Prognosis of inflammatory bowel disease across time and countries

An epidemiological study of population-based patient cohorts

Tine Jess

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Department of Medical Gastroenterology, Herlev Hospital, Herlev, Denmark.

Correspondence: Institut for Sygdomsforebyggelse, Øster Søgade 18, 1., 2100 Copenhagen K, Denmark.

E-mail: tj@ipm.regionh.dk

Official opponents: Finn Diderichsen and Anders Ekbom, Sweden.

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1. INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), commonly referred to as inflammatory bowel disease (IBD), are chronic intestinal diseases of partly unknown etiology.

UC has been recognized as a disease entity since the 19th century, whereas CD was not properly described until the 1930s [1, 2]. Both diseases are characterized by a chronic relapsing or continuous disease course with intestinal inflammation causing varying gastrointestinal symptoms, such as diarrhea, passage of blood, pus, or mucus, abdominal cramps, fever, and weight loss. Onset of disease frequently occurs at young age and the incidence of both diseases is continuously increasing [3]. Diagnosis is based on clinical, radiological, endoscopical, and histological findings according to internationally well-established criteria[4]. Since the middle of the 20th century, the treatment of both CD and UC has primarily consisted of maintenance therapy with 5-aminosalicylic acid preparations (5-ASAs, including sulfasalazine), corticosteroids in cases of flare, and surgery in lack of response to medical treatment. In recent decades, a number of immunosuppressive drugs have been added to the treatment regimen.

The course and prognosis of IBD has been assessed in varying patient settings throughout the years. *Truelove et al.* [5, 6]introduced the discipline of epidemiology in IBD research, recognizing the essentiality in using diagnostically well-defined and unselected patient groups for studies on disease course and prognosis. In Denmark, a country providing optimal conditions for epidemiological research due to free access to health care and thorough registration of citizens, the discipline was taken up by Professor Povl Riis in the late 1950s. Together with *Bonnevie et al.* [7] *Binder et al.* [9-11], and *Hendriksen et al*. [12], Riis founded the two population-based Copenhagen County cohorts of patients with CD and UC, which in the theses by *Munkholm* [13] and *Langholz* [14] were followed until 1987 regarding disease incidence, course and prognosis. These studies have been widely cited for their comprehensive description of demographic and clinical characteristics of patients with IBD, the influence of disease on working capacity and social life, and the frequency of surgery during the disease course. On the other hand, it has been questioned whether the promising prognostic findings were biased by a relatively short median follow-up time of patients (CD, 8.5 years; UC, 12 years) as results were in contrast to findings from other countries.

For many reasons, it is crucial to obtain reliable data on long-term prognosis of IBD and on factors influencing prognosis. As aforementioned, patients are often young when diagnosed with IBD and may have many concerns regarding the impact of disease on their life. Secondly, in many countries access to health care depends on health care insurances and reasonable access to such. Furthermore, with the continuous increase in the prevalence of IBD, knowledge of prognosis and prognostic factors is essential for optimal health care planning. Lastly, to be able to determine whether implementation of new treatment strategies impose a positive effect on long-term prognosis in patients with IBD – or whether the risk of cancer and death actually increases due to severe adverse events – it is crucial to have consistent prognostic data from phenotypically well-defined patient cohorts treated according to previous treatment regimens for comparison.

2. AIMS

With the ambition of mapping long-term prognosis in patients with IBD deriving from different parts of the world and diagnosed from the earliest of systematic registration of IBD patients and up to the new millennium, the aim of the present thesis became:

1. To assess long-term mortality and risk of cancer in the Danish 1962-1987 cohort of patients with CD after prolonging the observation time by another decade and to extend analyses to also include estimation of cause-specific mortality and extra-intestinal cancer occurrence.
2. To assess a population-based cohort of patients with IBD diagnosed in Olmsted County, Minnesota, 1940-2001, in order to describe cancer risk and mortality in a patient setting similar to the Danish, but of different geographic origin.
3. To assess occurrence and prognosis of colorectal dysplasia in the Olmsted County cohort.
4. To investigate putative risk and protective factors for colorectal neoplasia (dysplasia and cancer) in IBD by performing a nested case-control study of neoplasia cases and individually matched controls from Copenhagen County and Olmsted County.
5. To further evaluate differences in prognosis a) over time, by comparing course and prognosis in three consecutive Danish IBD cohorts, and b) across countries, by conducting two systematic reviews and meta-analyses of, respectively, cancer risk in patients with CD and mortality in patients with UC belonging to well-defined population-based patient cohorts.

Although the aims of the present thesis evolved in the above mentioned order, results will be presented in their expected sequence: 1) dysplasia, 2) cancer, and 3) mortality.

3. MATERIAL AND METHODS

3.1 PATIENT POPULATIONS

3.1.1 Copenhagen County

The Copenhagen County cohort consisted of 1534 county residents (374 CD, 1160 UC) diagnosed with IBD during 1962-1987. The strict diagnostic criteria were based on clinical, radiological, endoscopical, and histological characteristics and have been described in detail previously [13, 14]. Copenhagen County is a suburban area around central Copenhagen, comprising approximately 550,000 inhabitants (when excluding the two municipalities on the island of Amager) or 10% of the Danish population. Except for a slightly higher level of education, the socio-economic status of the Copenhagen County population is similar to that of the general Danish population.

All patients were followed until emigration, death, or end of the study (December 31, 1997) regarding occurrence of cancer and mortality. Information on vital status was retrieved from the Danish Central Person Registry.

Two additional inception cohorts of patients diagnosed with IBD during 1991-1993 and 2003-2004 in Copenhagen County, respectively, Copenhagen County and City were included in Paper VII and have been described in detail elsewhere [3, 15, 16].

Table 1. Demographic and clinical characteristics of patients with inflammatory bowel disease, Copenhagen, Denmark, 1962-2005 (Paper VII).

	COHORT I, 1962-1987		COHORT II, 1991-1993		COHORT III 2003-2004	
	CD	UC	CD	UC	CD	UC
No. of patients (% of cohort)	374 (24%)	1160 (76%)	58 (39%)	89 (61%)	209 (39%)	326 (61%)
Female:male ratio	58:42	53:47	66:34	57:43	54:46	51:49
Median age (range) at diagnosis, years	33 (8-84)	34 (2-88)	35 (16-79)*	40 (15-87)*	32 (10-85)	38 (2-95)
Median time (range) from onset to diagnosis, years	2.2 (0-27)	1.0 (0-37)	0.5 (0-9)	0.4 (0-8)	0.7 (0-48)	0.4 (0-34)
Extent of CD at diagnosis						
Ileum	29%		9%		31%	
Ileocolon	33%		29%		24%	
Colon	30%		43%		37%	
Other**	8%		19%		8%	
Extent of UC at diagnosis						
Proctitis***		44%		60%		31%
Leftsided/substantial colitis****		36%		16%		42%
Extensive colitis/pancolitis****		18%		25%		27%

*) Only patients aged > 15 years at diagnosis; **) Other extent of CD was defined as 'no ileal or colonic involvement' in Cohort I and as 'gastrointestinal involvement proximal to the terminal ileum regardless of any other disease location' in Cohort II and III; ***) Proctitis was defined as 'mucosal changes seen by rigid sigmoidoscopy and a normal appearance of the colon proximal to the rectum on barium enemas' in Cohort I, as 'inflammation limited to 15 cm from the anal verge' in Cohort II, and as 'inflammation limited to the rectum' in Cohort III; ****) Extent of disease proximal to the rectum was recorded as substantial colitis or pancolits in Cohort I and as leftsided or extensive colitis in Cohort II and III

3.1.2 Olmsted County

The Olmsted County cohort comprised 692 residents diagnosed with IBD (314 CD and 378 UC) between 1940 and 2001 according to well-defined criteria based on clinical, radiological, endoscopical and histological characteristics [17-19]. Olmsted County is situated in Minnesota, US, with the majority of people residing in Rochester, which is the urban center of an otherwise rural county. Olmsted County had a population of approximately 124,000 in the 2000 US Census. Eighty-nine percent were non-Hispanic white and a substantial part was of Northern European heritage. Although 25% of county residents are employed in health care services (versus 8% nationwide), and the level of education is consequently higher (30% have completed college versus 21% nationwide), the residents of Olmsted County are otherwise socio-economically similar to the U.S. white population.

Patients were followed from diagnosis until emigration, death, or end of the study (May 31, 2004) and until end of year 2002 regarding dysplasia and cancer.

3.2 METHODS OF DATA COLLECTION

3.2.1 Dysplasia and cancer

In Copenhagen County, information on intestinal and extra-intestinal cancer diagnoses was obtained from the Danish National Cancer Registry, containing information on cancer diagnosed by physicians, surgeons, pathologists, and general practitioners. In Olmsted County, the medical record linkage system contained information on dysplasia and cancer diagnosed at out-patients clinic visits, hospitalizations, surgical interventions, and pathology examinations, including autopsy.

In both counties, medical records were reviewed to verify the neoplasia diagnosis and to obtain demographic and clinical data on patients, including information on location, type, and stage of cancers, and details on dysplasia and recurrence or progression of such. Furthermore, family history of colorectal cancer (CRC), concomitant diagnosis of primary sclerosing cholangitis (PSC), smoking history, no. and type of procedures performed during the disease course, use of medications, and surgical interventions were recorded. For the nested case-control analysis, the same data were recorded for controls (outlined in Paper IX).

The original histology slides from colonoscopies or colectomies of patients with colorectal dysplasia were retrieved from the Mayo Clinic pathology archive and reviewed by a gastrointestinal pathologist blinded to the previous results. Since patients had been included in the cohort from year 1940 to 2001, the definition of dysplasia used by the original pathologists may not have been consistent. At review, the dysplasia diagnosis was determined by use of the IBD Morphology Study Group criteria [20].

3.2.2 Mortality

Both in Copenhagen and in Olmsted County, death certificates were retrieved for all patients who had died, in order to register the underlying cause of death according to the International Classification of Diseases (ICD), Ninth and Tenth Revision. Subsequently, hospital records were examined in order to confirm the cause of death and to reveal any relation to IBD.

3.2.3 Meta-analyses

In order to identify papers on intestinal cancer risk in CD, respectively, mortality in UC, two systematic MEDLINE searches were conducted using MESH terms in combination with a free text search. In addition, recent abstracts available on CD-rom from the American Digestive Disease Weeks and the United European Gastroenterology Weeks were searched for relevant literature. Reference lists of all included papers were scrutinized to disclose additional literature on the topic in a multiphase process. Papers were included in the meta-analyses if the patient group studied was a population-based cohort of CD patients, respectively, a population-based inception cohort of UC patients diagnosed according to well-defined criteria. In addition, papers should report the total number of patients observed, exact numbers of intestinal cancers or deaths occurring in the cohort during follow-up, expected numbers in a matched background population, and/or rates of observed to expected events with 95% confidence intervals (CI). In case of duplicate publications the paper providing the longest follow-up of patients was used.

3.3 STATISTICAL ANALYSES

For clinical characteristics, continuous variables were reported as median and range and dichotomous variables summarized using proportions.

3.3.1 Dysplasia

The overall cumulative probability of colorectal dysplasia from diagnosis of IBD and the cumulative probability of recurrence or progression of dysplasia in patients who had not undergone total proctocolectomy at the time of dysplasia diagnosis were estimated by use of the Kaplan-Meier method.

The univariate associations of clinical and demographic variables with the risk of recurrence or progression of dysplasia were assessed

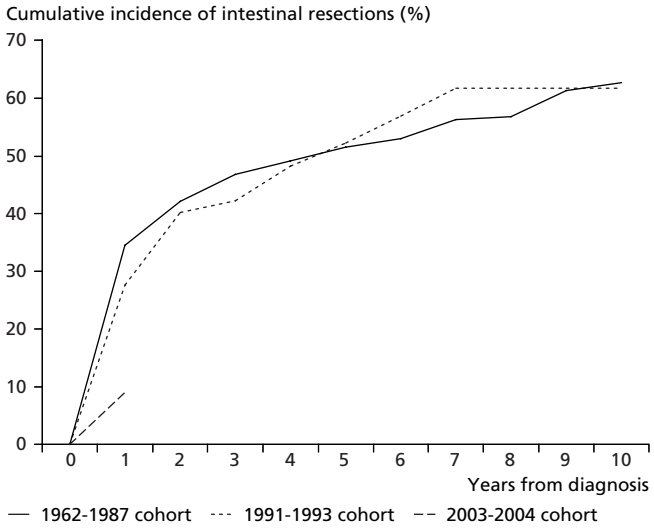

Figure 1. Cumulative incidence of intestinal resections according to calendar period of diagnosis among patients with Crohn's disease from Copenhagen, Denmark (Paper VII).

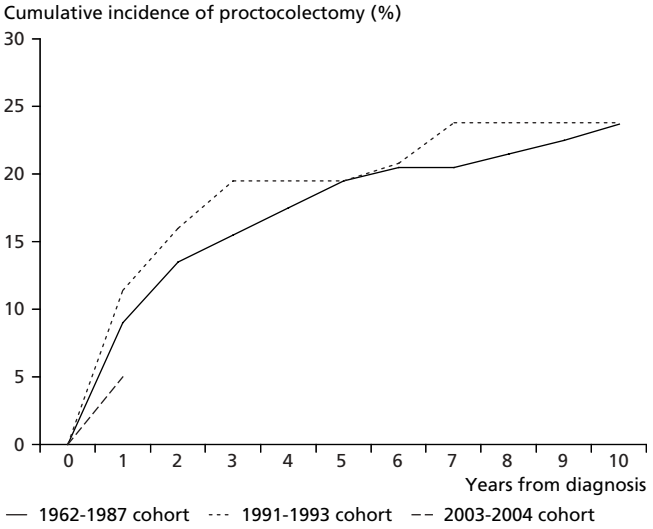

Figure 2. Cumulative incidence of proctocolectomy according to calendar period of diagnosis among patients with ulcerative colitis from Copenhagen, Denmark (Paper VII).

using Cox proportional hazards regression. Hazards ratios (HR) with 95% CIs based on the regression estimates were reported.

