CLINICAL OUTCOME OF INFLAMMATORY BOWEL DISEASE WITH SPECIAL EMPHASIS ON MORTALITY AND CANCER DEVELOPMENT

The IBSEN study.

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To have a physician as a husband and father might be challenging. My wife for more than 32 years, Eva, has been more than patient. As a nurse she knows what medical work is. Our children Harald, Marit, and Rune also deserve thank for their patience and encouragement. Since the two oldest, Harald and Marit, have gone into the medical/pharmaceutical field, they obviously have not felt that working in this area is too scaring.

When I decided to start my medical education, my parents, Ruth and Harald, always gave me support. My father passed away in 1995, but my mother is strong and healthy. I want to thank them a lot.
List of papers.

Paper I

Paper II
Mortality and causes of death in ulcerative colitis: Results from 20 years of follow-up in the IBSEN study. Øistein Hovde, Milada Cvancarova Småstuen, Marte Lie Høivik, Tomm Bernklev, Gert Huppertz-Hauss, Ole Høie, Jørgen Jahnsen, Njåle Stray, Magne Henriksen, Inger Camilla Solberg, Bjørn A. Moum. Inflamm Bowel Dis 2016; 22(1):141-145

Paper III
Malignancies in patients with inflammatory bowel disease (IBD): Results from 20 years of follow-up in the IBSEN (Inflammatory Bowel South-Eastern Norway) study. Øistein Hovde, Marte Lie Høivik, Magne Henriksen, Inger Camilla Solberg, Milada Cvancarova Småstuen, Bjørn A. Moum. Journal of Crohn’s and Colitis. Epub ahead of print November 17. 2016.

Throughout the thesis the papers are referred to by their Roman numerals.
**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-ASA</td>
<td>5-aminosalicylic acid</td>
</tr>
<tr>
<td>AZA</td>
<td>Azathioprine</td>
</tr>
<tr>
<td>CCC</td>
<td>Cholangiocellular carcinoma</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRC</td>
<td>Colo-rectal cancer</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>EIM</td>
<td>Extra-intestinal manifestation</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HGD</td>
<td>High grade dysplasia</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IBSEN</td>
<td>Inflammatory Bowel Disease South-Eastern Norway</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>LD</td>
<td>Lymphoproliferative disorder</td>
</tr>
<tr>
<td>6-MP</td>
<td>6-mercaptopurine</td>
</tr>
<tr>
<td>NMSC</td>
<td>Non melanoma skin cancer</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SIR</td>
<td>Standard incidence ratio</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized mortality ratio</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UDCA</td>
<td>Ursodeoxycholic acid</td>
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</table>
2 Introduction.

The focuses in this thesis are mortality and cancer development in a cohort of Norwegian patients with inflammatory bowel diseases (IBD) twenty years after the diagnosis.

2.1 Inflammatory bowel disease, historical aspects.

Inflammatory bowel diseases (IBD) are divided into ulcerative colitis (UC) and Crohn’s disease (CD). So far we do not know the exact cause(s) of the diseases, but the assumption is that a complex interaction between genetic and environmental factors plays a key role (1, 2). The result is an inappropriate activation of the immune system located in the mucosa. The term “ulcerative colitis” was first used in 1859 by Sir Samuel Wilks (3, 4). During the next decenniums more attention was drawn to complications from UC. A very interesting article from 1964 (5) found that the percentage of patients dying in the first referred attack of UC from the year 1938 to 1942 was as high as 21.7; from 1953 to 1957 the rate had been reduced to less than 2 %. The two main obvious reasons for this improvement were that a larger proportion of patients admitted had milder disease activity, and – most importantly- therapy with glucocorticosteroids was introduced. The association between UC and cancer was described as early as in 1928 (6).

CD was reported much later than UC. In 1932, at a meeting in New Orleans Crohn, Ginzburg and Oppenheimer described “regional ileitis”. (7). Their fourteen patients displayed “a disease of the terminal ileum affecting mainly young adults, characterized by a subacute or chronic, necrotizing and cicatrizing inflammation”. They further stated that (the condition) “...is clinically featured by symptoms that resemble those of ulcerative colitis; namely, fever, diarrhoea...”. Because of the similarities, still being biologically separate diseases, UC and CD are since the 1960’s united by the term “IBD”(8).
2.2 Classification of IBD.

Many diseases are classified according to their aetiology, but this is not the case in IBD, since the causes are unknown. Numerous studies have used accepted international diagnostic criteria based on Lennard-Jones´ publication from 1989. Since UC in typical cases affects the rectum and spread upward from there, the terms proctitis, left-sided colitis, and extensive colitis are used to describe the different subgroups of UC.

At the World Congress of gastroenterology in Vienna in 1998 a uniform clinical classification system for CD was agreed upon (9). Table I shows the different categories making it possible to allocate the patients into subgroups (10).

Table I.

The Vienna classification of Crohn´s disease.

<table>
<thead>
<tr>
<th>Vienna</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>A1 &lt;40 years</td>
</tr>
<tr>
<td></td>
<td>A2 ≥40 years</td>
</tr>
<tr>
<td>Location</td>
<td>L1 Terminal ileum</td>
</tr>
<tr>
<td></td>
<td>L2 Colon</td>
</tr>
<tr>
<td></td>
<td>L3 Ileocolon</td>
</tr>
<tr>
<td></td>
<td>L4 Upper gastrointestinal</td>
</tr>
<tr>
<td>Behaviour</td>
<td>B1 Non-stricturing, non-penetrating</td>
</tr>
<tr>
<td></td>
<td>B2 Stricturing</td>
</tr>
<tr>
<td></td>
<td>B3 Penetrating</td>
</tr>
</tbody>
</table>
3 Aspects of CD and UC

3.1 Incidence, prevalence, and time-trends
The incidence of CD and UC differ depending on the region studied. North America, The United Kingdom, and the northern part of Europe are the areas in the world with the highest incidences of IBD (11-14), although the incidences have more or less plateaued the last decade (15, 16). Globally a change in the epidemiology of CD has been seen the past decades. The incidence and prevalence have plateaued in North America and the northern part of Europe, but have continued to rise in less developed areas of the world. This shift in epidemiology is thought to – at least in part – be caused by westernization of the lifestyle, improved hygiene, and changes in diet. Studies indicate that the same changes in incidences have taken place also in UC (17, 18). From the existing data one can conclude that the incidence and prevalence rates of CD and UC have increased the past decades and in all parts of the world (15, 18). Noteworthy is the recent marked increase in incidence rates in children, especially in CD (19, 20).

