to patients with left-sided colitis. The endoscopy was performed at 1-3 year intervals depending on the duration and the extent of the disease (Lennard-Jones 1985, Jones et al. 1988, Fozard et al. 1989).

In recent recommendations (Table 11) by the ECCO, the British Society of Gastroenterology (BSG) and AGA the interval between endoscopies was 1-5 years depending on the risk factors, which include extent of the disease, family history of CRC, previous dysplasia or stricture, inflammation, post-inflammatory polyps and PSC (Cairns et al. 2010, Farraye et al. 2010, Annese et al. 2013). Inflammation of the mucosa is now considered to be a risk factor and warrants shorter intervals between surveillance endoscopies (Cairns et al. 2010, Annese et al. 2013). Chromoendoscopy is recommended for surveillance endoscopy and if not available random quadrant biopsies every 10 cm and targeted biopsies of visible lesions should be taken (Cairns et al. 2010, Annese et al. 2013, Laine et al. 2015).

Table 11. Recent recommendations for colorectal cancer screenings in patients with inflammatory bowel diseases.

	First screening colonoscopy	Interval (years)	Crohn's disease	Risk stratification
ECCO (Annese et al. 2013)	8 years	High risk: 1 year Intermediate risk: 2-3 years Neither intermediate nor high risk: 5 years	Same recommendation, patients involving only one segment or colorectum excluded	High risk: stricture or dysplasia within past 5 years, PSC, extensive colitis with severe active inflammation or a family history of CRC in first degree relative at <50 years Intermediate risk factors: extensive colitis with mild/moderate active inflammation, post-inflammatory polyps or family history of CRC ≥50 years Proctitis excluded
BSG (Cairns et al. 2010)	8-10 years	Lower risk: 5 years Intermediate risk: 3 years High risk: 1 year	Same recommendation	Higher risk: extensive colitis with moderate/severe active endoscopic/histological inflammation or stricture/dysplasia in past 5 years,

BSG continued				PSC or a family history of CRC in first degree relative at <50 years Intermediate risk: extensive colitis with mild active endoscopic/histological inflammation or post-inflammatory polyps or family history of CRC ≥50 years Lower risk: extensive colitis with no active endoscopic/histological inflammation or left-sided colitis or Crohn colitis of <50% colon Proctitis excluded
AGA (Farraye et al. 2010)	8-10 years	1-3 years	Same recommendation, if at least 30% of colon inflected	Same recommendation for both left-sided and extensive colitis Proctitis and proctosigmoiditis excluded

7 Mortality

7.1 Mortality in ulcerative colitis

7.1.1 Overall mortality

IBD may lead to life-threatening complications and result directly or indirectly in mortality. In UC the overall mortality is equal or slightly increased compared to that of general population (Table 12). In referral centre studies the prognosis tended to be poorer (Gyde et al. 1982) than in population-based studies (Winther et al. 2003, Selinger et al. 2013). In population-based studies mortality is reportedly increased in subgroups of newly diagnosed patients and in patients with extensive disease (Jess et al. 2013, Winther et al. 2003). Higher overall mortality has also been observed in patients under 30 years of age at diagnosis (Viscido et al. 2001, Jess et al. 2013) or over 50 years of age (Winther et al. 2003, Hoie et al. 2007). In a Danish population-based cohort mortality from UC had a decreasing trend from 1982 to 2010 as hazard ratio declined from 1.00 to 0.88 CI95% 0.82-0.95 (Jess et al. 2012).

7.1.2 Cause-specific mortality

The data on cause-specific mortality are inconsistent. A meta-analysis by Jess et al. (2007) including nine European population-based studies and one from New Zealand reported a greater risk of dying from gastrointestinal diseases (pooled SMR 2.5 95% CI 1.9-3.2) and UC associated mortality accounted for 17% of all deaths. The risk of dying from non-alcoholic liver diseases, pulmonary embolisms and respiratory diseases was significantly increased pooled SMR being 4.0 (95% CI 2.5-6.5), 4.0 (95% CI 1.5-8.7) and 1.6 (95% CI 1.3-2.0), respectively. Mortality from pulmonary cancer was reduced (pooled SMR 0.3, 95% CI 0.1-0.9) while overall risk of dying from cancer was similar to that in general population. The risk of dying from colorectal cancer was borderline significant (pooled SMR 1.9, 95% CI

Table 12. Overall mortality in ulcerative colitis.

First author	Year	Country	Study period	SMR	95% CI	N
Selinger CP	2013	Australia	1977-1992	0.82	0.68-0.986	401
Jess T	2013	Denmark	1982-2010	1.25 (HR)	1.22-1.28	36,080
Winther KV	2003	Denmark	1962-1997	1.05	0.92-1.19	1,160
Hoie O	2007	Europe	1990-1993	1.09	0.86-1.37	404
Jussila A	2014	Finland	1987-1993, 2000-2007	1.10	1.05-1.15	16,649
Masala G	2004	Italy	1978-2001	0.70	0.56-0.88	689
Viscido A	2001	Italy	1964-1995	1.0	0.8-1.2	2,066
Romberg-Camps M	2010	Netherlands	1991-2003	0.9	0.7-1.2	630
Ekbom A	1992	Sweden	1965-1983	1.4	1.2-1.5	2,509
Stewenius J	1995	Sweden	1958-1990	1.3	1.0-1.5	471
Persson PG	1996	Sweden	1955-1984	1.37	1.20-1.54	1,547
Probert CS	1993	United Kingdom	1972-1989	0.9	0.8-1.1	1,014
Card T	2003	United Kingdom	Unknown	1.44	1.31-1.58	8,301
Jess T	2006	United States	1940-2001	0.8	0.6-1.0	378
Hutfless SM	2007	United States	1996-2003	1.0	0.9-1.2	5,238

SMR = standardized mortality ratio

1.0-3.8) (Jess et al. 2007). In a population-based study from Denmark mortality from gastrointestinal causes including UC (HR 0.59, 95% CI 0.46-0.75) and from colorectal cancer (HR 0.69 95% CI 0.49-0.98) diminished significantly in the period 2000-2010 from that observed in the period 1982-1989 (Jess et al. 2012b).