3.3.2 Cancer

The risk of cancer relative to the general population was estimated using standardized morbidity or incidence ratios (SMR or SIR, observed/expected numbers) with 95% CI assuming a Poisson distribution for the observed number of cancers. Expected numbers were calculated using the observed age- and gender-specific person-years at risk in the cohort combined with age- and gender-specific cancer rates from the Danish National Board of Health (Danish population, 1995) and the Surveillance, Epidemiology, and End Results (SEER) database (Iowa white population, 1973-2000). For purposes of estimating CRC risk, person-years of follow-up were censored at total proctocolectomy. The overall SIR for intestinal cancer was stratified by gender, age at diagnosis, calendar year at diagnosis (Olmsted), duration of disease (Olmsted), initial extent of disease (Copenhagen) and maximal extent of disease (Olmsted).

In Olmsted, the cumulative incidence of CRC from time of IBD diagnosis was estimated using the Kaplan-Meier product-limit method and compared to expected occurrence by use of the one-sample log-rank test.

3.3.3 Mortality

Cumulative survival was calculated from the date of IBD diagnosis to last follow-up using the Kaplan-Meier product limit method and, in Olmsted County, compared to expected survival by use of the one-sample log-rank test. Expected numbers were calculated on the basis of person-years at risk in the cohort and age- and gender matched mortality figures for the background population (the 1995 Copenhagen County background population, respectively, the 1960-2000 U.S. White population).

For specific causes of death, standardized mortality ratios (SMR) for observed compared to expected deaths were calculated with 95% CI.

In sub-analyses, SMRs for overall mortality were stratified by gender, age at diagnosis, calendar period of IBD diagnosis, extent at diagnosis (Copenhagen), maximal extent (Olmsted), years of observation after diagnosis (Copenhagen), and by immunosuppressive/biological medication usage (any use of azathioprine, 6-mercaptopurine, methotrexate, or infliximab versus none; Olmsted).

In Olmsted County, Cox proportional hazards regression analysis was used to determine if age at diagnosis, gender, calendar period of diagnosis, or maximal extent were independent predictors of mortality. These results were expressed as HRs with 95% CI.

3.3.4 Meta-analyses

If SIRs, SMRs or identical estimates of cancer or mortality were reported without 95% CIs, the interval was calculated using observed and expected number of cancers and assuming a Poission distribution of observed cases. Subsequently, pooled SIRs or SMRs with 95% CIs were calculated using the STATA meta-analysis program (Stata Corporation, Texas; www.stata.com). According to the heterogeneity test (significance at a 5% level) either a fixed or a random effects model was applied.

Meta-regression analyses were performed in order to evaluate whether the SMR or SIR were influenced by cohort size, mean or median observation time, middle year in the inclusion and observation period, calendar year of publication, percentage of patients being males, percentage of patients aged <40 years at diagnosis, percentage of UC patients with proctitis only at diagnosis, and percentage of patients with colonic or small bowel CD.

3.3.5 Nested Case-control analysis

Each potential risk/protective factor was assessed using conditional logistic regression analysis in which the matched sets (cases and their controls) were considered as separate strata. All models included age and calendar year at diagnosis as co-variates, and the results were given as adjusted odds ratios (ORs) with 95% CIs (SAS®/STAT Users Guide Version 8, PROC PHREG, Example 49.3, [SAS Institute Inc., Cary, NC]). Subsequent to overall analysis, the same analyses were performed for: 1) cases from Olmsted County and cases from Copenhagen County separately; and for 2) Olmsted County cases with cancer, respectively, cases with dysplasia, each analysis incorporating the corresponding matched controls.

4. RESULTS

4.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENT POPULATIONS

4.1.1 Copenhagen County (Papers I, II, VII)

The 374 CD patients (58% women) were followed for a median of 17 years (range, 1-36 years) or 6569 person-years. The 1160 UC patients (53% women) were followed for a median of 19 (range, 1-36 years) or 22,290 person-years (prior to proctocolectomy). Among CD patients, approximately $^1/_3$ had ileal disease, $^1/_3$ had ileocolonic disease and $^1/_3$ had pure colonic disease at the time of diagnosis. Among UC patients, 44% had proctitis or proctosigmoiditis, 36% had more substantial colitis, and 18% had pancolitis at diagnosis. Demographic and clinical characteristics of the two following cohorts from Copenhagen (Cohort II, diagnosed during 1991-1993

Table 2. Medical treatment of inflammatory bowel disease in Copenhagen, Denmark, 1962-2005 (Paper VII) and Olmsted County, Minnesota, US, 1940-2001 (Paper IV).

	Copenhagen, 1962-1987		Copenhagen, 1991-1993		Copenhagen, 2003-2004		Olmsted, 1940 -2001	
	CD N=374	UC N=1160	CD N=58	UC N=89	CD N=209	UC N=326	CD N=314	UC N=378
Median follow-up time (yrs)	17	19	10	10	1	1	11	13
Ever treated with								
5-aminosalicylic acid*	83%	88%	90%	93%	61%	83%	71%	73%
Systemic steroids**	44%	53%	76%	56%	66%	40%	43%	30%
Azathioprine/6-MP			28%	13%	34%	10%	25%***	12%***
Cyclosporine/methotrexate			3%	1%	1%	1%		
Infliximab			10%	0%	5%	1%		

*) Oral administration of any 5-aminosalicylate including sulfasalazine; **) Oral administration of budesonide or prednisolone or intravenous hydrocortisone; ***) Any of azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, or infliximab. 6-MP: 6-mercaptopurine

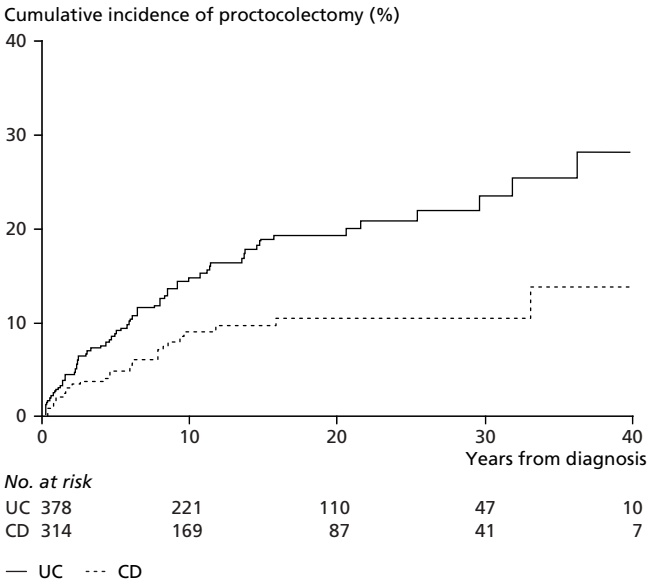

Figure 3. Cumulative incidence of proctocolectomy in patients with Crohn's disease and ulcerative colitis from Olmsted County, Minnesota, 1940-2001 (Paper VI).

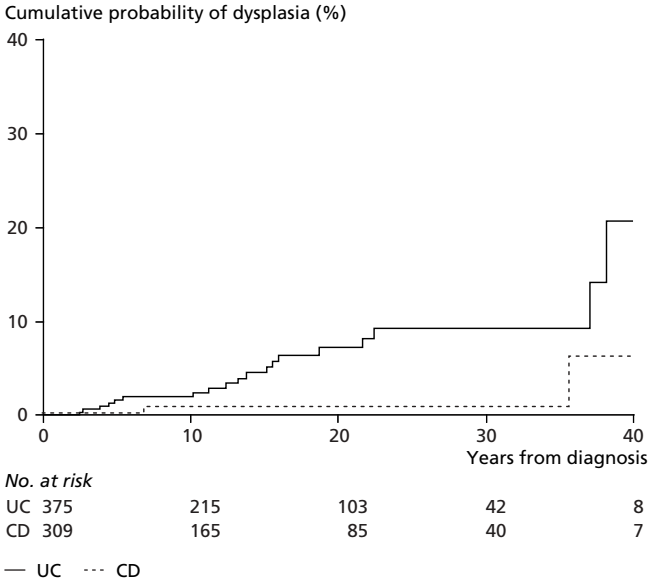

Figure 4. Cumulative incidence of dysplasia (flat dysplasia, dysplastic lesion or mass, and adenoma) among Olmsted County, Minnesota, residents diagnosed with Crohn's disease or ulcerative colitis in 1940-2001 (Paper V).

and followed until 2003; Cohort III, diagnosed during 2003-2004 and followed until 2005) appear from Table 1. The cumulative probability of intestinal resections in CD patients and of proctocolectomy in UC patients in Copenhagen during 1962-2005 is shown in Figure 1 and Figure 2, and medical treatment of the three cohorts is listed in Table 2.

4.1.2 Olmsted County (Papers IV, V, VI)

The 314 CD patients (51% women) were followed for a median of 13 years (range, 0-54 years) or 4946 person-years (4456 person-years prior to proctocolectomy). The 378 UC patients (44% women) were followed up for a median of 15 years (range, 0-58 years) or 6360 person-years (5567 person-years before proctocolectomy). Among CD patients, 29% had maximal extent involving the upper GI tract or ileum only, 41% had ileocolonic disease, and 30% had pure colonic disease. Among UC patients, 17% had proctitis, 35% had left-sided or substantial colitis, and 47% had pancolitis as maximal extent. The cumulative probability of total proctocolectomy after 15 years of disease duration was 10% in CD patients and 19% in UC patients (Figure 3). Medical treatment of the Olmsted cohort appears from Table 2.

4.2 INCIDENCE AND PROGNOSIS OF COLORECTAL DYSPLASIA

There is a lack of population-based studies on the incidence, fate and ideal management of dysplasia in IBD. In particular, it has not been possible to formulate a consistent international recommendation of either immediate prophylactic colectomy, increased frequency of surveillance colonoscopies, or unchanged regular clinical follow-up of patients with IBD who are diagnosed with flat low-grade dysplasia (fLGD).

4.2.1 Own results (Paper V)

During a median observation time of 13 years in UC, respectively, 11 years in CD prior to colectomy, 29 Olmsted County cohort patients (4%) developed flat dysplasia (n = 8), dysplasia associated lesions or masses (DALMs; n = 1), adenoma-associated lesions or masses (ALMs) in areas of IBD (n = 18), or ALMs outside areas of IBD (n = 2). The cumulative incidence of colorectal dysplasia (including flat dysplasia, DALM, or ALMs) among UC patients was 1.9% (95% CI, 0.4-3.5%) at 5 years and 9.2% (4.5-14.3%) at 25 years. Among CD patients, it was 0% at 5 years and 0.5% (95% CI, 0-2.2%) at 25 years (Figure 4).

At review of 24 available histology slides, the pathologist blinded to the previous results agreed with the original diagnosis in 83% of cases. Disagreement was observed in 43% of flat dysplasia or DALM cases and in 6% of adenoma cases. The 'worst' diagnosis given by one of the two pathologists was used in the following.

Among six patients with fLGD who did not undergo colectomy, none progressed to high grade dysplasia or cancer during a median of 18 years of observation (range, 6-21 years) with a median of 3 surveillance colonoscopies (range, 0-12). However, two patients had reoccurrence of fLGD (Figure 5).

Among 18 patients with ALMs in areas of previous or current in-

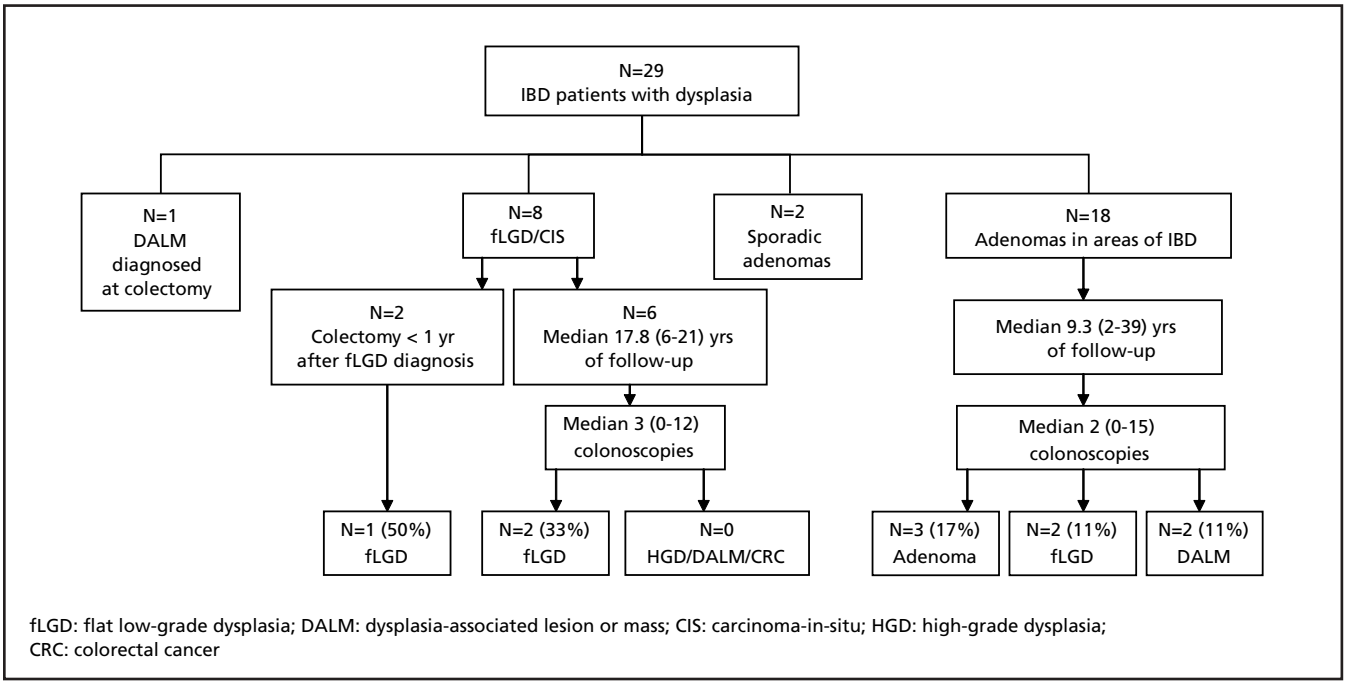

Figure 5. Flowchart of follow-up and progression of colorectal dysplasia in 29 Olmsted County, Minnesota, residents diagnosed with inflammatory bowel disease in 1940-2001 (Paper V).

flammation, followed for a median of 9 years (range, 2-39 years) with a median of 2 colonoscopies (range, 0-15), three patients (17%) had reoccurrence of ALMs, two (11%) developed fLGD in the area of the previous adenoma, and two patients (11%) developed DALMs (Figure 5).