3.2 Gender and age at diagnosis
Epidemiological studies have shown that 50- 62 % of the diagnosed CD patients are women, and the median age at diagnosis is about 30 years (11, 13, 21-24), see table II.
Table II.
Age at diagnosis (men and women) and percentage of female CD patients.

<table>
<thead>
<tr>
<th>Area, country</th>
<th>Time</th>
<th>Females (%)</th>
<th>Median age at diagnosis (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>1986-2003</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>Denmark</td>
<td>2003-2005</td>
<td>54</td>
<td>31</td>
</tr>
<tr>
<td>Minnesota, US</td>
<td>1949-1993</td>
<td>54</td>
<td>29.5</td>
</tr>
<tr>
<td>Norway</td>
<td>1990-1994</td>
<td>52.5</td>
<td>30</td>
</tr>
<tr>
<td>Finland</td>
<td>1986-2007</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>

Usually UC is most often diagnosed between 15 and 40 years of age with a “second peak” in incidence between 50 and 80, although persons at any age can be affected (25, 26). Basically there is no gender difference in the prevalence of UC, although some studies find a slight over-representation of males (26-29).

3.3 Surgery
There have been varying reports of mortality after intestinal resection for IBD. Even if the postoperative mortality for emergency and elective cases is in the range 1-2 %, this is an important aspect to take into account (30).

3.4 Extra-intestinal manifestations
Extra-intestinal manifestations (EIMs) are common in IBD and about 25-46 % of the patients with CD will experience EIMs (31-33). The most common ones are arthritic (peripheral arthritis), dermatologic, ocular, and hepatobiliar (33, 34). Primary sclerosing cholangitis (PSC) in many ways is the most serious of them, and the most serious complication from this condition is cholangiocellular carcinoma (CCC) (32); 7 to 15 % of the patients with PSC eventually develop CCC (35, 36). PSC is associated with a four-fold increase in mortality, and main causes of death are hepatobiliary cancer, CCC and colo-rectal cancer (CRC) (37).
3.5 Mortality in CD

Population-based studies have shown a slightly decreased life expectancy in CD patients (38-40). The first one (38), a single unit study from 1981 in a series of 513 CD patients, found a two-fold increased risk of dying compared with a matched group from the general population. Men and women displayed the same overall relative risk although men were at greater risk of dying the first five years after diagnosis. Interestingly, no increase in risk of dying was found in either gender when CD was diagnosed after the age of 45. The second study (39), from Sweden, included 1469 CD patients diagnosed from 1965 to 1983. The relative survival in CD patients was found to be significantly lower than expected; 96.0 % (95 % CI 94.3-97.9) ten years after diagnosis. The extent of disease at diagnosis did not influence on the mortality. The third one, a population-based cohort study from Denmark from 2002 (40), included 374 CD patients diagnosed between 1962 and 1987. A Standardized Mortality Ratio (SMR) at 1.3 (95 % CI 1.01–1.65) was found. In this study significantly more than expected deaths in women, but not in men, were found. A meta-analysis from 2007 (41) identified 13 papers that reported SMR in CD. Most of these papers included patients diagnosed in the 1950s to the 1970s although four of them included patients diagnosed from 1980 to 1985. In this study an age-adjusted mortality risk in CD patients was more than 50% greater than in the general population, but three of the studies actually reported an SMR below 1.0. A meta-analysis from 2010 (42) also confirmed a slight increase in mortality in CD patients (SMR 1.39 (95 % CI: 1.30-1.50). Another study (43) did not show any decrease in survival curves for the total group of 373 CD patients followed for five years compared with the background population, although a small subgroup of patients diagnosed at the age of 20-29 and a subgroup with extensive small bowel disease had a slightly increased mortality. In the Netherlands 1187 patients diagnosed with IBD during a 12 years period from 1991 were included (44). The mortality in CD was comparable with the background population, but the disease-specific mortality risk was significantly increased for gastrointestinal causes. Overall, a slight increased mortality rate in CD patients has been found. This is mainly caused by malignant diseases in the
gastrointestinal tract and in the lungs (42). A nationwide study from Finland (45)
including 5315 CD patients diagnosed 1987 – 1993 and 2000 – 2007 followed up
to the end of 2010 revealed an overall increased mortality in CD patients
compared with the background population with a SMR at 1.33. A very recent
study from Quebec, Canada (46) found the all-cause mortality to be significantly
increased in CD compared with the general population; SMR was 1.45 (95% CI:
1.34-1.58), and mortality from conditions in the digestive system, all neoplasms,
digestive neoplasms, and colorectal, lymphatic, and lung cancer was significantly
increased compared with situation in the general population. A decreasing
trend, though, with time was observed in all-cause and some cause-specific
SMRs, but SMRs for lung cancer and respiratory conditions increased during the
observation period. A recent systematic meta-analysis and review of population-
based studies between 1990 and 2015 concluded that postoperative mortality in
CD patients undergoing elective surgery was significantly lower compared to
what was found in patients undergoing emergency surgery (47). In a Danish
population-based cohort study (40) 26 % (n = 22) of a total of 84 deaths observed
were directly/possibly related to the underlying CD. Fifteen of these 22 patients
died of complications of the clinical course or surgical treatment for CD.