In a recent Finnish population-based study by Jussila et al. (2014) the risk of dying from gastrointestinal diseases was significantly increased, SMR 2.81 (95% CI 2.32-3.33). Fifty per cent of the mortality from gastrointestinal diseases was directly related to UC. The risk of dying from primary sclerosing cholangitis was significantly increased, SMR 23.6. (95% CI 8.64-54.6). The risk of dying from cardiovascular diseases, SMR 1.14 (95% CI 1.06-1.22) and malignancies of colon, rectum and biliary tract was increased, SMR 1.90 (1.38-2.55), 1.79 (1.14-2.69) and 5.65 (3.54-8.54) respectively. The mortality from alcohol-related diseases and accidents was significantly reduced, SMR 0.54 (95% CI 0.39-0.71). (Jussila et al. 2014)

7.2 Mortality in Crohn's disease

7.2.1 Overall mortality

Patients with CD have a slightly increased mortality risk compared to general population (Table 13). There are also studies reporting no difference in mortality compared to general population (Probert et al. 1992, Romberg-Camps et al. 2010, Selinger et al. 2013, Hovde et al. 2014). A meta-analysis consisting of 12 European and one Japanese study reported a pooled SMR of 1.52 (95% CI 1.32-1.74) in CD. SMR was higher in hospital-based or referral centre studies (SMR 1.73, 95% CI 1.45-2.47) than in population-based studies (SMR 1.48, 95% CI 1.28-1.70) Mortality had decreased over 35 years although this was not statistically significant. (Canavan et al. 2007a) In another meta-analysis of mortality in CD Duricova et al. (2010) reported a pooled SMR of 1.39 (95% CI 1.30-1.49). A decreased survival in women compared to men was reported in a meta-analysis and in two population-based cohorts from Denmark and Australia (Duricova et al. 2010, Jess et al. 2013, Selinger et al. 2013) while studies from Finland, Cardiff (UK) and Minnesota (USA) reported poorer survival for men (Jess et al. 2006, Canavan et al. 2007b, Jussila et al. 2014). In a study by Canavan et al. (2007b) patients diagnosed at 10-26 years of age had poorer prognosis than patients diagnosed later in life.

Table 13. Overall mortality in Crohn's disease.

First author	Year	Country	Study period	SMR	95% CI	N
Selinger CP	2013	Australia	1977-1992	0.84	0.698-1.077	373
Jess T	2013	Denmark	1982-2010	1.73 (HR)	1.67-1.80	15,361
Wolters FL	2006	Europe	1991-1993	1.85	1.30-2.55	380
Jussila A	2014	Finland	1987-1993, 2000-2007	1.33	1.21-1.46	5,315
Masala G	2004	Italy	1978-2001	1.51	1.06-2.08	231
Romberg-Camps M	2010	Netherlands	1991-2003	1.1	0.7-1.6	476
Hovde O	2014	Norway	1990-1993	1.35 (HR)	0.94-1.94	237
Ekbom A	1992	Sweden	1965-1983	1.6	1.4-1.9	1,469
Persson PG	1996	Sweden	1955-1984	1.51	1.29-1.75	1,251
Probert CS	1992	United Kingdom	1972-1989	0.72	0.49-1.01	610
Card T	2003	United Kingdom	Unknown	1.73	1.54-1.96	5,960
Canavan C	2007	United Kingdom	1934-1984	1.29	1.12-1.45	394
Hutfless SM	2007	United States	1996-2003	1.4	1.2-1.6	3,241
Jess T	2006	United States	1940-2001	1.2	0.9-1.6	314

SMR = standardized mortality ratio

7.2.2 Cause-specific mortality

In a meta-analysis by Duricova et al. (2010), a significantly increased risk of death from overall cancer was observed (pooled SMR 1.50, 95% CI 1.18-1.92). This was explained by increased mortality from pulmonary cancer (pooled SMR 2.72, 95% CI 1.35-5.45) and malignant melanoma (10.0, 95% CI 1.21-36.1). The risk of dying from colorectal cancer was not significantly increased (pooled SMR 1.34, 95% CI 0.54-3.33). Mortality from chronic obstructive pulmonary disease (COPD) (2.55, 95% CI 1.19-5.47), gastrointestinal diseases (6.76, 95% CI 4.37-10.45) and genitourinary diseases (3.28, 95% CI 1.69-6.35) was significantly increased. Patients with CD include a greater proportion of smokers compared to unaffected individuals, which may be a major contributor to increased risk of dying from COPD (Jess et al. 2006).

In a Finnish population-based study by Jussila et al. (2014) mortality from overall cancer (SMR 1.32, 95% CI 1.08-1.58) and from malignancies of biliary tract (4.51, 95% CI 1.23-11.5) and lymphoid or hematopoietic tissue (2.95, 95% CI 1.85-4.45) was increased, but not from pulmonary cancer (0.91, 95% CI 0.50-1.52) or malignancies in colon (1.46, 95% CI 0.59-3.01) or rectum (1.55, 95% CI 0.42-3.97). Mortality from gastrointestinal diseases (6.53, 95% CI 4.91-8.52) and respiratory diseases (2.01, 95% CI 1.39-2.80) was likewise increased which was explained by COPD and pneumonia. Fifty-nine per cent of the mortality from gastrointestinal diseases was directly related to CD. (Jussila et al. 2014)

1 Aims of the study

The aim of this study was to evaluate the epidemiology and outcome of adult patients with inflammatory bowel diseases monitored in the catchment area of Tampere University Hospital, Finland and with a special focus was on colorectal cancer and mortality.

The specific aims were

1. To evaluate the incidence and prevalence of IBD and to describe the clinical features of this cohort (I).
2. To evaluate the risk of CRC in this cohort and to evaluate the efficacy of endoscopic monitoring in cancer prevention; to estimate the risk of CRC and CCA in a subgroup of patients with concomitant IBD and PSC (II, III).
3. To evaluate the overall and cause-specific mortality risk in the cohort of adult patients with IBD (IV).

2 Patients and methods

2.1 IBD register (Studies I, II, III, IV)

The IBD register in Tampere University Hospital, Finland was set up in 1986 to enable more rigorous follow-up of patients with IBD. The catchment area covered both urban and rural areas and comprised 446,000 inhabitants in 1999, which was 9% of the total population of Finland. All patients ≥ 15 years of age with IBD were included in the IBD register from this catchment area, with 363,000 inhabitants in this age group. All new patients and patients diagnosed before 1986 were put into the register. Small centres, which included one large health care centre and four regional hospitals, were contacted regularly in order to obtain information on all new cases. The follow-up of patients diagnosed in smaller centres generally took place in the study centres. In each centre there was one specialist physician responsible for data collection. Every centre had a pathologist, in cases of uncertain diagnoses, specialists in Tampere University Hospital were consulted.

The data included in the register comprise demographical data, extent of IBD, current medication, concomitant PSC, colorectal cancer and colectomy in patients with UC. The data are saved at the Department of Gastroenterology and Alimentary Tract Surgery in Tampere University Hospital, Finland.