The actuarial risk of recurrence or progression of dysplasia among patients with flat dysplasia or ALMs in areas of IBD was 8% (95% CI, 0-19%) at 5 years, 27% (95% CI, 6-45%) at 10 years, and 47% (95% CI, 9-71%) at 20 years.

Univariate analyses showed a significantly increased risk of recurrence or progression of neoplasia in patients with a concomitant diagnosis of PSC (HR, 5.0; 95 % CI, 1.1-23) and in patients with first event of dysplasia localized proximal to the splenic flexure (HR, 5.4; 95 % CI, 1.0-28). Age at diagnosis of IBD, age at diagnosis of dysplasia, gender, disease location, smoking habits (categorized as current, former, never), and use of 5-ASA drugs for more than three months during the disease course were not significantly associated with risk for recurrence/progression of neoplasia.

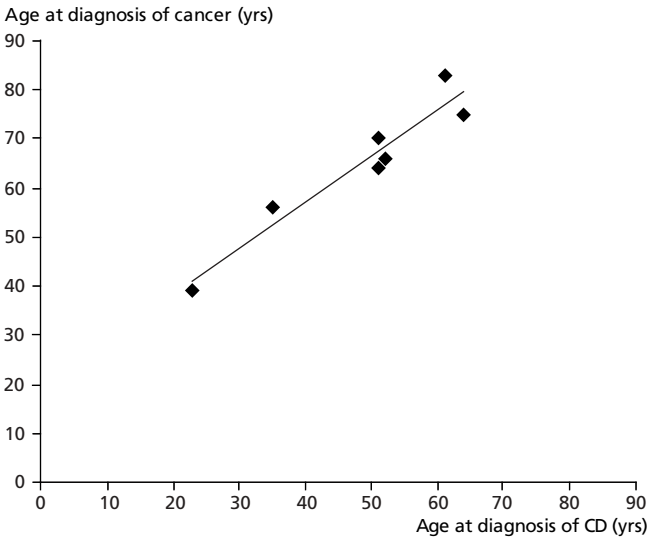

Figure 6. Eight intestinal cancers were observed in 7 of 374 patients with Crohn's disease (CD), Copenhagen County, 1962-1997. The age at CD diagnosis was significantly correlated to the age at cancer diagnosis, as cancer occurred after 11-22 years disease duration (median 16 years) (p = 0.03, Spearman's test; Paper II).

4.2.2 Discussion

In accordance with data from a colonoscopic surveillance program in Leads, UK [21] but not with other American studies [22, 23], this population-based study from North America showed a surprisingly low progression rate for colorectal fLGD and a relatively high progression rate for ALMs in IBD.

There are several explanations for the discrepancy in reported results. First of all, studies from referral centers are typically based on selected patient populations with extensive, long-standing and probably not well-controlled disease, whereas our study was based on an unselected cohort of patients with all variants of IBD. Furthermore, studies become less comparable when different outcome measures are used, such as progression to more severe stages of dysplasia or cancer, cancer only, or mortality from cancer. Obviously, the magnitude of risk increases with number of outcome measures applied, and one has to question whether it is reasonable to use anything 'less' than cancer as a measure of outcome, since only cancer per se may have a fatal ending. In our study, cancer was not the only measure of outcome. Otherwise, prognosis had looked even better, since no patient actually developed cancer during follow-up. Lastly, studies should ideally compare risk of CRC in patients with and without an initial diagnosis of fLGD belonging to the same patient population. This was not done directly in our study, but Paper VI revealed that the risk of CRC was not increased in the overall patient population either.

The overall inter-observer agreement was fairly good (83%), but less so when looking at the fLGD diagnosis only (57%). In the study from Leeds, pathologists from different institutions reached consensus on a diagnosis of fLGD in 38% of cases only [21], thus delineating the problem with recommending immediate proctocolectomy to patients with fLGD. This problem will probably not be solved until better endoscopic detection techniques [24] are implemented, and even then, the risk of progression of fLGD still has to be questioned and held against the risk of morbidity and mortality in relation to surgery.

Regarding other neoplastic lesions in IBD, several referral centers have reported relatively favorable experiences with endoscopic man-

Table 3. Colorectal cancer risk in inflammatory bowel disease during 1962-2005 in Copenhagen County, Denmark (Paper II and VII).

	Crohn's disease				Ulcerative colitis			
	total	observed/ expected cancers	SIR	95% CI	total	observed/ expected cancers	SIR	95% CI
COHORT I (1962-1987)	374	4/3.5	1.1	0.3-2.9	1160	13/12.4	1.04	0.6-1.8
Women	217	2/1.8	1.1	0.1-3.9	619	6/6.2	1.0	0.4-2.1
Men	157	2/1.7	1.2	0.1-4.2	541	7/6.3	1.1	0.5-2.3
COHORT II (1991-1993)	58	1/0.6	1.6	0.04-9.1	89	1/0.3	3.1	0.1-17
Women	38	1/0.4	2.7	0.1-15.1	51	1/0.2	5.8	0.2-32
Men	20	0/0.2	-	-	38	0/0.2	-	-
COHORT III (2003-2004)	209	1/0.1	11.1	0.3-62	326	0/0.3	-	-
Women	113	0/0.1	-	-	166	0/0.1	-	-
Men	96	1/0.04	25.0	0.6-139	160	0/0.1	-	-
Total	641	6/4.2	1.4	0.5-3.1	1575	14/13.0	1.1	0.6-1.8

*95% confidence interval excluding 1.0 (p<0.05)

Table 4. Population-based literature on intestinal cancer occurrence in patients with Crohn's disease (Paper III).

Author, Country	Calendar period (publication year)	Patients No.	Mean or median follow-up	Patients with CD affecting colon, No. (%)	Observed/ Expected no. of CRC	SIR of CRC (95% CI)	Patients with CD affecting the small bowel, No. (%)	Observed/ Expected no. of SBC	SIR of SBC (95% CI)
Jess T, USA	1940-2002 (2005)	313	14 yrs	-	6/3.2	1.87 (0.69-4.07)	-	3/0.07	41.1 (8.5-120)
Persson PG, Sweden	1955-1984 (1994)	1251	15 yrs	790 (63%)	5/5.63	0.89 (0.29-2.07)	1019 (81%)	4/0.26	15.6 (4.3-40)
Jess T, Denmark	1962-1997 (2004)	374	17 yrs	250 (67%)	4/3.52	1.14 (0.31-2.92)	244 (65%)	4/0.06	66.7 (18.1-171)
Ekbom A, Sweden	1965-1983 (1990)	1469	11 yrs	830 (50%)	-	2.20 (1.0-4.3)	1040 (63%)	1/0.3	3.4 (0.1-18.6)
Fireman Z, Israel	1970-1980 (1989)	274	10 yrs	155 (57%)	1/0.88	1.14 (0.03-6.33)	196 (72%)	0/ -	0.0 (-)
Bernstein C, Canada	1984-1997 (2001)	2857	7 yrs*	-	29/13.72	2.11 (1.41-3.04)	-	5/0.29	17.4 (4.2-73)

*) Calculated as no. of person-years of observation divided by no. of patients in cohort.

Table 5. Standardized incidence ratio (SIR) of extra-intestinal malignancies in 374 patients with Crohn's disease, Copenhagen County, Denmark, 1962-1987 (Paper II).

Category (ICD-10)	Observed cancers	Expected cancers	SIR	95% CI
Upper GI (140-151)	1	1.8	0.6	0.01-3.1
Liver and bile ducts (155-156)	2	0.9	2.2	0.3-8.0
Pancreas (157)	0	0.8	0.0	-
Lung (162-163)	9	4.5	2.0	0.9-3.8
Breast (170)	5	5.4	0.9	0.3-2.2
Cervix uteri (171)	2	0.9	2.3	0.3-8.1
Corpus uteri (172-174)	1	0.9	1.1	0.03-6.0
Prostate, testis (177-178)	1	1.5	0.7	0.02-3.7
Kidney, bladder (180-181)	1	2.6	0.4	0.01-2.2
Melanoma (190)	3	1.5	2.0	0.4-5.9
Skin squamous (191)	11	6.9	1.6	0.8-2.9
Brain (193)	1	1.1	0.9	0.02-4.9
Thyroid (194)	1	0.2	5.6	0.1-30
Lymphomas (200-203)	0	1.4	0.0	-
Leukemia (204-205)	1	0.7	1.4	0.04-8.0
Other (ICD remaining numbers)	1*	3.7	0.3	0.01-1.5
Total (140-205)	40	34.7	1.2	0.8-1.56

*) A female patient with a non-specific abdominal cancer

agement of polypoid dysplastic lesions [25-27]. In a recent review it was therefore recommended that sporadic adenomas in patients with IBD, in contrast to flat dysplasia and DALMs, should not lead to increased surveillance or to proctocolectomy [28]. However, the results of the present study, with 22% of ALM patients developing fLGD or DALMs during follow-up, one has to question whether ALMs require the same degree of vigilance and surveillance as fLGD in IBD, and further population-based studies on the subject are clearly needed.

- For the time being, colectomy for fLGD in IBD only seems justified in subgroups of patients with PSC or other accepted risk factors for CRC and only after the diagnosis has been confirmed by a second independent gastrointestinal pathologist.
- In $^1/_5$ of patients, ALMs arising in areas of IBD progress to more advanced stages of dysplasia.

4.3 CANCER RISK IN CROHN'S DISEASE

Although focus in the literature has been more on risk of CRC in UC than in CD, quite a few studies on intestinal cancer risk in CD have been published throughout the years [29-34]. The conflicting results of these studies may partly be due to differences in study populations. Relatively few studies have been population-based, and even fewer have assessed the risk of both intestinal and extra-intestinal malignancies in patients with CD.

4.3.1 Own results (Papers II, III, VI, VII)

In Copenhagen County, the risk of CRC was still close to unity after a median observation time of 17 years of the 1962-1987 cohort (SIR, 1.1; 95% CI, 0.3-2.9) and a median observation time of 10 years of the 1991-1993 cohort (SIR, 1.6; 95% CI, 0.04-9.1). The overall SIR in the three Copenhagen cohorts was 1.4 (95% CI, 0.5-3.1) (Table 3). Still, all intestinal cancers occurred in areas affected by CD and a significant correlation between age at diagnosis of CD and age at diagnosis of intestinal cancer (i.e. disease duration prior to cancer) was observed in Paper II (Figure 6).

In Olmsted County, a non-significantly increased risk of CRC (SIR, 1.9; 95% CI, 0.7-4.1) was observed. The meta-analysis of all identified population-based studies on the subject (Paper II, VI and [32-35]; Table 4) revealed a similar but now significantly increased SIR of 1.9 (95% CI, 1.4-2.5) which was later corrected to 1.8 (95% CI, 1.4-2.5; Figure 7) after inclusion of an Italian study not identified in the original literature search [36]. The meta-analysis also showed that the risk of colonic cancer among patients with CD (SIR, 2.5; 95% CI, 1.7-3.5) was higher than the risk of rectal cancer (SIR, 1.4; 95% CI, 0.8-2.6).

In Olmsted County, the actuarial analysis showed a cumulative incidence of CRC among CD patients of only 2.4% (95% CI, 0.0%-5.8%) as compared with 1.6% expected after 25 years (log-rank, p = 0.66).

Stratification by age, gender, disease extent at diagnosis, and disease duration did not reveal any subgroups at significantly increased risk of CRC in Copenhagen County, whereas in Olmsted County,

male patients younger than 30 years at diagnosis of CD were at increased risk of CRC (SIR, 22; 95% CI, 2.7-80). The meta-analysis showed that patients with pure colonic CD carried a higher risk for CRC (SIR, 4.3; 95% CI, 2.0-9.4) than patients with ileocolonic CD (SIR, 2.6; 95% CI, 0.8-8.2) or pure ileal disease (SIR, 0.9; 95% CI, 0.2-4.1).

The risk of small bowel cancer was increased both in Copenhagen County (SIR, 67; 95% CI, 18-171), Olmsted County (SIR, 41; 95% CI, 8.4-118) and in the pooled meta-analysis estimate (SIR, 27; 95% CI, 15-49) (Figure 8). Risk estimates were in general high due to the rarity of this condition in the background population. No small bowel cancers were observed in the more recent Copenhagen cohorts. In the 1962-1987 cohort, the excess risk was found to be confined to patients with pure ileal disease at diagnosis of CD (SIR, 200; 95% CI, 54-512) whereas all but one had developed ileocolonic CD at the time of cancer diagnosis. Likewise in Olmsted County, the three small bowel cancers all occurred in patients with ileocolonic CD. All cancers (four adenocarcinomas in Copenhagen and an adenocarcinoma, a lymphoma, and a leiomyosarcoma in Olmsted) occurred in areas of previous or present inflammation.

In Copenhagen, a total of 40 extra-intestinal cancers were observed as compared to 34.7 expected (SIR, 1.2; 95% CI, 0.8-1.6). There was no significant difference between observed and expected numbers in any of the classification groups. However, a trend towards increased risk of pulmonary cancer (SIR, 2.0; 95% CI, 0.9-3.8) and squamous skin cancer (SIR, 1.6; 95% CI, 0.8-2.9) was observed. No lymphomas were observed (Table 5).