3.6 Mortality in UC
In a Swedish study from 1992 survival was analysed for all patients diagnosed
with UC (n= 2509) in a certain region from 1965 to 1983. Ten year relative
survival rate for patients with ulcerative proctitis, left-sided colitis, and pancolitis
at diagnosis was 98 %, 96 %, and 93 %, respectively (39) and the overall relative
survival rate was 95.9 % (95 % CI 94.3-97.5). Patients with ulcerative proctitis did
not have a significantly decreased survival ten years after diagnosis (97.9 % CI
95.2- 100.0). Deaths from CRC, but not from other cancers, increased the
mortality rate.
The earlier mentioned Dutch study from 2010 (44) found that the overall
mortality in UC was comparable to the background population, but the disease-
specific mortality risk was significantly increased for gastrointestinal causes. The median follow-up time, though, for the UC patients was only 7.0 (0.1-15.0) years. A population-based study from Quebec, Canada (46), found an all-cause mortality in UC patients that was significantly increased compared with the general population (SMR 1.21, 95 % CI 1.12-1.32). Mortality from digestive, respiratory, and infectious conditions was increased compared with the background population. For patients refractory to treatment with 5-aminosalicylic acid (5-ASA) therapy options include immunosuppressive medication and surgery. The question if either surgery or long-term immunosuppressant therapy has a mortality benefit compared to the other option was raised in a retrospective matched cohort study where data from all states in the US were included (48). A total of 830 UC patients pursuing elective colectomy and 7541 matched patients with UC pursuing medical therapy were evaluated. The primary outcome was time to death, and Cox proportional hazard models were used to compare the two groups. Significant comorbid conditions were controlled for. In the elective surgery group the mortality rate was 34/1000 person-years, and in the medical therapy group the mortality rate was 54/1000 person-years. A population-based surveillance from Canada (49) using administrative databases to identify all adults (>18 y) who had been colectomized between 1996 and 2009 showed that in the 666 UC patients who underwent colectomy the mortality rate was 1.5 %. A UK study from 2007 (50) compared the mortality three years after elective surgery, no colectomy, or elective colectomy in patients admitted to hospital for IBD. One cohort was from the Oxford region in 1968-1999 and the other was from England in 1998-2003. In the Oxford region, three year mortality was lower after elective colectomy than after either no colectomy or emergency colectomy, but the differences were not significant. For England, mortality three years after elective colectomy for UC was 3.7 %. In the group without colectomy the mortality rate was 13.6 % and in the group with emergency colectomy the mortality was 13.2 %. Adjusting for comorbidity did not affect the findings. Limitations to this study are lack of detailed information about the
severity and history of the patients’ disease. As in CD mortality in emergency surgery is significantly higher than is the case in elective surgery (47). A population-based nationwide Danish cohort study found the 30-day mortality among IBD patients undergoing total colectomy to be 5.2 % (55/1056) among emergency UC cases compared with 0.9 % (8/938) among elective UC cases (51). Comorbidity, surgery in hospital performing few colectomies per year, and age > 40 years were factors associated with increased mortality in emergency cases with UC. Limitations in this study include coding error as 16 % of the patients had codes corresponding to both UC and CD. The investigators also lacked clinical parameters, and registration of rescue therapy with cyclosporine or infliximab was incomplete.

3.7 Malignancy in IBD

Epidemiological data on IBD patients based on unselected population-based cohort studies have shown increased risk of developing CRC, small bowel cancer, and extra-intestinal cancers such as lymphoproliferative disorders, skin cancers, and CCC (52). Patients exposed to thiopurines are at additional risk of lymphoproliferative disorders and skin cancers, and recent data also suggest that patients exposed to tumor necrosis factor (TNF)-α inhibitors are at a mildly increased risk of developing melanoma (53). Grade of inflammation and disease duration seem to be the main driving forces of CRC development. In extra-intestinal cancers duration of the disease and degree of immunosuppression are important risk factors (54).
4 Aims of the thesis

1. To calculate the mortality rates and risk-ratios of all cause and cause-specific mortality in a cohort of IBD patients 20 years after diagnosis.
2. To determine the prevalence of intestinal and extra-intestinal cancers.
3. To assess whether IBD patients were at an increased cancer-specific risk compared with an age- and gender-matched population.
5 Material and methods

5.1 Sample description and study design

The IBSEN study is a prospective, population-based inception study. In this study we have prospectively followed all patients (n= 756) diagnosed with IBD in the four-year period from January 1, 1990, to December 31, 1993, in four geographically well-defined areas in southeastern Norway (the counties of Oslo, Østfold, Telemark and Aust-Agder). The cohort included 519 patients diagnosed with UC and 237 patients diagnosed with CD. On January 1, 1992, the total population in the area was 966,427. The organization of the study has been described elsewhere (55, 56). Prescheduled follow-up visits were carried out at one, five, 10, and 20 (+/- 12 months) years after inclusion. At each scheduled visit the patients’ diagnoses were systematically reviewed. At the 10 years follow-up CD patients were prospectively classified according to the Vienna Classification (9). The later Montreal classification (57) did not change the parameters age, location, and behaviour. The diagnoses at the 10 years follow-up were set as the final diagnoses.

All visits included a clinical examination, a structured interview and laboratory tests. All Norwegian citizens are assigned a unique digital identification number, which makes it possible to link data from several registries and enables highly reliable epidemiological research.

Mortality data were retrieved from the Cause of Death Registry, Statistics Norway, and from hospital records. The causes of deaths were divided into four groups according to the International Classification of Diseases (ICD)-10: (1) gastrointestinal (GI) cancer (ICD-10 diagnoses C15- C26); (2) all other cancers (ICD-10 diagnoses C00-C97, except C15-C26); (3) cardiovascular diseases (ICD-10 diagnoses I00-I99); and (4) other causes (all other ICD-10 diagnoses).

Data on all cancer cases, deaths, and causes of death were collected from the Cancer Registry of Norway and from the Cause of Death Registry in Norway. All medical doctors in Norway are, by law, obliged to report new and suspected cancers to the Cancer Registry and whether the cancer is first diagnosed by
autopsy. With regard to malignancies, all individuals were observed from the date of IBD diagnosis until the first occurrence of cancer, death or end of follow-up, whichever came first. The International Classification of Diseases is the standard diagnostic tool for epidemiology, clinical purposes, and health management. All cancer diagnoses from the Cancer Registry of Norway used in this study are coded according to the ICD-10, and the first occurrence of cancer in each patient and in each of the controls is the diagnosis used in the registration.

5.2 Data management and validation
A project coordinator monitored the incoming data from the visits at one, five, ten, and 20 years. Subsequently all data were entered into a central database. At the 20 years’ visit patients were seen and examined by a nurse and a physician. Blood samples were taken, and a standardized form was filled in by the physician. In addition all the patients filled in a comprehensive questionnaire. All information was extracted from these records and manually transferred into a database. Ten percent of all the records were examined and compared with the information transferred to the computer and the proportion of incorrect data transfer was less than 0.5 %, which is acceptable.

5.3 Statistical analyses
In all papers in this thesis continuous variables were described as the median and range and categorical variables as proportions and percentages. Crude differences between proportions were assessed with the chi-square test. Each IBD patient in the IBSEN cohort was age- and sex- matched with 25 controls from the same county. Thus, each patient and his/her controls formed a unit referred to as matched set. We do not have information about regional differences in occurrence of cancer or mortality in Norway, but to exclude this possible confounder, controls were selected from the same county as their respective patients. Crude cumulative mortality, both for the entire cohort and separately for each sex, was determined using the Kaplan-Meier method. Event was defined as the
occurrence of any cancer or the first occurrence of a specific cancer. Mortality causes were based on the public death certificates. The risk ratios of all-cause and cause-specific mortality (GI cancer, all other cancers, heart disease and “other”) for the patients, compared to matched controls, were modeled with Cox regression analyses stratified by matched sets. Results are expressed as Hazard ratio (HR) with 95 % confidence intervals (CIs). Due to small number of dead patients, we have grouped causes of death as described above. Data analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 16.0 for Windows; SPSS, Chicago, IL, USA) and Stata software, version 13 (StataCorp 2013. Stata Statistical Software: Release 13. College Station, TX: Stat Corp LP).