2.2 Study population

The patient population in Studies I-IV was drawn from the IBD register. The register included in 1986-2007 a total of 1915 patients with IBD, 1,253 with UC, 551 with CD and 111 with IBDU. Of these patients 501 were diagnosed before 1986. The characteristics of the patients are shown in Table 14. In the PSC-IBD study (III), the study population included patients from the IBD register but also eleven patients outside the catchment area who were on regular follow-up at Tampere University Hospital; characteristics are shown in Table 15.

Table 14. Characteristics of patients in the IBD register.

	Total	UC	CD	IBDU
Number of patients 1986-2007	1915	1254	550	111
Female %	47	45	51	54
Age at diagnosis, years, median (range)	33 (1-89)	34 (1-89)	30 (1-81)	37 (7-88)
Follow-up time, years, median (range)	13.5 (0.2-42.5)	13.1 (0.2-42.5)	13.0 (0.2-42.5)	17.5 (0.5-33.5)
Concomitant PSC (n)	40	36	4	0

2.3 Methods

2.3.1 Study I: incidence and prevalence

The diagnosis of IBD was set in one university hospital, four regional hospitals and one health centre (in the city of Tampere, population of 200,000 inhabitants). All physicians diagnosing IBD were experienced physicians. The diagnosis of IBD was based on history of diarrhoea or blood in stools (or abdominal pain in CD) and characteristic endoscopic and histopathological findings (or radiological in CD) (Lennard-Jones 1989). Chronic colitis without definite characteristic histopathological signs of CD or UC was classified as IBDU, previously indeterminate colitis. In cases of incomplete colonoscopy, the endoscopy was repeated. Malignancies and enteric infections were excluded. Diagnosis and the endoscopic and histopathological extent of the disease were recorded prospectively. The annual number of inhabitants in the area was obtained from Statistics Finland, Helsinki.). The endpoint of the analysis was set at 31 December, 1999 for the incidence and prevalence study.

Table 15. Characteristics of PSC-IBD patients compared to patients without PSC.

	IBD patients	
	PSC-IBD patients*	IBD patients without PSC
Male N(%)	40 (78.4)	987 (52.4)
IBD diagnosis N(%)		
UC	46 (90.2)	1222 (65.1)
CD	5 (9.8)	542 (29.0)
IBDU	0 (0)	111 (5.9)
Age at IBD diagnosis	21 (6-89)	33 (0.1-89)
Years, median (range)		
Age at PSC diagnosis	32 (5-89)	-
Years, median (range)		
Follow-up time from IBD diagnosis	19 (0.5-3.8)	14 (0.2-43)
Years, median (range)		
Duration of PSC	13 (0.5-37)	-
Years, median (range)		

*11 patients in the PSC-IBD cohort came from outside the catchment area,
N=number of patients

2.3.2 Study II: colorectal cancer

First surveillance colonoscopy was offered eight years after diagnosis in extensive colitis and 15 years after diagnosis of left-sided colitis. Colonoscopies were performed at 1-3 year intervals according to recommendations at the given time (Lennard-Jones 1985). Patients with extensive colitis with over 30 years from diagnosis and patients with concomitant PSC attended colonoscopy annually. Ileocolonoscopy was the standard procedure during throughout the study period. Severe dysplasia confirmed by two pathologists was an indication for prophylactic colectomy. When mild dysplasia was seen repeatedly in control samples prophylactic colectomy was also considered. Long duration of the disease, active inflammation, pseudopolyposis and PSC were contributing factors.

The follow-up started at the time of diagnosis and ended at emigration, total colectomy in patients with UC, death or at closing date of the study (31 December 2007), whichever occurred first. Cases with CRC were drawn from the IBD register. In addition, patient records were reviewed by linkage with UC, CD, IBDU or indeterminate colitis and CRC diagnosis (ICD-9, ICD-10 codes). The figures on general population with CRC were obtained from the Finnish Cancer Registry, where all cases of cancer in Finland are reported (www.cancer.fi).

2.3.3 Study III: concomitant primary sclerosing cholangitis and inflammatory bowel disease

The PSC-IBD cases with CRC or CCA were drawn from the IBD register and patient records were reviewed by linkage with UC, CD, IBDU and CRC or CCA diagnosis (ICD-9, ICD-10). The figures for CRC and CCA in the general population were obtained from the Finnish Cancer Registry.

2.3.4 Study IV: mortality

Mortality figures were updated annually and were based on death certificates. The follow-up started at the time of diagnosis and ended at emigration, death or closing date of the study (31 December 2007) while the endpoint of analyses was set at 31 December 2007. The causes of death in IBD patients and mortality data in general population were obtained from Statistics, Finland.

2.3.5 Statistical analysis

All statistical analyses were performed in collaboration with the School of Health Sciences, University of Tampere, Finland. In the incidence and prevalence study (I) analyses were performed with SPSS software 14.0 (SPSS Inc., Chicago, USA). The χ^2 test was used for independence. Data were given as numbers and percentages, medians and ranges.

In the colorectal cancer study (II) and the PSC-IBD study (III) the expected numbers of colorectal cancer cases were calculated by multiplying person-years at risk by the national incidence figures for colorectal cancer or cholangiocarcinoma stratified by gender, five-year calendar period and five-year age group. SIR (standardized incidence ratio) was calculated as the ratio of observed to expected numbers of cases. Analyses were carried out using statistical software R (version 2.15.1) and CIA 2.2 software.

In the mortality study (IV) person years at risk were calculated at five-year age and calendar intervals using the R environment (version 2.10.1, R Foundation for Statistical Computing, Vienna, Austria). The confidence intervals were calculated with CIA 2.1.2 software (University of Southampton, UK). The 95% confidence interval (CI) was estimated assuming that the observed number followed a Poisson distribution. The expected numbers of deaths were calculated separately for UC and CD using gender, age and calendar-year-specific mortality in the Finnish population. Standardized mortality ratios (SMR) were calculated by dividing observed numbers of deaths by expected numbers.

2.3.6 Ethical considerations

This study was approved by the Ethics committee of the City of Tampere. The IBD register has since 1986 held a person registry licence, which was renewed in 2006. No informed consent was required in accordance with the Finnish regulations for registry-based studies without contact with the study subject.