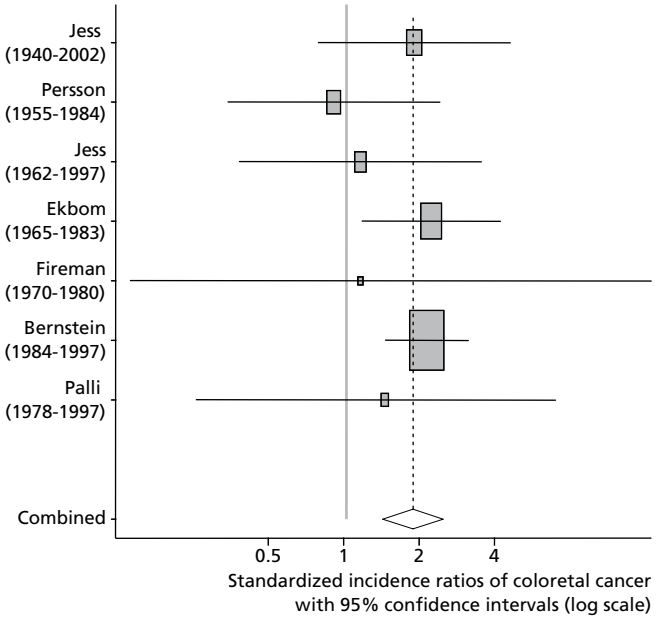

Figure 7. Individual and combined standardized incidence ratios (with 95% confidence intervals) of colorectal cancer in patients with Crohn's disease belonging to population-based patient cohorts (Paper III).

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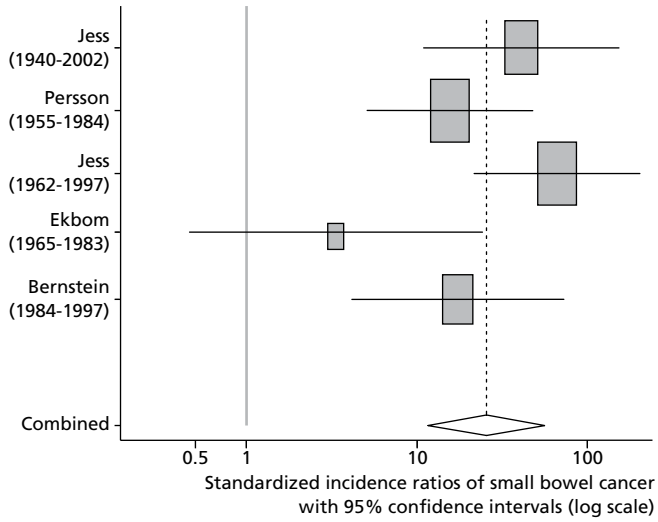

Figure 8. Individual and combined standardized incidence ratios (with 95% confidence intervals) of small bowel cancer in patients with Crohn's disease belonging to population-based patient cohorts (Paper III).

4.3.2 Discussion

Even when studying population-based cohorts exclusively, a slightly – but significantly – increased long-term risk of CRC and a significantly increased risk of small bowel cancer were observed among patients with CD, in part confirming results from former referral center studies [29-31]. The overall risk of extra-intestinal malignancies was not increased, whereas patients carried a trend towards increased risk of pulmonary cancer and squamous skin cancer.

One objection which could be raised against the studies from Copenhagen County and Olmsted County is that they were both extensions of former studies. However, extending the observation period to >10 years, assumingly increased the likelihood of detecting cancers caused by long-standing intestinal inflammation. Accordingly, the median time from diagnosis of CD to diagnosis of cancer was 16 years in Paper II. The question remains, whether further extension of the observation period would reveal a more pronounced excess risk of CRC or not.

The results of the meta-analysis were employed in the chapter on cancer occurrence and prevention in a recent national consensus on treatment of IBD (National Board of Health, Denmark, 2006). However, a meta-analysis is never better than the studies upon which it is based and identification of relevant papers is not implicit, despite well-defined search criteria, as objected by *Palli et al.* [37] and acknowledged by our group. The finding of an increased risk of CRC should be interpreted with caution, since most of the available studies were older of date and therefore representing patient populations belonging to former treatment eras. On the other hand, the follow-up time of patients diagnosed in the new millennium (the 2003-2004 cohort) – with access to biological agents from time of diagnosis – was by natural means low. The essential question therefore remains, whether new treatment strategies will effectively reduce the risk of intestinal cancer by reducing the time with active CD and if a putative reduction in intestinal cancer risk will be truly beneficial to patients or instead be counterweighted by an increased risk of opportunistic infections and other types of cancer, such as lymphoma, as suggested by *Ljung et al* [38] and *Kandiel et al.* [39]. When it becomes possible in the future to assess the impact of new treatment strategies on long-term cancer risk in patients with CD, former results from well-characterized patient populations may erve as the best standard of comparison.

Analyses of extra-intestinal cancer risk were limited by lack of power. However, the trend towards increased risk of pulmonary cancer observed in Copenhagen was in accordance with former studies by *Persson et al.* [32] and *Palli et al* [40]and may be explained by the high frequency of smokers among patients with CD [41, 42]. Likewise, the risk of squamous skin cancer was significantly increased among patients with CD in a study from Sweden [43]and one could hypothesize that the excess risk was confined to patients with dermatologic manifestations of CD. This remains, however, to be investigated.

A recent study of Swedish IBD patients belonging to regional cohorts and/or identified in the Swedish Inpatient Register suggested an increased risk of lymphoma among patients with CD early in the disease course but not long term [44]. In accordance with other population-based studies [32, 40, 43, 45], we did not observe an increased risk of lymphoma among patients with CD.

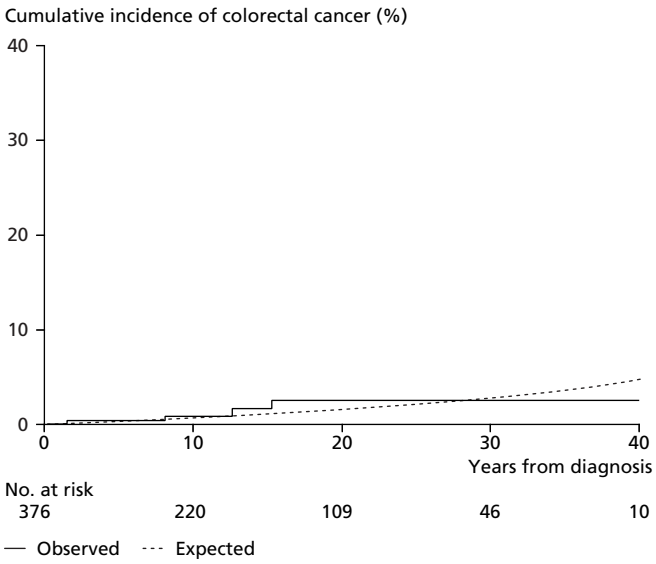

Figure 9. Cumulative incidence of colorectal cancer in patients with ulcerative colitis, Olmsted County, Minnesota, 1940-2002, compared to expected incidence of cancer (SEER, Iowa Whites, 1973-2000) (Paper VI).

– Clinicians should be aware of the slightly increased risk of CRC in patients with especially colonic CD. Still, prospective studies of patients treated according to contemporary guidelines are needed.
– The seemingly increased risk of pulmonary cancer in CD is yet another reason for encouraging patients to quit smoking.

4.4 COLORECTAL CANCER RISK IN ULCERATIVE COLITIS

The risk of CRC in UC has been widely debated and presumptions based on often selected patient materials have led to guidelines regarding both treatment and surveillance of patients.

4.4.1 Own Results (Papers VI, VII)

In Copenhagen, the risk of CRC in patients with UC was not significantly increased in any of the three regional cohorts and the overall SIR for the last five decades was 1.1 (95% CI, 0.6-1.8) (Table 3).

In Olmsted County, the risk of CRC in patients with UC followed for a median of 13 years prior to proctocolectomy was close to unity (SIR, 1.1; 95% CI, 0.4-2.4). The SIR stratified by maximal extent increased from 0 (95% CI, 0.0-3.5) in patients with proctitis only to 2.4 (95% CI, 0.6-6.0) among those with extensive colitis or pancolitis. No excess risk of CRC was observed in any subgroup when stratifying SIR by gender, age at diagnosis, or disease duration. All cancers occurred in patients diagnosed with IBD before 1980. The median age at diagnosis of IBD among cancer patients was 34 years (range, 30-58 years), and the median age at CRC diagnosis was 51 years (range, 38-66 years). The median survival with CRC was one year (range, 1-20 years). The cumulative incidence of CRC (after exclusion of two cases diagnosed within 30 days of IBD diagnosis) was 2.0% (95% CI, 0%-4.9%) vs. 2.3% expected after 25 years of observation (log-rank test, p = 0.55; Figure 9).

4.4.2 Discussion

The most important lesson to draw from Papers VI and VII was the consistent finding of a non-increased overall risk for CRC among patients with UC. The Danish and American cancer estimates were markedly lower than the ones reported in population-based studies from Canada [35], Israel [46], and Sweden [47]. Furthermore, the cumulative probability of CRC of 2% after 25 years as observed in Olmsted County was noticeably lower than the 5.9% after 20 years and 8.7% after 30 years reported by *Eaden et al.* in a recent meta-analysis of CRC in UC [48].

The variations in risk estimates between different population-based cohorts could be due to differences in 1) study designs or population characteristics, 2) treatment regimens, or 3) background populations used for calculation of risk estimates.

The study by *Bernstein et al* [35] may be the largest one of its kind, but the method of patient collection differed markedly from the other population-based studies and phenotypic characterization of patients was partly lacking. If a large number of patients in the Canadian study had extensive disease, which was found to be a risk factor for CRC in the Olmsted study, this may have explained the increased overall risk of CRC in the Canadian cohort. The Israeli study [46] was older of date – in accordance with the fact that all CRCs in Olmsted County occurred in UC patients diagnosed prior to 1980. The Swedish study [47] was somewhat larger than the Olmsted County study, whereas results from Copenhagen cannot be explained by small number of patients or person-years of follow-up.

Regarding treatment policies – especially the potential influence of close follow-up with early onset corticosteroid treatment in case of flare and/or early colectomy in case of medical treatment failure – available data were primarily descriptive and not straightforwardly comparable.

The observed difference in risk estimates between regions could also reflect differences in cancer-related background population characteristics, as for example the prevalence of smokers, which secondly would affect the denominator of reported SIRs. Actually, in the American study, we observed slightly different SIRs when using background rates from, respectively, Olmsted County (SIR, 1.5; 95% CI, 0.5-3.2) and SEER (SIR, 1.1; 95% CI, 0.4-2.4).

The meta-analysis by *Eaden et al* [48] is widely cited although the design of the study was somewhat problematic. Due to broad inclusion criteria, the analysis was based on a variety of literature, from true population-based cohort studies to referral center studies, surgical series, and surveillance programs. Expected numbers were in general lacking and it was therefore not possible to calculate pooled SIRs. The results of the meta-analysis should therefore be interpreted with caution and should not be used uncritically for prognostic information of newly diagnosed UC patients or for justification of surveillance or other cancer preventive interventions in these patients in general.

The promising finding of the Olmsted study was acknowledged in an Editorial called 'The changing face of colorectal cancer in inflammatory bowel disease: progress at last!' [49], although results were similar to those already reported from Copenhagen [50]. The editorial raised the important question, if results of the Olmsted study reflected a successful prevention strategy?

Based on results from the above mentioned population-based studies from other regions and the meta-analysis by *Eaden et al.*, it is reasonable to assume that selected subgroups of UC patients, especially those with extensive disease, are at increased risk of developing cancer. It also seems reasonable to believe that our own promising results reflect the handling of patients in Copenhagen and Olmsted County. The present studies could, however, not be used to determine whether it was the medical/surgical treatment, the close follow-up, surveillance (only practiced in Olmsted), or yet other causes that resulted in an overall risk of CRC in UC similar to that of the background population.

– The newly diagnosed patient with UC has a future risk of CRC similar to that of the background population.

4.5 RISK FACTORS FOR COLORECTAL NEOPLASIA

It is of clinical importance to identify subgroups of IBD patients at increased risk of developing colorectal neoplasia and, as outlined above, to elucidate the ideal management of such subgroups in order to avoid occurrence of neoplasia. Studies on this issue all seem to differ in design and in variables assessed or adjusted for, and they have in general not been based on case-control data from true population-based IBD cohorts.

Table 6. Univariate analyses of potential risk factors for colorectal neoplasia in patients with inflammatory bowel disease: A nested case-control study from Copenhagen County (1962-1997) and Olmsted County (1940-2002) (Paper IX).

Variable	Cases (N = 43)	Controls (N = 102)	Adjusted OR*	95% CI
Patient factors, n (%)				
Colorectal cancer in a first degree relative	4/33 (12)	6/77 (8)	1.4	0.3-5.9
Primary sclerosing cholangitis	6/43 (14)	2/102 (2)	6.9	1.2-40
Smoking during the disease course	7/42 (17)	26/99 (26)	0.3	0.1-1.1
Disease activity				
Percentage of disease course with active disease (per 5% increase), median (range)	20 (5-100)	19 (27-100)	1.2	0.99-1.4
Period of > 1 year with continuous symptoms, N (%)	13/43 (50)	11/102 (11)	3.2	1.2-8.6
X-ray procedures, median (range)				
No. of barium enemas during the disease course	2 (0-14)	3 (0-12)	1.1	0.9-1.3
No. of small bowel x-rays during the disease course	1 (0-9)	0 (0-14)	1.3	0.96-1.6

*Odds ratios are adjusted for age and calendar year at diagnosis

Table 7. Univariate analyses of potential protective factors for colorectal neoplasia in patients with inflammatory bowel disease: A nested case-control study from Copenhagen County (1962-1997) and Olmsted County (1940-2002) (Paper IX).