5.4 Ethics
The Regional Committee for Medical Research Ethics for the South-Eastern Norway Regional Health Authority (REK, Helse Sør-Øst) approved the IBSEN-study. The confidentiality of patient identity and records was maintained using the guidelines suggested by the National Health Department. The study was conducted in accordance with the Helsinki declaration. All of the patients attending the 20 year follow-up study provide their written informed consent before participating.
6 Results

6.1 Mortality in CD
In our cohort, 237 patients were diagnosed with CD, including 119 (50.2%) males and 118 females. These patients were age- and sex- matched with 5876 controls (24.8 controls per CD patient). Twenty years after the diagnosis, the proportions of individuals who died in both groups were similar; 33 (13.9%) patients compared to 746 (12.7%) controls (p = 0.578). No marked differences in death from any cause were revealed. No deaths caused by small bowel malignancy were found.

Figures 2 and 3 in paper I display the cumulative mortality from the date of birth for males and females. CD patients displayed slightly higher mortality rates compared to their controls; however, the difference did not reach statistical significance (HR = 1.35, 95% CI = 0.94-1.94, p = 0.10).

When analyzed separately for each of the four main causes of death, there were no statistically significant differences in mortality risk between the patients and their controls, except for death caused by cancers excluding GI-related cancer; however, this trend was only borderline significant (HR = 2.01, 95% CI = 0.95-4.49, p = 0.07).

6.2 Mortality in UC
In our study a total of 519 patients were diagnosed with UC; 267 (51.4%) were male and 252 female patients. The patients were matched with a total of 12925 controls (24.9 controls per patient). Twelve patients had been treated with TNF-α inhibitors in the period between 10 and 20 years after diagnosis. The first ten years in the IBSEN study no patients were treated with TNF-α inhibitors. There were no deaths in the TNF-α inhibitor treated group. In the whole cohort, 61 of 263 (23%) of the men and 47 of 246 (19%) of the women had died. No significant differences between patients and controls regarding deaths from any of the causes were revealed.

Figures 1 and 2 in paper II display the cumulative mortality risk for each gender separately. When comparing overall mortality, UC patients had a slightly higher
overall mortality risk than the controls. However, the risk ratio did not reach statistical significance (HR=1.14, 95% CI 0.93 -1.40, p=0.20). Ten years after the diagnosis 49 patients had been colectomized; 25 of these colectomies were carried out the first two years after diagnosis (58). Between 11 and 20 years after the diagnosis eight more patients were colectomized. The colectomized patients were not excluded from the statistical analyses after the surgery because we wanted to follow all initial cases classified with UC for 20 years whether they had their colon intact or not. No mortality was found 30 days postoperatively. No statistically significant differences in cause-specific mortality risk between the UC patients and the controls were found when analyzed separately for each of the four main causes of death.

6.3 Malignancies in IBD
In the cohort a total of 756 patients with IBD were followed-up for 20 years. Data on all cancer cases, deaths, and causes of death were collected from the Cancer Registry of Norway and from the Cause of Death Registry. A total of 13.9 % in the IBD group and 9.7 % in the control group developed cancer. IBD patients had higher risk of cancer development compared with their matched controls. This increased risk was, however, significant only for UC patients. Male UC patients had more than twice increased overall risk of developing CRC compared with their controls (HR = 2.41, 95 % CI 1.09-5.31, p=0.029). UC patients did not have more extra-intestinal cancers than their controls. CD patients had an increased HR for trachea/lung cancer development compared with the controls. In both groups breast cancer was seen more often than expected (paper III).
6.4 Summaries of articles

Paper I:
Øistein Hovde, Irl Kempski-Monstad, Milada Cvancarova Småstuen, Magne Henriksen, Jørgen Jahnsen, Njål Stray, Inger Camilla Solberg, Bjørn Moum. Mortality and causes of death in Crohn’s disease: Results from 20 years of follow-up in the IBSEN study. Published online June 6, 2013 in advance of the print journal. Doi:10.1136/gutjnl-2013-304766

Patients with Crohn’s disease (CD) in population based studies, have been shown to have a slightly decreased life expectancy compared with the “normal population”. The primary aim of the study was to evaluate mortality and causes of death 20 years after diagnosis in a well defined population-based cohort of CD patients in Norway.

All 237 patients were age- and sex-matched with 25 persons from the same geographical area (county) randomly selected from the general population. Data on death and Causes of death were collected from the Norwegian Causes of Death Register.

There was no significant difference between CD patients and controls in overall mortality (HR = 1.35, 95 % CI 0.94 – 1.94, p = 0.10). No marked differences in deaths from GI cancer, other cancers or cardiovascular diseases in the CD group compared with the controls were found. 13.9 % and 12.7 % had died in the CD group and in the control group, respectively (p=0.578).

The conclusion was that there was no increased mortality or more deaths from cancer in the CD group compared with the general population.
Paper II:

Øistein Hovde, Milada Cvancarova Småstuen, Marte Lie Høivik, Tomm Bernklev, Gert Huppertz-Hauss, Ole Høie, Jørgen Jahnsen, Njaal Stray, Magne Henriksen, Inger Camilla Solberg, Bjørn A. Moum. Mortality and causes of death in ulcerative colitis: Results from 20 years of follow-up in the IBSEN study. Inflamm Bowel Dis 2016; 22(1):141-145

The best way to obtain knowledge about the natural history, including mortality, of ulcerative colitis (UC) is to conduct a longitudinal, population-based, prospective study. The aims of the present study were to calculate the mortality rates and causes of death in patients with UC.

A total of 519 patients (51.4 % men) with UC were included in the study over a four-year period. Mortality data were retrieved from the Cause of Death Registry and from Statistics Norway.

No statistically significant increases in total mortality or cause-specific mortality between the UC patients and the controls were found.

The conclusion was that this 20-year population-based cohort study revealed a good prognosis with regard to the mortality, which partially might be explained by the patients’ coverage by a generally well-functioning healthcare system.
Paper III:


IBD-related cancers are those attributable to chronic inflammation and/or to drug-induced immunosuppression. A broad specter of both intestinal and extra-intestinal malignancies has been linked to the occurrence of IBD. Previous research has shown that patients with longstanding IBD have had an increased risk of developing both CRC and small bowel cancer. Few longitudinal, prospective studies with focus on the association between IBD and development of malignancies have been published.