3 Results

3.1 Incidence and prevalence

The annual incidence of IBD increased from 19.5 per 100,000 inhabitants in 1986 to 29.2 in 1999. The increase was evident in both UC and CD. The incidence of IBDU remained stable throughout the study period (Figure 1). The peak incidence was in the age group of 25 to 45 years of age (Table 16). The prevalence of IBD increased from 168 per 100,000 in 1986 to 441 in 1991, an increase was observed in every subgroup of IBD (Table 17). The distribution of IBD did not change during the study period except for the distal ileal CD, where the proportion of ileal disease in CD increased from 5.9% to 21.4% (Table 17). The diagnostic delay was similar in UC and CD, 1.7 and 1.8 years (mean), respectively, but longer in IBDU at 2.3 years.

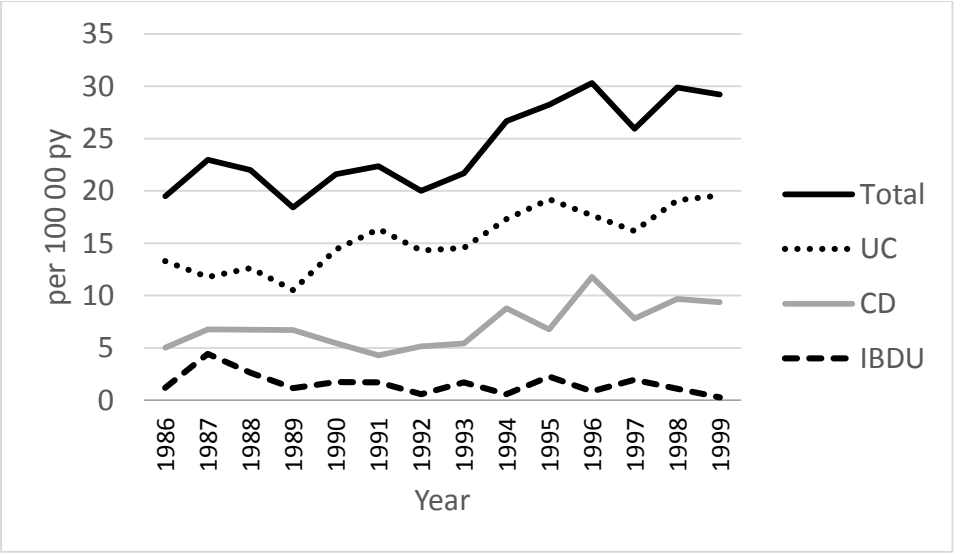

Figure 1. Incidence of inflammatory bowel diseases per 100,000 person-years in the Tampere University Hospital catchment area from 1986 to 1999.

Table 16. Age distribution of all patients in the IBD register at time of diagnosis.

Age at time of diagnosis	Number of patients	%
≤ 25 years	505	29.9
26-35 years	459	27.1
36-45 years	284	16.8
46-55 years	187	11.1
56-65 years	136	8.0
≥ 66 years	120	7.1
Total	1691	100

3.2 Colorectal cancer

3.2.1 Incidence of colorectal cancer

CRC was found in 21 IBD patients during follow-up from 1986 to 2007, giving a standardized incidence ratio (SIR) of 1.83 (95% CI 1.13-2.79) (Table 18). Sixteen patients with UC and five patients with CD developed CRC, SIR 1.99 (95% CI 1.14-3.25) and 1.92 (95% CI 0.62-4.49), respectively. There was no difference in relative CRC risk between males and females.

The median age at the time of CRC diagnosis was 41.0 years (range 31-88 years). The highest relative risk of CRC was in the youngest age group of those under 30 years of age, SIR being 8.89 (95% CI 3.84-17.51). The risk was also significantly elevated in extensive UC and CD of the colon, SIR 3.09 (95% CI 1.5-5.75) and 3.62 (95% CI 2.00-11.87), respectively. None of the UC patients with proctitis, CD patients with ileal CD or patients with IBDU developed CRC. There were four patients with a simultaneous diagnosis of IBD and CRC; if these cases were excluded from the analysis, SIR would remain at 1.55 (95% CI 0.90-2.27).

Table 17. Prevalence and extent of inflammatory bowel diseases in the study.

	1986	1999
Prevalence per 100,000		
Total	168	441
UC	119	291
CD	40	124
IBDU	9	27
Extent of IBD (%)		
UC, extensive	40.0	42.9
UC, left-sided	48.9	41.3
UC, proctitis	11.1	15.9
CD, terminal ileum	5.9	21.4
CD, colon	47.1	31.0
CD, ileocolon	41.2	45.2
CD, upper gi-tract	5.9	2.4

IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease, IBDU = inflammatory bowel disease unspecified

Table 18. Standardized incidence ratios of CRC in patients with IBD.

		Patients	Person-years	O/E	SIR	95% CI
All IBD patients	Male	1009	12654	12/6.5	1.85	0.95-3.23
	Female	906	11929	9/5.0	1.80	0.82-3.42
	Total	1915	24584	21/11.5	1.83	1.13-2.79
Age at diagnosis	0-29	818	10650	8/0.9	8.89	3.84-17.51
	30-49	688	9385	4/3.5	1.14	0.31-2.93
	>50	409	4549	9/7.1	1.27	0.58-2.41
UC	Extensive	619	6932	10/3.2	3.09	1.50-5.75
	Left-sided	433	5795	6/3.4	1.75	0.65-3.84
	Proctitis	199	2872	0/1.3	0.00	0.00-2.84

	Total	1253	15635	16/8.0	1.99	1.14-3.25
CD	Ileal	98	1205	0/0.4	0.00	0.00-9.22
	Ileocolonic	232	3080	1/0.9	1.11	0.03-6.19
	Colonic	208	2783	4/1.1	3.62	2.00-11.87
	Total	551	7265	5/2.6	1.92	0.62-4.49

O = observed, E = expected, SIR = standardized incidence ratio, IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease

Table 19. Patients with inflammatory bowel disease and colorectal cancer during the study period between 1986 and 2007.