Variable	Cases (N = 43)	Controls (N = 102)	Adjusted OR *	95% CI
Follow-up and surveillance				
> 2 outpatient clinic visits per year on average, N (%)	26/41 (63)	60/95 (63)	2.7	0.8-8.4
No. of out-patient clinic visits per year, median (range)	1.3 (0-9)	1.3 (0-9)	1.4	0.96-2.0
> 2 hospitalizations during disease course, N (%)	14/42 (33)	17/98 (17)	3.8	1.1-13
No. of hospitalizations during disease course, median (range)	2 (0-15)	1 (0-20)	1.3	1.0-1.6
No. of proctoscopies during disease course, median (range)	6 (0-49)	7 (0-54)	1.0	1.0-1.1
≥ 1 sigmoidoscopy during disease course, N (%)	15/43 (35)	24/102 (24)	4.1	1.1-14
No. of sigmoidoscopies during disease course, median (range)	0 (0-11)	0 (0-18)	1.2	1.0-1.5
≥ 1 colonoscopy during disease course, N (%)	32/43 (74)	45/102 (44)	5.1	1.9-14
No. of colonoscopies during disease course, median (range)	0 (0-10)	0 (0-5)	1.4	1.0-2.1
≥ 1 surveillance colonoscopy during disease course, N (%)	16/43 (37)	18/102 (18)	5.3	1.4-20
No. of surveillance colonoscopies during disease course, median (range)	0 (0-10)	0 (0-5)	1.5	0.8-2.5
Macroscopic inflammation score (grade 0-4), median (range)	2 (0-4)	2 (0-4)	1.3	0.6-2.9
Microscopic inflammation score (grade 0-4), median (range)	2 (0-4)	3 (0-3)	0.7	0.3-1.5
Biopsies from no. of different sites of colon (1-8), median (range)	7 (0-8)	6 (0-8)	1.4	0.7-2.6
Treatment				
Sulfasalazine – cumulative dose (per 1000 gram), median (range)	2.9 (0-29)	2.2 (0-19)	1.1	1.0-1.3
Sulfasalazine – > 2g/day during entire disease course, N (%)	36/43 (84)	88/102 (86)	1.1	0.3-3.7
Mesalamine – cumulative dose (per 1000 gram), median (range)	0 (0-17)	0 (0-7)	1.3	0.9-1.9
Mesalamine – > 1.2g/day during entire disease course, N (%)	9/43 (21)	23/102 (23)	1.6	0.3-7.1
Regular use of any 5-ASA last five years, N (%)	16/40 (40)	32/99 (32)	2.3	0.9-6.0
Use of any 5-ASA at end of follow-up, N (%)	22/43 (51)	42/102 (41)	2.4	1.0-6.1
Any intestinal resection prior to cancer resection, N (%)	6/43 (14)	14/102 (14)	1.5	0.3-7.1

*) Odds ratios are adjusted for age and calendar year at diagnosis

4.5.1 Own results (Paper IX)

We performed a combined Copenhagen County – Olmsted County nested case-control study of colorectal neoplasia cases from the two cohorts (n = 43) and 1-3 controls per case (n = 102) individually matched by subtype of IBD, gender, duration of IBD (until total colectomy, death or end-of follow-up), calendar year at IBD diagnosis, age at diagnosis, and maximal extent of disease.

Potential risk factors for neoplasia assessed were: patient factors (PSC, family history of CRC, smoking habits), disease activity, and x-ray procedures. A diagnosis of PSC was the only patient factor associated with colorectal neoplasia (OR, 6.9; 95% CI, 1.2-40) (Table 6). Although not significantly, cigarette smoking seemed to be protective of neoplasia and results were similar in separate analyses of patients with UC and CD. Regarding disease activity, the risk of colorectal neoplasia increased with increasing frequency of exacerbations (comparing patients with, respectively, flares only every 10 years or less, every 1-10 years, and more than once a year; $p < 0.001$). Similarly, cumulative time with active disease as a percentage of the total disease course and occurrence of more than one year of continuous moderate to severe symptoms during the disease course increased the odds of neoplasia (Table 6). Lastly, a borderline-significantly increased risk of neoplasia was observed with increasing number of small bowel x-ray procedures performed (Table 6). In an additional analysis for the present thesis, we pooled the number of small bowel x-rays and barium enemas performed in each patient to estimate the overall effect of x-ray procedures on neoplasia risk (OR, 2.3; 95% CI, 0.8-6.5).

Putative protective factors were divided into follow-up/surveillance factors and treatment factors. A significantly higher frequency of hospitalizations and a borderline-significantly higher frequency of out-patient clinic visits were observed among patients with neoplasia as compared with controls (Table 7). Cases had also undergone more sigmoidoscopies and colonoscopies, including surveillance colonoscopies, than controls during the disease course (Table 7). No cancer cases had been diagnosed with flat dysplasia or adenomas prior to cancer.

Cases had been on maintenance treatment with sulfasalazine or other 5-ASAs (mainly mesalamine) slightly longer (42% of disease

Table 8. Overall mortality in inflammatory bowel disease during the last five decades: A comparison of three population-based inception cohort studies from Copenhagen, Denmark, 1962-2005 (Paper VII).

	Crohn's disease					Ulcerative colitis				
	total	observed/ expected deaths	SMR	95% CI	CD related deaths*	Total	observed/ expected deaths	SMR	95% CI	UC related deaths*
COHORT I (1962-1987)	374	84/67.0	1.3	1.0-1.6**	22 (26%)	1160	261/249.1	1.1	0.9-1.2	33 (13%)
Women	217	45/31.9	1.4	1.0-1.9**	14 (31%)	619	116/114.4	1.0	0.8-1.2	12 (10%)
Men	157	39/35.2	1.1	0.8-1.5	8 (21%)	541	145/134.8	1.1	0.9-1.3	21 (14%)
COHORT II (1991-1993)	58	10/4.4	2.3	1.1-4.2**	3 (30%)	89	15/9.9	1.5	0.9-2.5	1 (7%)
Women	38	5/2.4	2.1	0.7-5.0	2 (40%)	51	9/5.9	1.5	0.7-2.9	1 (11%)
Men	20	5/2.0	2.5	0.8-5.8	1 (20%)	38	6/4.0	1.5	0.5-3.2	0 (0%)
COHORT III (2003-2004)	209	1/1.3	0.8	0.02-4.2	1 (100%)	326	4/4.3	0.9	0.3-2.4	1 (25%)
Women	113	1/0.6	1.7	0.04-9.6	1 (100%)	166	3/2.6	1.2	0.2-3.4	1 (33%)
Men	96	0/0.8	-	-	-	160	1/1.7	0.6	0.01-3.3	0 (0%)
Total	641	95/72.7	1.3	1.1-1.6**	26 (27%)	1575	281/262.7	1.1	1.0-1.2	34 (12%)

*) Including deaths due to severe disease, postoperative complications, and intestinal cancer; **) 95% confidence interval excluding 1.0 (p<0.05)

Table 9. Causes of death among 62 patients with Crohn's disease in Copenhagen County, 1962-1997 (Paper I).

	Women				Men			
Causes of deaths (ICD-10)	observed deaths	expected deaths	SMR	95% CI	observed deaths	expected deaths	SMR	95% CI
Infections (A00-09, A20-99, B00-89, B91-97, B99)	2	0.2	8.3	1.01-30*	1	0.5	2.1	<0.1-12
Cancer (C00-D09)	9	9.9	0.9	0.4-1.7	6	9.7	0.6	0.2-1.4
Senile decay and apoplexia (F03.9, I60-71, R54)	2	3.1	0.7	0.1-2.4	4	2.6	1.5	0.4-3.9
Cardiovascular diseases (I00-25, I27, I30-52)	5	7.1	0.7	0.2-1.6	10	9.6	1.0	0.5-1.9
Respiratory diseases (J00-99)	4	2.8	1.4	0.4-3.7	4	3.0	1.3	0.4-3.4
Gastrointestinal diseases (K00-93)	3	1.6	1.9	0.4-5.6	5	1.7	3.0	1.0-7.0
Genitourinary tract diseases (N00-99)	3	0.3	10.3	2.1-30*	1	0.4	2.8	0.1-15
Suicide (X60-84, Y87.0)	1	0.5	2.0	0.1-11	0	0.8	0.0	-
Other causes	2	6.3	0.3	0.04-1.1	0	7.0	0.0	-
Total	31	31.8	1.0	0.7-1.4	31	35.2	0.9	0.6-1.3

*) 95% confidence interval excluding 1.0

course) than controls (39% of disease course) and no protective effect of these drugs was observed, neither when analyzing increased cumulative dose (significantly higher in cases than controls), regular use during the last 5 years, use at the time of neoplasia/last follow-up, or when dichotomizing the amount of medications used during the disease course (Table 7). Furthermore, no significant protective effect of partial colorectal resections was observed (Table 7).

4.5.2 Discussion

According to the present nested case-control analysis of IBD patients with and without colorectal neoplasia belonging to the Copenhagen County and Olmsted County patient cohorts, the primary risk factors for colorectal neoplasia in patients with IBD were a diagnosis of PSC and long-standing active intestinal inflammation, whereas no specific follow-up or surveillance related factors were found to be preventive.

An objection against the present study could be that assessment of two cohorts from different geographic areas was not an ideal approach. However, the primary reason for combining Danish patients and Minnesota patients was to obtain a sample size that would provide reasonably good power to detect associations. The two populations were from similar calendar periods, included according to essentially the same well-defined diagnostic criteria, and a substantial part of Minnesota patients were of Scandinavian or northern European heritage. We used a nested case-control approach where cases were matched with controls from their own respective cohorts, and all results were tested by secondary analyses of each county separately. A possibility of Type I errors existed due to the relatively large number of variables assessed and we attempted to minimize this problem by restricting our analyses to factors related to a clear hypothesis.

The finding of an increased risk of neoplasia related to PSC, long-standing disease activity and probably to x-ray procedures was in accordance with former studies of neoplasia risk in patients with IBD [47, 51-53] and with the generally accepted association between exposure to medical radiation and development of cancer [54]. However, x-ray procedures could also be a surrogate marker for long-standing active disease.

We were not able to prove a protective effect of close clinical follow-up, surveillance colonoscopies, medical treatment with 5-ASAs, or partial colorectal surgery. The results of the study gave the impression that a subgroup of patients with high disease activity and/or PSC were at increased risk of neoplasia despite closer follow-up, more intense medical treatment, and closer surveillance than controls with the same phenotypic characteristics but less severe disease activity. In fact, these differences between cases and controls diminished when adjusting for PSC and disease activity.

Our findings put a question mark to the suggested protective effect specific to treatment with 5-ASAs [55] and the 'indirectly suggested benefit' from surveillance colonoscopies [56]. A suggestion of influence of treatment policy on the risk of CRC in IBD is the phenomenon that cancer risk tends to be the same among CD and UC patients within specific regions. The low cancer risk observed among IBD patients from Denmark has been hypothetically explained by the use of 5-ASA maintenance therapy and high surgery rates in this area, whereas the low risk observed in the US was thought to be at least partly due to effective surveillance. However, another hypothesis arising from the present findings is that general control of disease (be it due to medications, close follow-up or other factors) rather than specific factors, keeps the overall risk of CRC low in most population-based settings, whereas a minor (in referral centers probably larger) subgroup of patients suffering from uncontrollable disease (despite medications, follow-up and surveillance) remains at high risk of CRC, unless they undergo total proctocolectomy.

Actually, in a recent meta-analysis showing a protective effect of 5-ASA (based on varying and often selected patient populations), authors pointed out that 5-ASA use might just be a surrogate measure for patient compliance in general [57]. Furthermore, a Cochrane review from year 2006, regarding detection of colorectal neoplasia among patients with extensive colitis, did not find clear evidence that surveillance colonoscopy prolonged survival [58]. This is in line with the observation from Olmsted County, that despite surveillance, none of the cancer cases had been diagnosed with dysplasia prior to CRC. However, it should still be emphasized that despite no clear evidence of a protective effect of specific interventions such as medications and surveillance in patients with IBD, it is likely that the overall close control of disease activity, including proctocolectomy when necessary, is of great importance in neoplasia prevention. This is what we aimed to underscore in our reply to a Letter to the Editor [59] related to Paper VI.

– Longstanding active disease and a diagnosis of PSC are risk factors for colorectal neoplasia in patients with IBD.
– Well-controlled disease seems to be the key factor in reducing colorectal neoplasia risk in IBD, whereas the means by which it is done (5-ASA treatment, surveillance, or surgery) seem of less importance.

4.6 MORTALITY IN CROHN'S DISEASE

Overall mortality in CD remains debated as most studies are either based on older [60, 61] or selected referral center populations [31, 62, 63] or represent relatively short follow-up of population-based inception cohorts [17, 64]. Furthermore, only few studies have assessed cause-specific and CD related mortality in population-based patient settings.

4.6.1 Own results (Papers I, IV, VII)

In Copenhagen County, 84 of 374 CD patients died during a median of 17 years of follow-up (SMR, 1.3; 95% CI, 1.0-1.6) (Table 8). The slightly increased mortality was due to increased mortality in women (SMR, 1.4; 95% CI, 1.0-1.9), especially in women aged <50 years at diagnosis (SMR, 3.4; 95% CI, 2.2-5.0) and with more than 20 years of disease duration (SMR, 2.9, 95% CI, 1.3-5.4). Accordingly, cumulative survival was lower (67%) than expected (80%) after 25 years of observation (Figure 10). The increased mortality was primarily due to CD related deaths, which accounted for 26% of all deaths and encompassed early complications of either the clinical course or surgical treatment of CD (median disease duration, 8 years; median age at death, 50 years) and later occurrence of gastrointestinal cancers (median disease duration, 17 years; median age at death, 67 years). The median age at death among patients who died from other causes than CD was 70 years. In women, an increased mortality from infections and genitourinary tract diseases was observed, and in women and men combined, mortality from gastrointestinal diseases was increased (Table 9).

Comparison with the 1991-1993 and 2003-2004 cohorts from Copenhagen County revealed that mortality from CD had remained fairly stable during the last five decades, with an overall SMR of 1.3 (95% CI, 1.1-1.6) (Table 8).