The aims of the present study were to determine intestinal and extraintestinal cancer prevalence in a well-defined, unselected, population-based cohort of IBD patients 20 years after diagnosis and to assess if IBD patients had an increased cancer-specific risk compared with the normal age- and gender-matched population.

The conclusion was that patients with a 20 years’ history of IBD had about 50 % increased risk of cancer compared with matched control from the general population; most of the excess risk was comprised by increased risk for CRC in male UC patients. In both CD and UC patients an increased HR for breast cancer compared with the controls was found and the CD patients exhibited an increased HR for trachea/lung cancer.
7 Discussion

7.1 Methodological considerations.

7.1.1 Sample description and study design.

In population-based studies like the IBSEN-study, completeness of case ascertainment is an important – perhaps the most important – factor. In the present study several steps were taken to ensure as high completeness of inclusion as possible. An extensive collaboration between general practitioners (GPs), internists, surgeons and pediatricians led to, as far as we understand, a complete inclusion of the catchment’s IBD-patients in the early 1990s. The health care system in the area was uniform with a good access to GPs, specialists, and colonoscopy. The relatively short inclusion period indicates that the study population was exposed to homogenous diagnostic methods and treatment. The follow-up rate in the study was high; five years after inclusion, up-to date clinical information was available for 94 % of the initial cohort, and five years later complete data was obtained from 90 % of patients alive. Twenty years after inclusion a total of 470 of 599 still living patients were included, resulting in completeness of 78 %. The main reason for matching is to control for confounding variables that might influence the comparison. Common variables used are age, sex, and area of living. Generally the principle in selecting controls is to select subjects who might have been cases in the study (i.e. they are “identical” except for the condition studied). To choose an appropriate control population is of very high importance to interpret the results correctly. Ordinarily, control groups should represent the source population for cases, rather than the whole non-diseased population, since the latter may differ from the source population by age, race, sex, occupation etc. In the study we had 25 controls per IBD patient. The statistical literature has discussed whether one gains precision when increasing the number of controls. To further explore this issue, our statistician performed several analyses: Cox regression model stratified by type of diagnosis (UC/CD) was fitted with two, five, ten, and 25 controls per
patient, and the conclusion was that the number of controls did not seem to influence on the HR estimates. The narrowest CI, though, was found when using 25 controls (95% CI; 1.386-2.023 vs. 1.270-2.138 when using two controls).

7.1.2 Mortality and causes of death in CD
CD is a chronic disorder that, at least so far, is not curable. Induction and maintenance of improvement of the symptoms, and, at best, induction and maintenance of mucosal healing, are the goals of treatment. Disease location, disease severity, and complications should be taken into consideration when therapeutic approach is to be decided. The present study (paper I) demonstrates that CD patients have a good prognosis without statistically significant differences in overall mortality or deaths compared with the matched control group. In none of the cases where the deaths were considered as related to CD (a total of three cases) a direct association with surgery was demonstrated. Categorizing causes of death might be complex and are not always precise. In the present study there is no reason to think that there are any differences in the classification of causes of death in the patient group compared with the control group. We chose to divide causes of death into four groups, and no statistically significance difference in mortality risk between the patients and the controls was found, although a trend towards higher mortality was seen in the non-GI cancer group. Studies conducted before the introduction of the immunomudulating agents (38, 39)(Azathioprine (AZA), methotrexate, TNF-α inhibitors) found up to two-fold increased risk of dying compared with matched groups from the general population. Since we now have other therapeutics, these results might not reflect the situation nowadays.

The cumulative use of AZA, TNF-α inhibitors, and methotrexate in the CD group in our study our study was 51%, 23.9%, and 4%, respectively. Fifty-four per cent of the patients treated with TNF-α inhibitors stopped the treatment at an early stage due to side-effect or lack of effect, giving too small numbers to outline any association between TNF-α inhibitors use and mortality.
Nine population-based studies on cause-specific and overall mortality in CD patients were used for a systematic review and meta-analysis (42). A slightly increased mortality rate in CD patients compared with the background population was confirmed (SMR 1.39, 95% CI 1.30 – 1.50). In this study a significantly increased risk of death from cancer was found (SMR 1.50, 95% CI 1.35-1.49), but no increase in CRC. We, in our study, found a trend for CD patients for a higher risk of dying from cancers outside the GI tract; the trend was only borderline significant (HR = 2.01; 95% CI 0.95-4.49; p= 0.07). In our study the median year of diagnosis (and inclusion) was 1992. In four of the nine studies in the meta-analysis (42), patients diagnosed before 1969 were included. Six of the studies had a median year of inclusion between 1971 and 1985. Thus, one possible explanation for the difference in total mortality between these two studies might be that newer diagnostic and therapeutic tools might have altered the course of the disease and also the overall mortality.

Another meta-analysis with included patients diagnosed between 1980 and 1985 (41) found the age-adjusted mortality in CD patients to be more than 50 % greater than in the general population. One of the 13 papers in this meta-analysis was “community-based” and had a SMR below 1.0 but, unlike our study, had a median observation period of six years, which makes the comparison with our study difficult.

A population-based study from Denmark including 374 CD patients diagnosed between 1962 and 1987 observed until 1997 (40) found a total of 84 deaths vs. 67 expected (SMR 1.3; 95% CI 1.01-1.56). Twenty-two of the deaths had a possible or certain connection to their CD, and an overrepresentation of gastrointestinal diseases, infections, and diseases of the urinary organs was found.

A recent, interesting prospective registry based study from Finland, with a medium follow-up time of 13.5 years included 550 CD patients (59). Fifty-one deaths were observed as compared to 45 expected giving a SMR of 1.14 (95% CI 0.84-1.49). Most of the difference was caused by deaths from disorders of the digestive system (ICD-codes K00-K93). Interestingly deaths related to mental/behavioral disorders due to alcohol use were significantly less common
in CD compared to the background population. In our study no deaths were
categorized as related to mental/behavioral disorders.