IBD subtype	Gender	Age at diagnosis	Maximal extent of UC	Location of CRC	TNM	Disease duration at the time of CRC	Dysplasia-follow-up	PSC	Risk factors in previous colonoscopy
UC	Male	15	Extensive	Rectum	T2N0M0	16	Yes	Yes	Dysplasia
UC	Male	21	Extensive	Transverse	T4N2M1	32	No	No	No risk factors
UC	Female	28	Extensive	Rectum	T4N1M1	27	No	No	No risk factors
UC	Male	28	Left-sided	Rectum	T3N2M1	22	Yes	No	Active inflammation
UC	Male	30	Extensive	Transverse	T3N0M0	19	Yes	Yes	Dysplasia
UC	Female	35	Left-sided	Sigmoid	T4N2M1	9	Yes	No	No risk factors
UC	Male	36	Extensive	Rectum	T3N2M0	14	No	No	No risk factors
UC	Female	41	Extensive	Transverse	T3N1M0	23	Yes	No	Active inflammation

UC	Male	46	Left-sided	Caecum	T3N1M0	33	Yes	No	Adenoma
UC	Female	55	Extensive	Caecum	T1N0M0	15	Yes	No	Dysplasia
UC	Female	61	Left-sided	Rectum	T3N2M0	20	No	No	No risk factors
UC	Female	63	Left-sided	Caecum	T1N0M0	25	Yes	No	Dysplasia
UC	Male	68	Extensive	Rectum	T3N0M0	0	*	No	-
UC	Female	72	Left-sided	Transverse	T1N1M0	1	**	No	-
UC	Male	79	Extensive	Rectum	T1N0M0	3	**	No	-
UC	Female	85	Extensive	Caecum	T1N0M0	0	*	No	-
CD	Male	12	Colonic	Ascending colon	T4N2M1	19	No	No	No risk factors
CD	Male	27	Ileocolonic	Descending colon	T3N0M0	17	Yes	Yes	Active inflammation

CD	Male	28	Colonic	Descending colon	T3NXM0	16	No	No	No risk factors
CD	Female	57	Colonic	Rectum	T2N1M0	0	*	No	-
CD	Male	65	Colonic	Transverse	T3N1M0	0	*	No	-

*IBD and CRC diagnosed concurrently, **Disease duration less than 8 years, TNM = the TNM classification of malignant tumours, IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease

3.2.2 Other risk factors for colorectal cancer

Three IBD patients with concomitant PSC developed CRC during follow-up. In their most recent colonoscopies, four patients had had dysplasia, one adenoma where the severity of dysplasia was not known, and three had had active inflammation in the colon (Table 19). The duration of IBD at the time of CRC varied from nine to 33 years, median 20.5 years, patients with concurrent CRC and IBD excluded.

Forty per cent (6/15) of the patients had not participated in the monitoring programme; here patients with concurrent CRC and IBD and less than eight to ten years from diagnosis were excluded. Thirty per cent (5/17) of these patients were not taking medication. Twenty-two per cent (2/9) of the patients who attended the monitoring programme and developed CRC did not have any previous risk factors other than disease duration.

3.2.3 Stages of colorectal cancer

Fourteen out of 21 (67 per cent) patients had advanced stage of CRC at the time of detection, TNM stage IV or III. The remaining seven patients had less invasive stages of CRC. (Table 19).

3.2.4 Colectomies

During the follow-up from 1986 to 2007 14% (176/1254) of the patients with UC and 5% (26/551) with CD had undergone colectomy or proctocolectomy. Altogether 32% (178/551) of CD patients had been operated on, ileocecal resection being the most common operation (80/551). Ten proctocolectomies were performed on UC patients during the study period the indication being cancer risk or dysplasia. Eight out of 10 patients had other risk factors for colorectal cancer including extensive disease, concomitant PSC, pseudopolyposis or active histological inflammation (Table 20).

Table 20. Patients with ulcerative colitis and colectomy with ileoanal anastomosis due to cancer risk during the study period between 1986 and 2007.

Gender	Age at diagnosis	Maximal extent of the disease	Disease duration at the time of surgery	Year of the surgery	Dysplasia	Other risk factors
Female	9	Extensive	18	1993	Mild	Active inflammation
Male	17	Extensive	3	1986	Mild	PSC
Male	19	Extensive	21	2005	Mild	PSC
Male	25	Extensive	26	1986	Severe	PSC
Female	28	Left-sided	17	2004	Mild	Severe pseudopolyposis
Male	29	Left-sided	15	1989	No dysplasia	Severe pseudopolyposis
Male	32	Extensive	6	2005	No dysplasia	Severe pseudopolyposis
Male	35	Extensive	16	2001	Mild	No other risk factors, frequent mild dysplasia
Female	35	Extensive	17	1995	Mild	Active inflammation
Male	47	Extensive	22	1994	Severe	No other risk factors

3.2.5 Colorectal cancer in patients with concomitant primary sclerosing cholangitis and inflammatory bowel disease

Three out of 51 PSC-IBD patients developed CRC, giving an SIR of 20.71 (95% CI 5.62-79.70). All three had a long duration of IBD and extensive disease; two had UC and one ileocolonic CD. Both UC patients had previous dysplasia and CD patient had active inflammation in previous ileocolonoscopy. All three had participated in dysplasia monitoring (Table 19). The median age at the time of CRC was 39.5 years (range 31-49 years).

Of all PSC-IBD patients, 89% (41/46) with UC had extensive disease, 60% (3/5) of all PSC-IBD patients with CD had colonic CD. Colectomy was performed on 30% (14/46) of PSC-IBD patients with UC.

3.3 Cholangiocarcinoma in patients with concomitant primary sclerosing cholangitis and inflammatory bowel disease

Five PSC-IBD patients out of 51 developed CCA during follow-up, SIR being 916.63 (95% CI 297.88-2140.99). Two of the CCAs were detected in liver biopsy during assessment for liver transplantation. The median age at the time of CCA diagnosis was 54 years (range 45-63) and the median time from diagnosis of PSC to detection of CCA 21 years (range 4-25 years). The characteristics of PSC-IBD patients with CCA are presented in Table 21.

3.4 Mortality

3.4.1 Overall mortality

During the median follow-up of 13.5 years and 29,644 person-years 223 deaths were reported among 1,915 patients with IBD. The causes of death are presented in Table 22.

Table 21. Patients with concomitant primary sclerosing cholangitis, inflammatory bowel disease and cholangiocarcinoma during the study period between 1986 and 2007.

IBD Subtype	Gender	Age at IBD diagnosis	Age at PSC diagnosis	Age at CCA diagnosis	Extent of IBD	Disease duration at the time of CCA	Clinical features	Outcome
UC	Female	17	29	46	Extensive	17	Dominant bile duct stenosis, CA19-9 elevated	Death at the age of 47
UC	Male	17	37	45	Extensive	8	Detected in liver transplant evaluation	Death at the age of 50
UC	Male	20	46	50	Extensive	4	CA19-9 elevated	Death at the age of 63
UC	Female	37	37	62	Extensive	25		Death at the age of 64
UC	Male	53	54	62	Extensive	9	Detected in liver transplant evaluation	Death at the age of 62

CCA = cholangiocarcinoma, CD = Crohn's disease, IBD = inflammatory bowel diseases, IBDU = inflammatory bowel disease unspecified, PSC = primary sclerosing cholangitis, UC = ulcerative colitis

Compared to the general population, overall mortality was not increased in patients with IBD, SMR being 0.97 (95% CI 0.85-1.11). There was no statistically significant change in overall mortality in patients with UC or CD, even though the tendency was to decreased mortality in UC and increased mortality in CD (Table 23). The number of deaths among patients with IBDU was too small to permit valid statistical analysis.