In Olmsted County, 56 of 314 CD patients had died during a median of 13 years of follow-up (SMR, 1.2; 95% CI, 0.9-1.6). The median age at death in the cohort was 79 years in women and 70 years in men. Cox-regression analysis revealed that age was independently associated with mortality (HR 1.6 per five year increment; 95% CI, 1.4-1.7) and a trend for male gender to be associated with mortality was also observed (HR, 1.7; 95% CI, 1.0-3.1). Calendar year at diagnosis, extent of disease, and treatment with immunosuppressive drugs did not affect mortality. Cumulative survival was close to expected, at least until 30 years after diagnosis (log-rank test, p=0.13; Figure 11). Thirty-two percent of deaths were definitely or possibly related to CD – either to complications of the clinical course or sur-

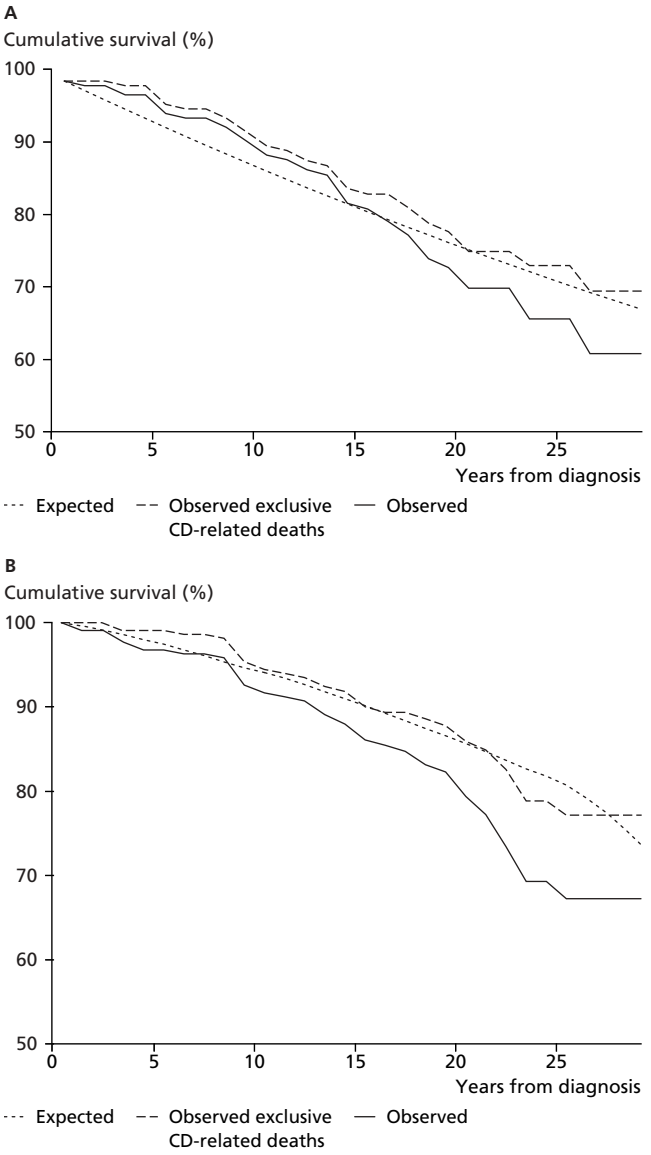

Figure 10. Observed and expected cumulative survival from time of diagnosis in male (**A**) and female (**B**) patients with Crohn's disease from Copenhagen County, 1962-1997. Observed numbers are presented both inclusive and exclusive Crohn's disease related deaths (Paper I).

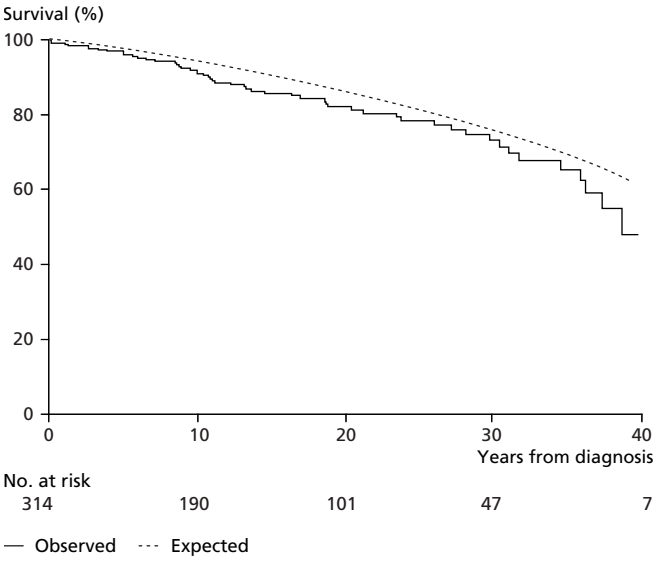

Figure 11. Observed and expected cumulative survival from time of diagnosis in 314 Olmsted County, Minnesota, residents with Crohn's disease diagnosed in 1940-2001 (log-rank, p=0.13) (Paper IV).

Table 10. Causes of death among 56 patients with Crohn's disease in Olmsted County, Minnesota, 1940-2004 (Paper IV).

	Women				Men			
Causes of deaths (ICD-9)	observed deaths	expected deaths	SMR	95% CI	observed deaths	expected deaths	SMR	95% CI
Infections (001-139)	0	0.3	0.0	0.0-12	1	0.6	1.7	<0.1-9.6
Cancer (140-239)	6	5.3	1.1	0.4-2.5	10	5.7	1.8	0.8-3.2
Intestinal cancer (152-154)	3	0.6	4.7	1.0-14	3	0.6	4.7	1.0-14
Pancreas cancer (157)	1	0.3	3.8	0.1-21	1	0.3	3.9	0.1-22
Pulmonary cancer (162)	0	1.0	0.0	0.0-3.6	3	2.0	1.5	0.3-4.4
Malignant melanoma (172)	1	0.1	14.8	0.4-82	1	0.1	9.6	0.2-53
Leukemia (204-208)	0	0.2	0.0	0.0-20	0	0.2	0.0	0.0-18
Diseases of blood and blood forming organs (280-289)	0	0.1	0.0	0.0-41	0	0.1	0.0	0.0-47
Nervous system (320-359)	0	0.4	0.0	0.0-9.1	0	0.4	0.0	0.0-9.8
Diseases of the circulatory system (390-459)	11	10.8	1.0	0.5-1.8	8	10.4	0.8	0.3-1.5
Respiratory diseases (460-519)	3	1.8	1.7	0.4-5.0	4	2.0	2.0	0.5-5.1
Pneumonia (485)	0	0.8	0.0	0.0-4.6	1	0.7	1.5	<0.1-8.1
COPD (490-496)	3	0.7	4.3	0.9-13	3	1.0	2.9	0.6-8.5
Gastrointestinal and liver diseases (520-579)	6	0.8	7.3	2.7-16*	5	0.9	5.6	1.8-13*
Genitourinary tract diseases (580-629)	0	0.4	0.0	0.0-8.4	1	0.4	2.9	0.1-16
Suicide (950-959)	0	0.2	0.0	0.0-18	0	0.6	0.0	0.0-5.8
Accidents (800-949)	0	0.7	0.0	0.0-5.5	1	1.4	0.7	<0.1-4.1
All other causes	0	1.4	0.0	0.0-2.6	0	1.4	0.0	0.0-2.7
Total	26	22.1	1.2	0.8-1.7	30	23.9	1.3	0.9-1.8

*) 95% confidence interval excluding 1.0 (p<0.05)

Table 11. Causes of death among 62 patients with ulcerative colitis in Olmsted County, Minnesota, 1940-2004 (Paper IV).

	Women				Men			
Causes of deaths (ICD-9)	observed deaths	expected deaths	SMR	95% CI	observed deaths	expected deaths	SMR	95% CI
Infections (001-139)	0	0.5	0.0	0.0-7.4	0	0.9	0.0	0.0-4.0
Cancer (140-239)	5	8.2	0.6	0.2-1.4	10	11.0	0.9	0.4-1.7
Intestinal cancer (152-154)	1	1.0	1.0	0.1-5.3	4	1.2	3.3	0.9-8.4
Pancreas cancer (157)	1	0.4	2.3	0.1-13	0	0.5	0.0	0.0-7.4
Pulmonary cancer (162)	0	1.6	0.0	0.0-2.4	2	3.9	0.5	0.1-1.9
Malignant melanoma (172)	0	0.1	0.0	0.0-40	0	0.2	0.0	0.0-20
Leukemia (204-208)	0	0.3	0.0	0.0-13	2	0.4	5.2	0.6-19
Diseases of blood and blood forming organs (280-289)	0	0.1	0.0	0.0-26	1	0.1	7.1	0.2-39
Nervous system (320-359)	2	0.7	3.1	0.4-11	1	0.7	1.5	0.1-8.3
Diseases of the circulatory system (390-459)	8	18.1	0.4	0.2-0.9*	15	18.9	0.8	0.4-1.3
Respiratory diseases (460-519)	4	2.9	1.4	0.4-3.5	2	3.6	0.6	0.1-2.0
Pneumonia (485)	3	1.3	2.2	0.5-6.5	0	1.1	0.0	0.0-3.2
COPD (490-496)	0	1.2	0.0	0.0-3.2	2	2.0	1.0	0.1-3.7
Gastrointestinal and liver diseases (520-579)	2	1.3	1.5	0.2-5.5	4	1.7	2.4	0.7-6.2
Genitourinary tract diseases (580-629)	2	0.7	2.7	0.3-10	0	0.6	0.0	0.0-6.1
Suicide (950-959)	0	0.2	0.0	0.0-16	1	1.0	1.0	<0.1-5.6
Accidents (800-949)	1	0.9	1.2	<0.1-6.5	1	2.0	0.5	<0.1-2.8
All other causes	2	2.2	0.9	0.1-3.4	1	2.3	0.4	0.1-2.4
Total	26	36.3	0.7	0.5-1.1	36	42.9	0.8	0.6-1.2

*) 95% confidence interval excluding 1.0 (p<0.05)

Table 12. Standardized mortality ratios (SMRs) and patient population characteristics: A meta-analysis of population-based inception cohort studies of patients with ulcerative colitis (Paper VIII).

Author, Country	Calendar period (publication year)	No. of patients	Mean* or Median** follow-up	Males	Patients with proctitis at diagnosis	Patients aged <40 years at diagnosis	Observed/ Expected deaths	SMR (95 % CI)
Jess et al., USA	1940-2004 (2005)	378	15.0 yrs**	56 %	17 %	63 %	62/79.2	0.8 (0.6-1.0)
Persson et al., Sweden	1955-1990 (1996)	1573	-	53 %	26 %	67 %	255/186.8	1.4 (1.2-1.5)
Stewenius et al., Sweden	1958-1990 (1995)	471	14.8 yrs*	57 %	58 %	-	86/66.2	1.3 (1.0-1.5)
Winther et al., Denmark	1962-1997 (2003)	1160	19.0 yrs**	47 %	44 %	61 %	261/249	1.1 (0.9-1.2)
Ekbom et al., Sweden	1965-1983 (1992)	2509	-	57 %	43 %	62 %	505/360.7	1.4 (1.2-1.5)
Eason et al., New Zealand	1969-1978 (1982)	342	4.0 yrs*	60 %	-	63 %	10/13	0.8 (0.4-1.4)
Probert et al., UK	1972-1989 (1993)	1014	-	55 %	-	48 %	92/98.3	0.9 (0.8-1.1)
Masala et al., Italy	1978-2001 (2004)	689	14.8 yrs**	56 %	-	-	81/115.7	0.7 (0.6-0.9)
Jacobsen et al., Denmark	1978-2003 (2005)	1515	-	-	-	-	-	1.1 (0.9-1.3)
Høie et al., Europe	1991-2003 (2005)	792	10.0 yrs*	53 %	-	-	75/67.9	1.1 (0.9-1.4)

gery (median disease duration, 11 years; median age at death, 56 years) or to gastrointestinal cancers (median disease duration, 15 years; median age at death; 45 years). Accordingly, cause-specific analysis revealed an increased risk of dying from gastrointestinal diseases (SMR, 6.4; 95% CI, 3.2-12) and cancers (SMR, 4.7; 95% CI, 1.7-10) – and also from chronic obstructive pulmonary disease (COPD) (Table 10). In neither of the two counties was an increased risk of dying from lymphoma observed (Tables 9 and 10).

4.6.2 Discussion

The above mentioned studies showed a slightly increased mortality from CD, most pronounced in Copenhagen, where the median

follow-up time was longer than in Olmsted County. Mortality patterns seemed stable over time. Disease related deaths accounted for approximately 30% of all deaths in both counties and were due to severe disease and/or surgery related complications occurring early in the disease course and to intestinal cancers occurring later on.

The finding of an unchanged mortality pattern over time in patients with CD was in contrast to the decline in mortality observed during recent decades amongst patients with UC (please see below), but in accordance with a recent review on prognosis of CD during the last four decades performed by *Wolters et al.* [65]. One would intuitively expect prognosis to improve second to better diagnostic tools, earlier diagnosis (Paper VII), and the availability of more efficacious treatments, such as immunosuppressive drugs. However, one could also speculate that the similar prognosis observed in different countries and in different treatment eras (Papers I, IV, VII) was coincidental and due to different underlying phenotypic characteristics counterweighing the effect of different treatments. As a matter of fact, the 1991-1993 cohort from Copenhagen, reporting the highest SMR in CD, differed phenotypically from the former and following cohorts from this area (Paper VII). In line with this, *Wolters et al.* [16] suggested that mortality might be a surrogate marker for disease severity and thereby reflect the underlying disease phenotypes. It is likely that the environmental changes, believed to explain the increasing incidence rates of IBD, also has led to changes in phenotypic presentation of the diseases over time. However, such changes may to some extent be overseen by focusing solely on age, gender, disease location, and disease behavior as phenotypic features of CD.