7.1.3 Mortality and causes of death in UC
Previous studies have shown an overall mortality in UC patients almost at the
same level as the background population (29). Treatment with biologics and
immunomodulators may increase the risk of malignancy and infections, and
hence the risk of death (60, 61). The present study did not demonstrate a
statistically significant increase in total mortality or cause-specific mortality in
UC patients compared with their controls (paper II). In the present study, 58 of
519 UC patients had been colectomized. No deaths were seen within the first 30
days after surgery. This is in contrast to what was found in a meta-analysis from
2007, in which 44 % of UC-related deaths were due to surgical complications
such as perforations and peritonitis (62). Although mortality related to severe
attacks of UC has substantially decreased to less than 1% in recent decades (63),
delay in time until surgery beyond 5-7 days can increase the risk of postoperative
complications and mortality (64).
The cumulative use of AZA and TNF-α inhibitors in the UC group in our study
was 12.8 %, and 3.2 %, respectively. The numbers of deaths are too small to
outline any association to AZA/TNF-α inhibitors use.

Even if colectomy in UC in many centers is performed with minimally invasive
techniques it is still regarded as a dramatic treatment option. Complications
include postoperative infections, anastomosis leakage, abscesses, reduced
fertility, sexual dysfunction, and mortality. Even if the general health improves
after removing a sick colon, and the chance of developing CRC is reduced to a
minimum, many patients experience psychosocial limitations living with an ileal
pouch anal anastomosis (IPAA) or an ileostomy. Over the past decades there has
been a decreasing colectomy rate (65, 66). This may be a consequence of a more
restrictive attitude towards surgery, as has been seen in Denmark (11, 67) or the
result of the increasing number of effective medical treatment options, such as
immune modulators and TNF-α inhibitors.
A prospective, registry-based study from Finland (24), in which 1254 patients with UC were followed for 13.5 years, showed that the overall mortality rate, in fact, was decreased (but not statistically significantly), compared with what was expected (SMR 0.90, 95% CI 0.77-1.06). In particular, there were fewer deaths from mental and behavioral disorders; this in accordance with our study.

7.1.4 Malignancy in IBD

IBD-related cancers are those attributable to chronic inflammation and/or to medical treatment of the diseases, i.e., immunosuppressive drugs/biologics (68). Both intestinal and extra-intestinal malignancies have been linked to IBD (69-74). Few longitudinal, prospective studies have focused on the association between IBD and the development of malignancies. We, in our study (paper III), found a higher risk of cancer development in IBD patients compared with their matched controls, but the increased risk was significant only for UC patients (HR = 1.40; 95% CI 1.08-1.81; p < 0.01). Stratified by gender, the data from our study revealed increased risk for all-cancers only for male UC patients (HR = 1.51; 95% CI 1.08 – 2.11, p = 0.017).

The increased risk of developing CRC in our UC cohort is in agreement with the findings in a recent meta-analysis of population-based cohort studies in UC patients (75), in which 1.6 % of the UC patients were diagnosed with CRC 14 years after diagnosis; SIRs ranged between 1.05 and 3.1, with a pooled Standard incidence ratio (SIR) of 2.4 (95% CI, 2.1-2.7). Among the factors in favor of developing CRC were male gender (men with UC had a greater risk than women with UC (SIRs 2.6 vs. 1.9)) and extensive colitis.

A Danish study (72) did not find an increased overall risk of CRC in UC patients compared with the general population during the first 10 years after diagnosis, which is in accordance with results from the IBSEN study 10 years after UC diagnosis (76). However, a colectomy rate more than twice as high as in other European centers indicates that there has been a different treatment approach in the Danish study (66, 76).
Risk factors for CRC include the duration of the colitis, together with the degree and extent of inflammation, in addition to the presence of PSC and family history of CRC (77). In a long-term, nationwide population-based Danish cohort study with 30 years of follow-up, the authors concluded that patients with CD and UC were at increased risk for developing intestinal and extra-intestinal malignancies (78). The authors further concluded that the risk of GI malignancy has decreased in recent years and that this decrease has occurred without an increase in the overall risk of malignancy. These findings suggest that the benefits of current treatment strategies outweigh the cancer-related risks. A large-scale Finnish registry study, where 21,964 IBD patients were followed up for 10.8 years (79) found a higher incidence of cancer in male patients compared with the background population; with a higher SIR for CD than for UC (1.23; 95 % CI, 1.09-1.38 vs. 1.08; 95 % CI, 1.02-1.14). The authors reported an SIR of 1.73 (95 % CI, 1.30-2.26) in male UC patients and 1.92 (95 % CI, 1.38-2.59) in female UC patients for colon cancer and 1.65 (95 % CI, 1.18-2.26) and 1.96 (95 % CI, 1.26-2.91) for male and female patients, respectively, for rectal cancer. In CD, no overall increased risk for developing CRC was found in either gender, which is in accordance with our findings. The Finnish study, though, found an increased risk of rectal cancers in patients aged 30-44 years (both genders), and also in colon cancer in males aged 30-44 years. They also found more anal cancers than expected (SIR 24.6: 95 %CI 5.07-71. 9), but the numbers of cancer were low. One possible cause for this increased risk might be long-standing perianal fistulae causing a challenging diagnostic problem. Our study included substantially fewer patients but involved a follow-up time that was almost twice as long as in the Finnish study. In addition we had a defined control group. The study from Finland also showed that UC patients had an excess number of biliary tract cancers (SIR, 7.26; 95 % CI, 4.37-11.13) and that male patients with UC had an increased risk of Hodgkin lymphomas (SIR, 2.45; 95 % CI, 1.06-4.81), although no association with use of immunomodulators was observed. In our study, we found a high HR for biliary tract cancers in UC
patients compared with the controls, but the CI was wide; therefore, straightforward conclusions cannot be drawn. A meta-analysis from 2006 found the relative risk (RR) of small bowel cancers in CD patients compared with the background population to be as high as 33.2 (80). The study from Finland (79) found the risk of small intestine cancer in CD patients to be about 10-fold higher than what was expected. In our cohort one case of small bowel cancer was found in the CD group and four cases were found in the controls, which means a six-fold increase in the CD group, but again, because of the low numbers, it is impossible to draw conclusions.

In general, there is a higher percentage of smokers/ex-smokers in the CD population than in the general population and in the UC population (76, 81). Therefore, it was surprising that the Finnish study did not find an increased SIR for lung/tracheal cancers (SIR, 1.14; 95 % CI, 0.71-1.74) in CD patients. The UC patients, however, were found to have a slightly reduced risk of developing lung/tracheal cancers (SIR, 0.79; 95 % CI, 0.62-0.98). In our study, CD patients had increased risk of lung/tracheal cancers (HR = 3.24; 95 % CI, 1.28-8.19; p = 0.013), whereas UC patients and their controls had equal incidences of these cancer types.