Table 22. Causes of death in patients with inflammatory bowel diseases.

Cause of death (ICD code)	Female (n)	Male (n)	Total (n)
Infectious diseases (A00-A99, B00-B99)	0	2	2
Malignant neoplasms (C00-C97)	17	31	48
Mental and behavioural disorders (F00-F99)	5	4	9
Diseases of the central nervous system (G00-G99)	8	6	14
Diseases of the circulatory system (I00-I99)	34	52	86
Diseases of the respiratory system (J00-J99)	4	8	12
Diseases of the digestive system (K00-K93)	7	13	20
Diseases of the genitourinary tract (N00-N99)	2	1	3
Injury, poisoning and other consequences of external causes (S00-T98)	7	17	24
Other	1	2	3
Not known	0	2	2
Total	85	138	223

3.4.2 Cause-specific mortality

The most common cause of death was disease of the circulatory system (ICD code I00-I99) in all subgroups of IBD with 86 deaths (Table 22). The second most common cause of death was malignancy (ICD code C00-C97) with 48 deaths. The most common malignances were those of the trachea and lung with nine deaths, and colorectal cancer likewise nine deaths. Four patients died of malignancies of the liver and biliary tract. There were 20 deaths from diseases of the digestive system; IBD was the cause of death in six cases (four deaths from CD and two from UC).

The risk of mortality from diseases of the digestive system was increased in overall IBD SMR being 3.33 (95% CI 2.04-5.15), in CD, SMR 5.83 (95% CI 2.35-12.02), and in UC in men, SMR 2.77 (95% CI 1.13-5.77). There was no difference compared to general population in deaths from diseases of the circulatory system in IBD altogether, UC or CD, SMR being 1.61 (95% CI 0.90-1.48), 1.04 (0.76-1.41) and 1.28 (0.68-2.18) respectively. Mortality from malignancies of the trachea and lung was not significantly increased, SMR being 1.09 (95% CI 0.50-2.08). Mortality of colorectal cancer was likewise not increased in either UC, SMR being 1.80 (95% CI 0.72-3.70) or in CD SMR being 1.88 (0.23-6.80). There were no deaths among IBD patients due to mental and behavioural disorders due to alcohol consumption (ICD-code F10) while the expected number was ten, SMR being 0.00 (95% CI 0.00-0.36). The decrease in risk was significant in men, SMR 0.00 (0.00-0.42) but not in women, SMR 0.00 (95% CI 0.00-2.31). The results of cause-specific mortality separately in UC and CD are summarized in Tables 24 and 25.

Table 23. Overall mortality in inflammatory bowel diseases.

	SMR	95% CI
IBD	0.97	0.80-1.31
UC	0.90	0.77-1.06
CD	1.14	0.84-1.49

SMR = standardized mortality ratio, IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease

Table 24. Standardized mortality ratios for ulcerative colitis.

Cause of death (ICD code)	Female			Male			Total		
	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI
All deaths	52/57	0.90	0.67-1.18	98/109	0.90	0.73-1.10	150/166	0.90	0.77-1.06
Diseases of circulatory system (I00-I99)	17/13	1.33	0.77-2.12	27/29	0.93	0.61-1.35	44/42	1.04	0.76-1.41
Diseases of digestive system (K00-K93)	17/13	1.08	0.13-3.80	7/2.5	2.77	1.13-5.77	9/4	2.05	0.94-3.88
Malignant neoplasms of colon and rectum (C18-C20)	3/1.6	1.91	0.39-5.48	4/2.3	1.71	0.47-4.45	7/3.9	1.80	0.72-3.70
Mental and behavioural disorders due to alcohol consumption (F10)	0/0.4	0.00	0.00-3.55	0/6.1	0.00	0.00-0.60	0/7.2	0.00	0.00-0.51

O = observed, E= expected, 95% CI = 95% confidence intervals, SMR = standardized mortality ratio, IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease

Table 25. Standardized mortality ratios for Crohn's disease.

Cause of death (ICD code)	Female			Male			Total		
	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI
All deaths	22/19	1.16	0.73-1.76	28/26	1.12	0.75-1.61	51/45	1.14	0.84-1.49
Diseases of circulatory system (I00-I99)	5/4	1.28	0.42-2.99	8/6	1.28	0.55-2.50	13/10	1.28	0.68-2.18
Diseases of digestive system (K00-K93)	3/0.6	5.08	1.02-14.61	4/0.6	6.76	1.82-17.07	7/1.2	5.83	2.35-12.02
Malignant neoplasms of colon and rectum (C18-C20)	1/0.5	1.91	0.05-10.61	1/0.5	1.86	0.05-10.36	2/1.1	1.88	0.23-6.80
Mental and behavioural disorders due to alcohol consumption (F10)	0/0.4	0.00	0.00-8.38	0/2	0.00	0.00-1.80	0/2.5	0.00	0.00-1.48

O = observed, E= expected, 95% CI = 95% confidence intervals, SMR = standardized mortality ratio, IBD = inflammatory bowel diseases, UC = ulcerative colitis, CD = Crohn's disease

4 Discussion

4.1 Incidence and prevalence

The incidence and prevalence of IBD increased during the study period in both UC and CD. With the annual incidence of IBD 29.2 per 100,000 in 1999 the results were comparable to those in other Scandinavian countries and puts Finland among the high-incidence countries (Tables 4 and 5). UC was twice as common as CD during the study period (Figure 1), which is consistent with other studies from Scandinavia (Tables 4 and 5).

Our data were based on a local register designed to find all IBD patients in the catchment area of Tampere University Hospital. The participating centres were contacted regularly in order to collect all new cases of IBD in the register. During the study period from 1986 to 1999 the follow-up and management of patients with IBD in our area were focused on the participating centres. A few milder cases with follow-up in the private sector or occupational health care may have been missed. In Finland, IBD patients on medications are entitled to reimbursement under the national health care system, which may have facilitated better diagnostic methods and increased patient adherence. In the 2000s the management and follow-up of patients with IBD were decentralized to smaller centres, the private sector and occupational health care, which means that data on incidence were no longer reliable, hence the closing date of analysis was set at 31 December 1999.