Mortality was found to be significantly increased after prolonged observation of the Copenhagen County cohort, i.e. in women with more than 20 years of disease duration. Likewise, *Truelove and Pena* [5] stated that 'CD emerges as a disease which becomes progressively more dangerous as the years go by, which is in sharp contrast with the findings in UC in which the main risk of dying is in the early years'. However, almost all CD related deaths (except for those related to cancer) occurred early in the disease course (in accordance with the findings of *Prior et al* [68]) and therefore did not explain this observation. Nor did analysis of cause-specific mortality reveal a reduced mortality from other causes early in the disease course.

The introduction of immunosuppressive drugs might be expected to improve both early and late mortality by reducing the risk of death from severe disease or surgical complications early in the disease cause and by reducing the long-term risk of intestinal cancer due to better disease control. But these early and late benefits could also be reduced by an increased risk of fatal opportunistic infections in immediate relation to therapy or by the initiation of other malignant processes with manifestation later on [38, 39]. In the 1991-1993 cohort from Copenhagen, 28% had received azathioprine/6-mercaptopurine, 3% methotrexate, and 10% infliximab during the disease course (10 years follow-up), whereas in the 2003-2005 cohort, the corresponding numbers were 34%, 1%, and 5% (one year follow-up) (Table 2). Still, no deaths could be ascribed to this treatment in Copenhagen (Paper VII). In Olmsted County, 11% of patients diagnosed between 1960 and 1979 and 37% of patients diagnosed between 1980 and 2001 had received any of azathioprine, 6-mercaptopurine, methotrexate, or infliximab during follow-up (median 13 years). Still, only one of 56 deaths (2%) among patients with CD from Olmsted County occurred in relation to such treatment – a 35-year old woman recently treated with infliximab who died of sepsis after surgery for an internal fistula. Similar population-based data for comparison are lacking.

In conclusion, the apparently unchanged prognosis in CD over time may hide environmentally caused changes in presentation, severity and natural course of the disease, outbalanced by the effect of new treatment regimens. Or it could simply be that new treatment options are not superior to former treatments when it comes to avoiding death, or that the effect of such treatments on long-term prognosis may only be apparent after further follow-up.

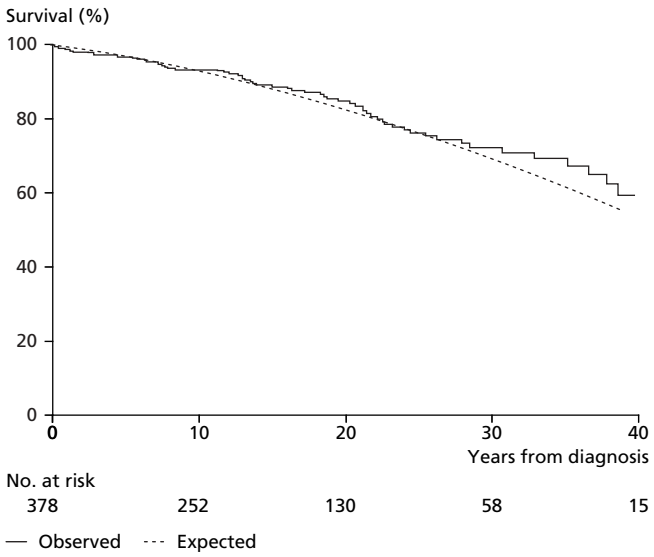

Figure 12. Observed and expected cumulative survival from time of diagnosis in 378 Olmsted County, Minnesota, residents with ulcerative colitis diagnosed in 1940-2001 (log-rank, p=0.06) (Paper IV).

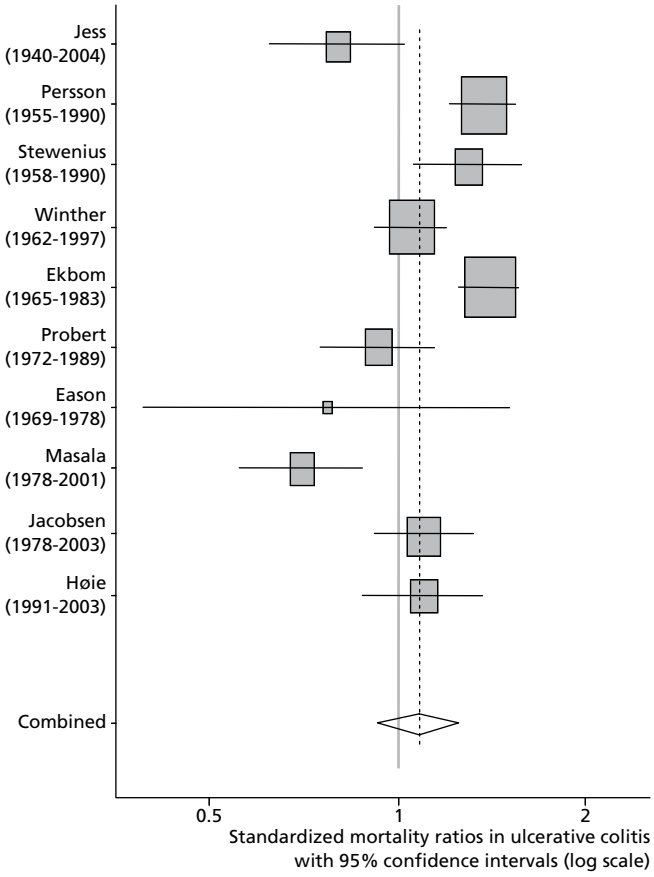

Figure 13. Individual and combined standardized mortality ratios (SMR) with 95% confidence intervals (CI) in ulcerative colitis patients belonging to population-based inception cohorts (Paper VIII).

– Mortality is slightly increased in patients with CD and prognosis seems fairly constant across time and countries.
– Prospective follow-up of contemporary cohorts will hopefully reveal an improvement in long-term prognosis among patients with CD who are treated according to current guidelines.

Table 13. Pooled estimates of mortality in patients with ulcerative colitis: a meta-analysis of population-based inception cohort studies (Paper VIII).

	No. of studies	Lowest SMR	95% CI	Highest SMR	95% CI	Pooled SMR	95% CI
Overall survival	10	0.7	0.6-0.9*	1.4	1.2-1.5*	1.1	0.9-1.2
Excluding the lowest and highest SMRs	8	0.8	0.4-1.4	1.4	1.2-1.5*	1.1	0.9-1.2
Excluding the two borderline studies	8	0.8	0.6-1.0	1.4	1.2-1.5*	1.1	1.0-1.3
Nationality	9						
Scandinavian studies	5	1.1	0.9-1.2	1.4	1.2-1.5*	1.2	1.1-1.4*
Non-Scandinavian studies	4	0.7	0.6-0.9*	0.9	0.8-1.1	0.8	0.7-0.9*
Gender	4						
Female	4	0.7	0.5-1.1	1.4	1.0-1.9	1.0	0.9-1.2
Male	4	0.8	0.6-1.2	1.1	0.9-1.3	1.0	0.9-1.1
Calendar year at diagnosis	2						
< 1980	2	0.9	0.6-1.1	1.1	0.9-1.3	1.0	0.9-1.2
≥ 1980	2	0.6	0.3-1.1	1.0	0.8-1.3	0.9	0.7-1.1
Age at diagnosis	3						
0-18/19 years	3	0.0	0.0-3.6	2.3	0.9-4.7	-	-
19/20-29 years	3	0.4	0.1-1.2	1.1	0.6-1.8	0.9	0.5-1.5
30-49 years	3	0.6	0.3-1.0	1.5	0.6-3.0	0.9	0.7-1.1
50+ years	3	0.9	0.7-1.3	1.1	0.9-1.2	1.0	0.9-1.1
Extent of disease	4						
Proctitis	4	0.8	0.5-1.2	1.0	0.9-1.2	1.0	0.9-1.1
More extensive colitis	4	0.9	0.7-1.2	1.5	1.4-1.7*	1.2	1.0-1.5*
Disease duration	2						
0-1 year	1	-	-	2.2	1.5-3.3*	-	-
0-5 years	1	-	-	1.4	1.1-1.8*	-	-
Immunosuppressive drugs	1						
No treatment	1	0.8	0.6-1.0*	-	-	-	-
Any treatment	1	-	-	1.3	0.3-3.8	-	-
Surgery	1						
No surgery	1	0.9	0.7-1.1	-	-	-	-
Proctocolectomy	1	-	-	1.3	0.7-2.2	-	-

*) 95% confidence interval excluding 1.0 (p<0.05)

4.7 MORTALITY IN ULCERATIVE COLITIS

Early studies from referral centers reported increased overall mortality in UC [6, 66]in accordance with some [60, 61, 67] but definitely not all population-based studies [68-70]. Other studies suggested a reduction in mortality from UC after the introduction of treatment with corticosteroids in the middle of last century [6, 71]. Relatively few studies have assessed cause-specific mortality among UC patients and results are to some extent conflicting [60, 61, 68, 69].

4.7.1 Own results (Papers IV, VII, VIII)

In Copenhagen, mortality in UC remained stable and close to expected during the last five decades with an overall SMR of 1.1 (95% CI, 1.0-1.2), although 12% of deaths had certain or possible relation to UC (Table 8).

In Olmsted County, mortality in UC patients was slightly lower than expected (SMR, 0.8; 95% CI, 0.6-1.0) after a median follow-up time of 15 years, although 19% of deaths could be ascribed to the underlying disease (i.e. death due to severe disease, postoperative complications, end stage liver disease due to PSC, and CRC). CRC caused 8% of all deaths in patients with UC.

Accordingly, a trend towards increased mortality from gastrointestinal diseases (SMR, 2.0; 95% CI, 0.8-4.4) and gastrointestinal cancer (SMR, 2.2; 95% CI, 0.7-5.2) was observed, whereas mortality from cardiovascular disease was significantly reduced (SMR, 0.6; 95% CI, 0.4-0.9) (Table 11).

Cumulative survival was *higher* than expected during all years of observation, with a 30 years cumulative survival of 72% (95% CI, 65-79%) vs. 68% expected (one sample log-rank test, p = 0.06) (Figure 12).

Cox proportional hazards regression analysis revealed that both age at diagnosis (HR, 1.7 [per five year increment]; 95% CI, 1.5-1.9), male gender (HR, 2.0; 95% CI, 1.2-3.4), and having extensive colitis (HR, 2.2; 95% CI, 0.9-5.1) were independently associated with increased mortality, whereas being diagnosed in the 1980-2002 period was associated with reduced mortality (HR, 0.2; 95% CI, 0.1-0.6).

In accordance with results from Copenhagen County and Olmsted County, the meta-analysis of ten population-based inception cohort studies (Paper IV and [60, 61, 67-70, 72-74], Table 12) revealed that overall mortality in UC was not increased (pooled SMR, 1.1; 95% CI, 0.9-1.2) (Figure 13). However, five Scandinavian studies reported higher mortality rates (pooled SMR, 1.2; 95% CI, 1.1-1.4) than did the non-Scandinavian countries (pooled SMR, 0.8; 95% CI, 0.7-0.9) (Table 13). Stratification of SMR revealed no impact of gender, age at diagnosis, or calendar period of diagnosis on mortality in UC, whereas patients with extensive colitis (SMR, 1.2; 95% CI, 1.0-1.5) or disease duration of only one (SMR, 2.2; 95% CI, 1.5-3.3) or five years (SMR, 1.4; 95% CI, 1.1-1.8) were at increased risk of dying. In contrast to this, mortality was reduced in patients who had never been treated with immunosuppressive drugs (SMR, 0.8; 95% CI, 0.6-0.99) (Table 13).

Seventeen percent of all deaths had possible or certain relation to UC, the most common causes being CRC (37% of UC-related deaths) and surgical or post-operative complications (44% of UC-related deaths), such as perforations, peritonitis, and cardiovascular complications. The remaining causes were primarily related to severe disease and end-stage liver disease second to PSC (Table 14).

The meta-analysis of cause-specific mortality in UC (Table 15) showed a borderline-significantly increased risk of dying from CRC (SMR, 1.9; 95% CI, 1.0-3.8) counterbalanced by a significantly reduced risk of dying from pulmonary cancer (SMR, 0.3; 95% CI, 0.1-0.9). Mortality from cardiovascular diseases was not significantly reduced (SMR, 0.9; 95% CI, 0.7-1.1), whereas mortality from respiratory diseases was significantly increased (SMR, 1.6; 95% CI, 1.3-2.0) due to a significantly increased risk of dying from pneumonia (SMR, 3.1; 95% CI, 2.0-4.6). The risk of dying from gastrointestinal and liver diseases was also increased (pooled SMR, 2.5; 95% CI, 1.9-3.2) although this finding did not reach statistical significance when excluding deaths from UC (SMR, 1.7; 95% CI, 0.8-3.6).

Table 14. Ulcerative colitis related mortality: a meta-analysis of population-based inception cohort studies (Paper VIII).

Author, Country	No of patients	Observed deaths	Deaths related to UC No. (% of all)	Deaths due to surgical/postoperative complications. No. (% of UC related)	Deaths due to colorectal cancer. No. (% of UC related)	Deaths due to PSC. No. (% of UC related)
Jess et al., USA	378	62	12 (19%)	2 (17%)	5 (42%)	1 (8%)
Stewenius et al., Sweden	471	103	13 (13%)	3 (23%)		
Winther et al., Denmark	1160	261	33 (13%)	19 (58%)	8 (24%)	
Eason et al., New Zealand	342	10	3 (30%)	3 (100%)		
Masala et al., Italy	689	81	9 (11%)	2 (22%)	4 (44%)	

Table 15. Cause-specific mortality in patients with ulcerative colitis: a meta-analysis of populationbased inception cohort studies (Paper VIII).