In a meta-analysis from 1996 to 2009 comprising approximately 17,000 patients with IBD, the patients were found to have the same overall risk of developing extra-intestinal cancers as the background population (74). In this study, CD patients had an increased risk of cancer of the upper GI tract, lungs, urinary bladder, and skin. UC patients, in contrast, had an increased risk of liver/biliary tract cancers and leukemia but a decreased risk of pulmonary cancer. Our study also found an increased risk for breast cancer in IBD patients compared with their controls. Breast cancer resistance protein (BCRP), an efflux transporter protecting the enterocytes from toxic compounds, has been reported to be downregulated in patients with active UC. In newly diagnosed drug-naive patients with UC, Gutmann et al found that BCRP was significantly reduced compared with controls without UC (82). Patients not responding to treatment with 5-ASA or prednisone also had reduced levels of BCRP. These data suggest
possible associations that might be relevant in the pathogenesis of breast cancer (83). A study from Taiwan (84) found that the incidence of breast cancer in the IBD group as a whole was similar to that found in the control cohort. Interestingly the risk was significantly increased in patients requiring hospitalization ≥ twice per year, compared with the control cohort (HR 8.45; 95% CI 4.64-15.4). A study that aimed to assess the prevalence of all malignancies in first-degree relatives of CD patients found a two-fold higher frequency of breast cancer in (female) relatives of the CD patients compared with the controls (85). It seems that the mothers are at particular risk (86). First degree female relatives were compared with relatives of patients that did not have evidence of GI disease. Mothers of CD patients had a higher risk for developing breast cancer than their controls (3.6% vs 1%, p = 0.009; Odds ratio (OR) = 3.7, 95% CI 1.4-10). The mechanisms behind this potential association are unclear; a common genetic factor for CD and breast cancer might be present (86). Long-lasting inflammation is known to upregulate oxidative stress and hence DNA damage. Whether immunosuppression is related to breast cancer development is a possibility. Of the 19 patients in our study diagnosed with breast cancer two had been treated with thiopurines, and no patients had been treated with methotrexate or biologics.

IBD patients, especially those treated with thiopurines, seem to be at increased risk of developing non melanoma skin cancer (NMSC) (87). In a recent European Crohn’s and Colitis Organization (ECCO) pathogenesis scientific workshop, the authors stated that the risk of developing melanoma in patients receiving thiopurines for IBD is not increased, whereas the risk is increased by the use of TNF-α inhibitors (68). Furthermore, in a retrospective cohort and nested case-control study (88), each of a total of 108,579 IBD patients was matched to four individuals without IBD. Patients with CD had the highest incidence rate of melanoma (incidence rate ratio (IRR), 1.45; 95% CI, 1.13-1.85) compared with the whole group of IBD patients (IRR 1.29; 95% CI 1.09 –1.53). The incidence rate of NMSC was also increased among patients with IBD (IRR, 1.46; 95% CI, 1.40-1.53). Patients treated with biologics displayed an increased risk of melanoma
compared with patients not treated with biologics (OR = 1.88; 95 % CI, 1.08-3.29). Patients treated with thiopurines had an increased risk of NMSC compared with patients not treated with thiopurines (OR, 1.85; 95 % CI, 1.66-2.05). Data from the IBSEN study did not reveal any statistically significant increase in risk of melanoma in either diagnosis, but an increase in risk of NMSC compared with the controls was found in UC patients (HR 2.95, CI 1.18-7.37, p= 0.021)(paper III). IBD patients treated with thiopurines seem to have a three- to five-fold increased risk of developing lymphoproliferative disorders (LDs) compared with the background population, especially three forms of LD: hepato-splenic T-cell lymphoma, Epstein- Barr-Virus-related post-transplant-like LD and post-mononucleosis lymphoproliferations (68, 89, 90). The overall risk of developing lymphoma in thiopurine treated patients, however, is low, and a lack of association in our study may be present because relatively few patients received immunomodulators. Interestingly, a pooled analysis of data from 1594 CD patients concluded that the incidence of malignancy with the TNF-α inhibitor adalimumab monotherapy was not greater than that of the general population, but co-administration of immunomodulator therapy was associated with a greater than expected incidence of malignancies other than NMSC (SIR = 3.04; 95 % CI, 1.08 -11.06) (91).

7.1.5 Medication and cancer.
Even if corticosteroids, in some studies, have been found to have beneficial effects on cancer development (in most of the studies, though, statistical significance was not reached), the frequent and serious adverse effects associated with chronic use more than outweigh the potential positive effects (92). The demonstrated clinical efficacy and favourable safety profile of the different 5-ASA derivates is the background for the advice for their use as the first-line therapy in the treatment of mild to moderate UC. Oral 5-ASA also has been, and still is, used in the treatment of CD. Even though treatment with 5-ASA seems to have a limited value in the treatment of CD, could it be that this treatment is beneficial in prevention of CRC? A Swedish landmark study found a relative risk
of CRC at 5.6 for CD patients with exclusively colonic involvement, as compared to a relative risk of 3.2 for patients with ileocolic involvement, and 1.0 for those with ileal involvement (93). The CRC risk in CD is comparable to that in UC when controlled for similar extent of disease (94). A meta-analysis including nine case control and cohort studies showed a protective association between regular use of 5-ASA and CRC in UC patients (OR = 0.51, 95 % CI, 0.37-0.69) (95). If we assume that the risk of CRC development in CD and UC are comparable, this meta-analysis supports a protective association between 5-ASA and CRC also in CD patients. Later, however, a study from the Manitoba IBD epidemiology database did not find a protective benefit in patients on 5-ASA therapy for one year or longer and five years or longer (OR 1.04, 95 % CI 0.67-1.62 and OR 2.01, 95 % CI 1.04-3.9, respectively) in IBD patients (96, 97). Interestingly this study (97) found that males who had been treated with 5-ASA for more than five years, had an increased risk of CRC-development. In our study 75 % of those still alive 20 years after diagnosis with a history of CRC had been treated with 5-ASA 2-3 grams daily during the last ten years. Exact information about the use of 5-ASA in the dead patients is lacking.