The increase in incidence cannot be explained by better diagnostic facilities. Colonoscopy was the method of choice in diagnosing IBD throughout the study period. The increase in ileal involvement in CD may be due to better endoscopic training and more successful ileal intubation but also due to better imaging modalities, including CT, MRI and capsule endoscopy. The switch in classification from ICD9 to ICD10 does not explain the increase as the guidelines for diagnosing IBD remained the same.

Earlier research has often been from referral or tertiary centres and has been retrospective. These studies have not been always been able to capture the milder cases and may have underestimated the true incidence. Population-based prospective studies have been considered more reliable. The present study commenced at 1986,

a prospective population-based study in a well-defined area, the inclusion of new cases of IBD was considered reliable and also extended to milder cases (182 patients with proctitis).

A further strength of this study was the design with a prospective population-based cohort. As the catchment area covered 9% of the total Finnish population including both rural and urban areas, it can be considered to be representative of Finland as a whole. This conclusion gains support from the data in the nationwide study by Jussila et al. (2012); even at the national level the incidence has continued to increase and the present and nationwide data are thus mutually supportive. The nationwide data included a large number of cases, while here it was possible to record individual patient characteristics prospectively in greater detail.

The limitations of the study were the large proportion of retrospective data. Prior to 1986, almost all patients with IBD were managed at the same centres which took part in the study. Despite this, the IBD prevalence in 1986 may have been underestimated.

IBD patients are usually young at the time of diagnosis and both UC and CD are associated with substantial morbidity and impaired quality of life (Nurmi et al. 2013). There was no significant increase in mortality in patients with IBD (Tables 12 and 13) and explains also partly explains why the prevalence was increasing. The increase thus means a burden on the community and creates pressure on the medical community. This must be taken into account when designing monitoring programmes.

4.2 Colorectal cancer

The risk of colorectal cancer was increased in IBD patients; SIR 1.83 (95% CI 1.13-2.79). When the cases with concurrent IBD and CRC removed from the analysis, the difference from general population was no longer statistically significant, SIR 1.55 (95% CI 0.90-2.27). Population-based studies from Denmark have reported of a similar risk of CRC in patients with IBD compared to general population (Jess et al. 2012a, Kappelman et al. 2013) (Table 9 and 10). In the present series, the relative risk of CRC was increased in UC, extensive UC and in young patients in total IBD population. This was also the case in a recent meta-analysis (Jess et al. 2012b). It must be noted that the absolute risk in young patients remains low.

Colonic CD increased the risk of CRC, SIR being 3.62 (95% CI 2.00-11.87) while the overall risk of CRC was not significantly increased in our series. For comparison,

a meta-analysis from 2005 noted that when the extent of the disease was stratified at diagnosis the colonic involvement without ileal involvement significantly increased the risk of CRC, SIR being 4.3 (95% CI 2.0-9.4) (Jess et al. 2005).

Closer scrutiny at the patients who developed CRC suggest that PSC, active inflammation, previous dysplasia and long duration of the disease are additional risk factors (Table 19), although the number of patients was too small to allow reliable statistical analysis. Nevertheless, the same factors have been associated with an increased risk of CRC in other studies (Rutter et al. 2004, Sebastian et al. 2014, Gupta et al. 2007). Non-compliance is an important factor; 40 per cent of the CRC patients in this study did not participate in the follow-up programme even though in terms of disease duration it would have been advisable. In a study from the United States, non-participation in follow-up colonoscopies in IBD patients was 25.5 per cent with colonoscopies over three year intervals or longer. (Friedman et al. 2013). It was not possible to estimate the participation rate in regular follow-up programme reliably, but the percentage of non-compliance in those who developed CRC (40%) was definitely high; a rough estimated is that 90% in the entire series participated regularly in the follow-up programme.

The present monitoring programme failed to prevent the development of CRC in 21 patients. In most cases the cancer was already at an invasive stage (TNM stages III and IV). Nevertheless, only two out of nine patients with CRC in the follow-up programme had no additional risk factors other than disease duration.

The PSC-IBD patients were at considerably increased risk of CRC, SIR being as high as 20.71 (95% CI 5.62-79.70). The annual surveillance colonoscopy did not prevent CRC in two out of three patients. In one patient the colonoscopy was delayed, the preceding colonoscopy having been performed three years previously; in one patient a mild dysplasia was detected one year earlier which should have warranted earlier control endoscopy. More rigorous colonoscopic follow-up might have prevented the development of CRC. Furthermore, during follow-up, two PSC-IBD patients underwent prophylactic colectomy, which also indicates some effect from the monitoring programme.

The monitoring programme was laborious and not particularly effective; during the period 1986 to 2007 approximately 5,000 colonoscopies were performed on almost 2,000 patients and as a result ten patients underwent prophylactic colectomy due to cancer risk. Furthermore, 21 CRCs developed, 67 per cent of these were detected at the invasive stage. This suggests that tailored follow-up programmes should be provided for patients at elevated risk of CRC (family history of CRC,

dysplasia, inflammation and disease extent); disease duration and PSC should not be the only determing factors

In the current guidelines from ECCO and BSG (Cairns et al. 2010, Annese et al. 2013) the interval between surveillance colonoscopies is based on individual risk stratification, which takes into account the risk factors of disease extent, inflammation, family history of CRC, dysplasia and PSC. Patients with low risk of CRC can be scheduled for follow-up colonoscopies at five year intervals. It has been estimated that the new guidelines could also reduce the costs of surveillance by 20,000 pounds in the United Kingdom (Cairns et al. 2010). These guidelines are in line with the findings in the present study and have been implemented in our area. Further studies are warranted to assess the efficacy of these new guidelines in preventing CRC.

The strength of this cancer study was the long prospective population-based follow-up from 1986 onwards. Referral or tertiary centre based studies may overestimate the risk of cancer and population-based studies have been considered more reliable. All surgical procedures due to CRC were performed at Tampere University Hospital. The estimates of CRC in general population obtained from the Finnish Cancer Registry are extremely reliable, covering more than 95% of malignancies in Finland.

The limitations of the study included the large number of retrospective cases before 1986, consequently the total drop-out rate was only an estimate. We had no data on family history of CRC which also increases the risk of CRC. We were able to investigate the number of prophylactic colectomies in UC reliably but not in CD. The PSC-IBD population contained eleven patients from outside our catchment area, but there were no differences between patients living within or outside our area. The number of PSC-IBD patients was too small to permit any meaningful epidemiological conclusions.