Causes of deaths	No. of studies	Lowest SMR	95% CI	Highest SMR	95% CI	Pooled SMR	95% CI
Cancer	5	0.7	0.5-0.9*	1.5	1.2-1.8*	1.0	0.7-1.3
Colorectal cancer	4	0.9	0.4-1.8	4.4	3.2-5.9*	1.9	1.0-3.8
Pulmonary cancer	2	0.3	0.1-1.0	0.4	0.1-1.3	0.3	0.1-0.9*
Leukemia	1	-	-	2.9	0.4-10.3	2.9	0.4-10.3
Non-Hodgkin's lymphoma	1	-	-	2.4	0.3-8.7	2.4	0.3-8.7
Cardiovascular diseases	5	0.6	0.4-0.9*	1.1	0.9-1.4	0.9	0.7-1.1
Ischemic heart disease	2	0.9	0.8-1.1	1.0	0.8-1.3	0.9	0.8-1.1
Pulmonary embolism	1	-	-	4.0	1.5-8.7*	4.0	1.5-8.7*
Respiratory diseases	5	0.9	0.3-2.0	2.0	1.1-3.5*	1.6	1.3-2.0*
COPD	4	0.6	0.1-2.3	3.4	1.7-5.9*	1.6	0.7-3.7
Pneumonia	2	1.3	0.3-3.7	3.4	2.1-5.0*	3.1	2.0-4.6*
Gastrointestinal and liver diseases	4	1.6	0.8-2.8	4.0	1.9-7.3*	2.5	1.9-3.2*
All exclusive ulcerative colitis	3	0.5	0.2-1.1	2.8	1.7-4.4*	1.7	0.8-3.6
Non-alcoholic liver diseases	3	0.9	0.1-4.9	4.8	2.1-9.5*	4.0	2.5-6.5*
Genitourinary tract diseases	4	1.0	0.4-2.3	1.6	0.4-4.1	1.2	0.7-2.2
Suicide	4	0.8	0.3-1.8	2.1	1.0-3.9	1.3	0.8-2.0
Accidents/Injuries	5	0.5	0.2-1.2	0.8	0.3-1.9	0.7	0.5-1.0

*) 95% confidence interval excluding 1.0 ($p<0.05$). COPD: chronic obstructive pulmonary disease (bronchitis, emphysema, and asthma)

4.7.2 Discussion

In contrast to earlier data from referral centers [6, 66]and some population-based studies [60, 61, 67], the above mentioned analyses covering the last six decades and summarizing results from patient populations worldwide showed that overall mortality among patients with UC is comparable to that of the background population.

The heterogeneity between the identified population-based studies, especially considering the excess mortality observed in Scandinavian countries vs. the reduced mortality observed in Italy, New Zealand, UK, and USA, may reflect the fact that the Scandinavian studies were based on some of the oldest patient populations. It could also be, that cohorts differed in composition (gender, age, and calendar periods of inclusion), in applied treatment strategies, or simply in basis for calculating SMRs.

The age- and gender distribution seemed fairly similar in the included studies, and meta-regression revealed no impact of calendar period of inclusion or observation on the observed SMR. Treatment regimens in different countries were mainly reported in a descriptive way (i.e. maintenance therapy with 5-aminosalicylates, corticosteroids in case of disease flare, and proctocolecomy in lack of response to medical treatment) which did not leave us the opportunity to perform direct comparison of data. It is likely that surgery rates may have had an impact on mortality, considering that 44% of UC-related deaths in the meta-analysis were due to post-operative complications. This is also in line with the excess mortality observed in newly diagnosed patients (in accordance with [61, 75, 76]) and in patients with extensive disease (in accordance with [6, 75-77]) in whom surgery rates are known to be high [14].

Another theoretical explanation for the observed heterogeneity between studies is that SMRs from different regions are not fully comparable. One could hypothesize that the absolute mortality rate among patients with UC was the same in different regions, whereas SMRs differed between regions due to differing background mortality rates. For example if the prevalence of smokers (smoking being a determinant for death) differed between regions but was fairly identical among UC patients, this would consequently result in the observed heterogeneity in SMRs. Also, differences in frequency of early detection (and early treatment) of other diseases among UC patients vs. background population, respectively, between background populations would cause heterogeneity in reported SMRs.

A clear limitation of the meta-analysis was the varying use of ICD-codes in different countries, which only left us with the possibility to study main categories of causes of deaths. Furthermore, death certificate information is known to be of questionable quality [78, 79], but advantageously, in many studies the cause of death had been confirmed via medical records.

UC-associated mortality (including death from CRC) accounted for approximately 17% of all deaths and, accordingly, cause-specific analyses revealed an increased risk of dying from gastrointestinal diseases and a borderline-significantly increased risk of dying from CRC. The importance of the latter finding and the appropriateness of including CRCs in 'UC-related deaths' can obviously be questioned considering the overall non-increased risk of CRC in patients with UC.

In addition to the increased mortality from gastrointestinal diseases and malignancies, mortality from non-alcoholic liver diseases (including PSC), pulmonary embolisms, and respiratory diseases was significantly increased, whereas mortality from pulmonary cancer was significantly reduced. UC patients are known to be at increased risk of PSC and of vascular complications, such as deep vein thrombosis and pulmonary embolism [80], and are intuitively expected to be at reduced risk of dying from chronic obstructive lung diseases and from pulmonary cancer due to the low prevalence of smokers [41, 42]. Accordingly, the excess mortality from respiratory diseases was mainly due to pneumonia, which is an expected complication both in chronically ill patients and post-operatively. Although we failed to confirm a statistically significant reduction in

the risk of cardiovascular mortality, as suggested in Paper IV and by other authors [66, 69], it is not unlikely that early intervention, low prevalence of cigarette smokers, and low blood pressure in patients with extensive disease second to sodium and water depletion [81] may have a positive impact on cardiovascular mortality among patients with UC.

– Overall mortality is not increased in patients with UC
– Patients with newly diagnosed extensive and surgery demanding disease may have a slightly increased mortality, counterbalanced by a reduced mortality from pulmonary cancer (and possibly from cardiovascular diseases) in other subsets of patients.

5. SUMMARY AND CONCLUSIONS

The present thesis was based on nine epidemiological studies on the prognosis of inflammatory bowel disease (IBD) covering the last six decades in different geographic settings.

The primary patient populations studied were the Copenhagen County cohort of patients diagnosed with Crohn's disease (CD) during 1962-1987 and followed until 1997 and the Olmsted County IBD cohort diagnosed during 1940-2001 and followed until year 2004. Results from these cohort studies were compared to results from the Copenhagen cohort of patients with ulcerative colitis (UC) diagnosed during 1962-1987, two later Copenhagen cohorts and, through systematic reviews and meta-analyses, to population-based IBD cohorts from the rest of the world.

The cumulative incidence of colorectal dysplasia (flat dysplasia, dysplasia associated lesion or mass [DALM[, or adenoma-associated lesions or masses [ALMs]) was 9.2% among UC patients and 0.5% among CD patients at 25 years. We could not confirm a high risk of progression of flat low-grade dysplasia (fLGD) to high-grade dysplasia, DALM, or colorectal cancer (CRC), whereas 39% had recurrence or progression of ALMs. The risk of recurrence and/or progression was confined to subgroups of patients with primary sclerosing cholangitis (PSC) and first event of dysplasia located proximally in the colon. Considering the promising prognosis of fLGD observed in this study and the poor inter-observer agreement on the fLGD diagnosis, a conservative approach should always be considered in these patients prior to recommending surgery.

Among patients with CD, the risk of small bowel cancer (standardized incidence ratio [SIR], 27) and CRC (SIR, 1.8) was significantly increased when pooling own results with estimates from other population-based studies. The risk of colonic cancer was higher than that of rectal cancer. Patients with colonic CD and male patients younger than 30 years at diagnosis were at a particular high risk of CRC, whereas patients with ileal disease were at risk of small bowel cancer. The overall risk of extra-intestinal cancers was not increased and, especially, no excess risk of lymphomas was observed.

In patients with UC, the overall risk of CRC was not different from that of the background population. Results were similar in Copenhagen and Olmsted County despite markedly different surveillance policies. All CRCs observed in Olmsted County occurred in patients diagnosed prior to the year 1980 and the overall cumulative incidence of CRC was only 2.0% at 25 years.

The nested case-control study (of Danish and American IBD patients with colorectal neoplasia and phenotypically matched controls from the same cohorts) confirmed that longstanding active disease, PSC, and possibly also x-ray procedures were risk factors for colorectal neoplasia. Well-controlled disease seemed to be the key factor in reducing colorectal neoplasia risk, whereas the means by which it was done (5-ASA treatment, surveillance, or surgery) seemed of less importance.

Mortality was slightly, but significantly, increased among patients with CD from Copenhagen (standardized mortality ratio [SMR], 1.3) and borderline-significantly increased in Olmsted (SMR, 1.2). In both counties, a deviation from expected mortality was observed after long disease duration, whereas results regarding the influence of gender and age on mortality were inconsistent, probably due to small numbers. Approximately 30% of all deaths could be ascribed to severe disease, postoperative complications of CD, or intestinal cancer and, accordingly, a significantly increased mortality from gastrointestinal diseases was observed in both counties, whereas an increased risk of dying from genitourinary diseases and infections among female patients was observed in Copenhagen and an increased risk of death from CRC and chronic obstructive pulmonary disease was observed in Olmsted.

Mortality among patients with UC was similar to expected, both in the three cohorts from Copenhagen, in Olmsted County and in the meta-analysis of all identified population-based inception cohort studies on the subject. However, a subgroup of UC patients with recently diagnosed extensive disease was at increased risk of dying, and consequently, 17% of all deaths had possible or certain relation to complications of UC. In line with this, analysis of cause-specific mortality revealed an increased risk of dying from gastrointestinal diseases. This finding was counterbalanced by a reduced mortality from pulmonary cancer, presumably due to the low prevalence of cigarette smokers among patients with UC.

All epidemiologic studies, including the ones presented here, must be interpreted with caution, although they are believed to be based on the most reliable and objective study methods available. First, the results of population-based inception cohort studies do probably never reveal the 'true' prognosis as regards the natural course of disease, as patients are typically followed closely after enrollment and receive medical and surgical treatment when needed. Observed prognosis does therefore represent therapeutic outcome, which is probably also the most relevant outcome to report, since no patients should be left without follow-up and relevant treatment. Secondly, measures of cancer risk and mortality are typically based on observations in the patient cohorts compared to observations in age- and gender matched background populations. However, patient behavior may not always reflect background population behavior when it comes to factors with influence on cancer risk and mortality, such as smoking, life style, and frequency of physician visits (which may lead to early detection and treatment of other diseases). Therefore, heterogeneity in reported results from patient cohorts of different geographic origin or from different calendar periods may sometimes mirror differences in behavior between patients and their respective background populations rather than reflecting true differences in natural course or therapeutic outcome of IBD.

Another limitation of the present and former studies is that such studies typically focus on prognosis in subgroups of patients defined by a limited number of phenotypic characteristics, such as age, gender, and disease extent at diagnosis. Especially the latter is questionable, just considering the potential 'change' over time due to improved diagnostic tools, such as the introduction of endoscopy (including capsula endoscopy) as an alternative to x-ray procedures.

This characterization of patients may also be of limited clinical relevance in view of the increased understanding of the etiology of IBD. Therefore, as outlined in the following section, future studies should add immunogenetic patient features to the phenotypic description of patients when aiming to predict clinical response to treatment, course of disease, and long-term outcome among patients with IBD.

Still, it is my belief that the presented studies have been based upon the most reliable methods available at present, and it is my hope that the overall promising results can be used for informing patients, for education of physicians, and to help patients to obtain reasonably priced medical and life insurances.

6. FUTURE PERSPECTIVES

Future research on prognosis in IBD should focus on prospective follow-up of patients included according to strict diagnostic criteria. Applied diagnostic tools should be noted and patients should be characterized according to demographic, clinical, genetic, and sero-

logical features. Furthermore, medical and surgical treatments should be recorded in detail during the entire disease course for the purpose of assessing the influence of treatment strategies (and changes in such) on the course and long-term prognosis of IBD.

One of the interesting questions to be answered in the future is whether the use of immunosuppressive drugs will decrease the risk of intestinal cancer and death due to better disease control and lowering of surgery rates and complications hereof or, alternatively, affect prognosis negatively due to adverse events such as opportunistic infections and occurrence of extra-intestinal malignancies. As mentioned previoulsy, the phenotypic characterization of patients needs to be both conservative – for proper comparison with previous results – and at the same time progressive, with focus on immunogenetic features, in order to improve prediction of outcome.

The Danish Crohn Colitis Database (DCCD), aimed to cover the whole nation within the near future, will hopefully provide excellent epidemiologic conditions for studies on course and long-term prognosis in prospectively followed, clinically and immuno-genetically well-characterized and population-based inception cohorts of patients with IBD. Along with this, enhanced understanding of the etiology of IBD will hopefully lead to a better phenotypic characterization of patients, which will enable clinicians to identify subgroups with particular need of, and response to, specific treatment strategies. This would undoubtedly further improve the course and prognosis for patients with IBD.

THE PRESENT THESIS IS BASED ON THE FOLLOWING PUBLICATIONS, WHICH WILL BE REFERRED TO IN THE TEXT BY THEIR ROMAN NUMERALS

I. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. Gastroenterology 2002;122:1808-1814

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III. Jess T, Gamborg M, Matzen P, Munkholm P, Sørensen TIA. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol 2005; 100:2724-9

IV. Jess T, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ 3rd, Munkholm P, Sandborn WJ. Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. Gut 2006;55:1248-54

V. Jess T, Loftus EV Jr., Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Tremaine WJ, Melton LJ 3rd, Munkholm P, Sandborn WJ. Incidence and prognosis of colorectal dysplasia in inflammatory bowel disease: a population-based study from Olmsted County, Minnesota. Inflamm Bowel Dis 2006;12:669-76

VI. Jess T, Loftus EV Jr, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schleck CD, Tremaine WJ, Melton LJ 3rd, Munkholm P, Sandborn W. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted County, Minnesota. Gastroenterology 2006;130:1039-46

VII. Jess T, Riis L, Vind I, Winther KV, Borg S, Binder V, Langholz E, Thomsen OØ, Munkholm P. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last five decades: a population-based study from Copenhagen, Denmark. Inflamm Bowel Dis 2007;13:481-9

VIII. Jess T, Gamborg M, Munkholm P, Sørensen TIA. Overall and cause-specific mortality in ulcerative colitis: Meta-analysis of population-based inception cohort studies. Am J Gastroenterol 2007;102:609-17

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