A recent review on the effect of AZA or 6-mercaptopurine (6-MP) for the maintenance of remission in CD (98) concluded that both AZA and 6-MP had positive effects on maintaining remission, but if they have any antineoplastic effects is questionable. The initial studies evaluating the chemopreventive benefits from AZA/6-MP showed divergent results; most of them demonstrating no benefit, but also no increased cancer risk (96). The first prospective study of the epidemiology of high grade dysplasia (HGD) and cancer in IBD patients treated with thiopurines concluded that in patients with long-standing, extensive colitis (>10 years) and extent of at least 50 % of the colon, multivariate adjusted HR for colorectal HGD and CRC was 0.28 (95 % CI 0.1-0.9; p = 0.03)(99). However, thiopurines per se lack evidence of demonstrating antineoplastic mechanisms to suggest any benefit in reducing the risk of HGD/CRC; therefore, these effects most likely are due to the anti-inflammatory effects. The molecular mechanisms of TNF-α inhibitors in colitis have suggested a possible
antineoplastic effect from TNF blockade. In a study in mice (100) an increase in the levels of TNF-α and infiltrating TNF receptors in the colonic mucosa/submucosa before the development of colonic tumours were found. The cumulative use of AZA in our study was 51% in the CD group and 12.8 % in the UC group, and the cumulative use of TNF-α inhibitors was 16 % in the CD group and 2.3 % in the UC group. The numbers of CRCs are too small to outline any association to use of AZA/ TNF-α inhibitors.

One crucial question is whether medical treatment for IBD can be a potential risk for cancer development. A recent review (101) supports that TNF-α inhibitors used alone or in combination with thiopurines do not increase the overall cancer risk in IBD. There is evidence that use of TNF-α inhibitors and thiopurines used alone or in combination are associated with increased risk of lymphoma. Methotrexate may be considered instead of AZA in young males with a need for TNF-α inhibitors in combination with an immunomodulator (102). Treatment with thiopurines is associated with increased risk of NMSC. TNF-α inhibitors may increase the risk of developing melanoma (103). Still, the absolute rates of these malignancies are low, and should be weighed against the benefits that these therapies give. The IBSEN study started earlier than the introduction of TNF-α inhibitors. During the study period, this therapeutic approach came into use; in fact, 23.9 % of our CD-patients have been treated with TNF-α inhibitors. As is the case with AZA the numbers are too low to draw conclusions on the association between treatment and cancer development.

In patients with concomitant diagnosis of CD and PSC the risk of development of CRC/colonic dysplasia was examined in a retrospective study with 35 CD patients with PSC. Follow-up was 10 years, and no increase in risk for dysplasia of the colon was found (104). Ursodeoxycholic acid (UDCA) has a molecular mechanism that decreases the colonic concentration of bile acids. The results from clinical studies (105, 106) are conflicting. At present the use of UDCA for chemoprotective reasons is not recommended.
7.1.6 Strengths and limitations of the present studies

The strengths of the present studies include the longitudinal follow-up of an unselected and well-defined cohort within a well-characterized geographical area. The limited time during which inclusion took place and the fact that dedicated specialists and hospitals were responsible for the diagnostic procedures are factors that contribute to a uniform diagnostic and therapeutic approach. People in Norway do not tend to move very often, and it is therefore easier to conduct prospective studies that last for many years. All living patients had the same length of follow-up, and each patient had 25 age- and sex-matched controls from the same geographical area. There is no reason to assume that inclusion in the IBSEN study influenced on the diagnoses made or on the classification of cause of death in the IBD patients compared with the background population. All citizens in Norway are assigned a unique ID number, which enables easy and accurate identification and linkage of medical and death certificate records.

There were some limitations to the studies. Even with the high number of patients in this follow-up study, the occurrence of cancers seen implied a limited statistical power. At diagnosis, the median age of the UC and CD patients was 38 and 29 years, respectively (107, 108), indicating that the patients were relatively young, even 20 years later. Hence it is possible that an extended observation period would reveal increased numbers of IBD-related cancers and mortality within this group.

Finally, one could argue that the present study already is outdated; new therapies, including immunomodulators and biologics, might have changed the prognosis in IBD patients. In the last years of the study period a certain number of patients were treated with these “new” drugs, but mainly we can argue that this study reflects the course of the diseases on “traditional” IBD treatment, which is useful as background data for future studies.
7.1.7 What have we learned from the first 20 years in the IBSEN study?

- A prerequisite for performing these studies is the fact that there are trustworthy registries, like the Cancer Registry of Norway and the Cause of Death Registry in Norway. The unique digital identification number assigned to all Norwegian citizens makes it possible to link data from several registries and enables highly reliable epidemiological research.
- The overall mortality risk in UC patients was slightly higher than in the controls, but the risk ratio did not reach statistical significance.
- No increase in cause-specific mortality risk in the UC patients was found.
- No overall increase or cause-specific mortality in CD patients was found.
- IBD patients had a higher risk of cancer development than their matched controls.
- The cancer-specific risk was higher in UC than in CD patients compared with their controls.
- Males with IBD had an overall increased risk of developing CRC compared with their controls.
- Women with IBD had an overall increased risk of developing breast cancer compared with their controls.
8 Summary
The IBSEN study has prospectively followed all patients diagnosed with IBD in a defined four-year period at the beginning of the 1990s. It was designed as a prospective population-based inception cohort-study, used internationally accepted diagnostic criteria and had standardized, prescheduled follow-up visits. This approach, together with the limited time during which the inclusion took place and the fact that dedicated specialists and hospitals were responsible for the diagnostic procedures, represent major strengths of the present study. The fact that dedicated clinicians have been in charge of the study, intellectually and practically, increases the quality of the study. In addition there has been meetings and discussions about practical and theoretical issues throughout the years. Norwegians do not tend to move very often; his makes it easier to perform prospective studies that continue for many years. Other strengths in the present study are the fact that all patients had the same duration of follow-up in identical period of time, and each patient was age- and sex-matched with controls with the same age, gender and area of living. The fact that each individual born in Norway is assigned a unique ID-number enables easy and accurate identification and linkage of medical and death records. There were some limitations to the study: The number of patients – even so large in a prospective, inception cohort for a long follow-up, had occurrence of few cancers and also few deaths, due to the fact that the patients, on average, still were quite young twenty years after being diagnosed with IBD. The number of patients implied a limited statistical power.

8.1 Future research
From this population-based cohort study we have learned a lot about long-term mortality risk and cancer development. A longitudinal study with larger numbers of patients would have given more robust information. If such studies are to be conducted the influence of the “newer” drugs also could have been assessed, but in this field the evolution goes fast, so what we call “new drugs” today will be “old drugs” tomorrow. In future epidemiological studies focus
could be on etiology, microbiota, risk factors for cancer development, epigenetic considerations, but also on quality of health, health economy, and extraintestinal manifestations. Such longitudinal studies require dedicated researchers with long perspectives. The Nordic countries are well suited for studies like this.
9 References


10 Articles I-III