4.3 Cholangiocarcinoma

The relative risk of CCA was very high in PSC-IBD patients, SIR 916.63 (95% CI 297-2140). The risk may have been overestimated due to the contemporary diagnostics and mild cases of small-duct PSC may have been missed. Liver biopsy in IBD patients undergoing colectomy showed PSC type changes in 10.5%, so PSC may be more common than we think (Aitola et al. 2000). A more active approach is warranted when a suspicion of PSC arises.

Liver transplantation is the only effective treatment to prevent CCA. In this study, two out of five patients were already in liver transplantation evaluation, which indicates the difficulty in timing liver transplantation correctly. In order to reduce the risk of CCA, the Mayo clinic has advocated surveillance of PSC patients with annual MR imaging and MRCP or ultrasound and measurement of CA19-9. ERC should be considered when CA19-9 levels are increasing or when dominant strictures are found (Razumilava et al. 2011). In Finland the systematic follow-up of patients with PSC started only recently, in 2007. This follow-up includes ERC with brush cytology and in more severe bile duct changes, DNA flow cytometry. In the case of aneuploidic flow cytometry or brush cytology RIII, a control ERC is performed within three months together with CT or MRI. If aneuploidic or RIII findings are repeated, liver transplantation is considered (Färkkilä 2013). There are new techniques such as single operator peroral cholangioscopy (SOC), which together with flow cytometry, brush cytology and CA19-9 may help to evaluate the PSC-related strictures and thereby the CCA risk in PSC patients (Siiki et al. 2014). To prevent CCA in PSC patients remains a challenge and further studies are warranted to assess these new guidelines and techniques and their long-term effects.

4.4 Mortality

Compared to general population, overall mortality was not statistically increased in UC, CD or IBD altogether (Table 23). This study was in line with population-based studies from Denmark, the Netherlands and Australia (Winther et al. 2003, Romberg-Camps et al. 2010, Selinger et al. 2013) and also a large European cohort study (Hoie et al. 2007) (Tables12 and 13). Nevertheless, the recent nationwide study from Finland demonstrated a slightly increased risk in patients with UC (SIR 1.10, 1.05-1.15) and CD (1.33, 1.21-1.46) (Jussila et al. 2014). Compared to the nationwide study, we found no increased mortality from cardiovascular diseases in patients with UC. The differences in smoking habits in different areas of Finland are insignificant and do not explain the difference in cardiovascular mortality (Vartiainen et al. 2010). Similarly, this study did not find increased mortality due to CRC which was evident in the nationwide study on patients with UC (Jussila et al. 2014). The study populations may be different, the majority of the present patients were under regular surveillance, while there was no data on the nationwide study, and patients may have been lost to follow-up. The present data may suggest that the outcome may be better with regular surveillance.

Similarly to the nationwide study we found the relative risk of dying from gastrointestinal diseases increased in patients with IBD altogether, CD, in men with UC but not in women with UC, and reduced mortality was noted in mental and behavioural disorders due to alcohol consumption (ICD-code F10). In the nationwide study F10 was included in the category of alcohol related diseases and accidents, SMR 0.54 (95% CI 0.39-0.71) (Jussila et al. 2014). The F10 category includes acute drunkenness, harmful effects of alcohol and withdrawal state with delirium. High alcohol intake has been associated with an increased risk of relapses in IBD (Hey et al. 2007), which may reduce heavy drinking in IBD patients in a country where binge drinking and alcohol-related mortality are high (Herttua et al. 2008). Whether alcohol consumption is lower in IBD population than general population is a subject for further studies.

5 Summary and conclusions

This study demonstrated a high incidence and prevalence of IBD in the catchment area of Tampere University Hospital during study period from 1986 to 1999. The catchment area covered one ninth of the population of Finland and is representative to the country as a whole. The result places Finland among the high-incidence countries alongside the other Scandinavian countries. UC was twice as common as CD in the study period. Suprisingly, similar results of an increasing incidence of IBD, especially in UC, have been reported in a nationwide study in Finland (Jussila et al. 2012), which renders the present finding more reliable. For purposes of comparison, the incidence of IBD among children has nearly tripled from 1987 to 2003 (Lehtinen et al. 2011). The reason for the increase is unknown, although environmental factors are suspected of playing an important role in the aetiology of IBD (Bernstein 2012). IBD is often diagnosed at young age and is associated with substantial morbidity (Nurmi et al. 2013). In the follow-up from 1986 to 2006 no increased overall mortality in IBD was observed, which is reflected in the increasing prevalence. This imposes a burden in the medical community; the follow-up of patients with IBD in Finland in the 1990s was focused mainly in specialized health care but has already spread to primary health care.

This population-based study on patients with IBD in the catchment area of Tampere University Hospital was based on a local IBD register. The register was established in 1986 and designed to include every adult patient with IBD in the area. The register included 1,915 patients during the follow-up period from 1986 to 2007. Meticulous efforts were made to ensure that all cases fulfilling the diagnostic criteria of IBD were indeed found. Even before 1986, nearly all symptomatic IBD patients were treated in the same centres, which participated in the prospective study, therefore the retrospective cases diagnosed before 1986 were included in the register. Diagnostic facilities including colonoscopy were readily available throughout the study period.

The relative risk of CRC in patients with IBD increased to almost a double that of general population in the follow-up from 1986 to 2007. CRC was mainly detected in patients with other risk factors than mere disease duration. These risk factors included concomitant PSC with a 20-fold relative risk of CRC, previous dysplasia,

active inflammation, extensive disease and young age at diagnosis. This study had no data on family history of CRC, which is also considered a risk factor. The surveillance programme was not very effective in finding CRC at an early curable stage, since 67% had already reached an invasive stage. Patients with concomitant PSC carry a huge, almost 900-fold relative risk of cholangiocarcinoma.

Recent recommendations from the ECCO and BSG recommend tailored monitoring according to individual risk stratification (Annese et al. 2013, Cairns et al. 2010). The present findings are in line with these recommendations; the endoscopic monitoring should be focused on patients with risk factors for CRC. High risk patients should undergo colonoscopy annually, patients with intermediate risk at two to three-year intervals. Annual colonoscopy is warranted for patients with concomitant PSC, preferably from the time of diagnosis. Patients with no additional risk factors apart from disease duration and no inflammation in the colon could be screened at five-year intervals in order to ascertain that the disease is indeed in remission. Regular follow-up is especially encouraged as it may increase adherence to treatment and reduce non-compliance. The risk of active disease and CRC may be common in patients who have been lost to follow-up. In this age of increasing prevalence the monitoring of these low-risk patients can be conducted in primary health care.

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