REVIEW

CME

Risk of Extra-Intestinal Cancer in Inflammatory Bowel Disease: Meta-Analysis of Population-Based Cohort Studies

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OBJECTIVES: **Extra-intestinal manifestations of inflammatory bowel disease (IBD) are relatively common, whereas the risk of extra-intestinal cancer (EIC) remains uncertain. The aim of this study was to obtain a reliable estimate of the risk of EIC in Crohn's disease (CD) and ulcerative colitis (UC) by performing a meta-analysis of population-based cohort studies.**

METHODS: **A systematic literature review was performed using MEDLINE (1966–2009) and abstracts from recent international conferences. Eight population-based cohort studies comprising a total of 17,052 patients with IBD were available. Standardized incidence ratios (SIRs) of EICs were pooled in a meta-analysis approach using STATA software.**

RESULTS: **Overall, IBD patients were not at increased risk of EIC (SIR, 1.10; 95% confidence interval (CI) 0.96–1.27). However, site-specific analyses revealed that CD patients had an increased risk of cancer of the upper gastrointestinal tract (SIR 2.87, 95% CI 1.66–4.96), lung (SIR 1.82, 95% CI 1.18–2.81), urinary bladder (SIR 2.03, 95% CI 1.14–3.63), and skin (SIR 2.35, 95% CI 1.43–3.86). Patients with UC had a significantly increased risk of liver–biliary cancer (SIR 2.58, 95% CI 1.58–4.22) and leukemia (SIR 2.00, 95% CI 1.31–3.06) but a decreased risk of pulmonary cancer (SIR 0.39, 95% CI 0.20–0.74).**

CONCLUSIONS: **Although the overall risk of EIC was not significantly increased among patients with IBD, the risk of individual cancer types differed from that of the background population as well as between CD and UC patients. These findings may primarily be explained by smoking habits, extra-intestinal manifestations of IBD, and involvement of the upper gastrointestinal tract in CD.**

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INTRODUCTION

Inflammatory bowel diseases (IBDs), Crohn's disease (CD) and ulcerative colitis (UC) are chronic disorders of unknown etiology with a potentially severe disease course, involvement of other organs, and an increased risk of intestinal cancer at least in subsets of patients (1,2).

The incidence and prevalence of IBDs have increased substantially in recent years and half of the patients are younger than 32 years of age when first diagnosed (3–7). Hence, knowledge of prognosis in these patients is central.

The risk of intestinal cancer in IBD has already been analyzed thoroughly (1,2), presumably because of the fact that IBD primarily affects the small and large intestine. On the other hand, the risk of extra-intestinal cancer (EIC) in IBD has obtained less focus (8), although extra-intestinal manifestations are observed in up to 35% of patients (9,10). Among the most common extra-intestinal manifestations of IBD are rheumatologic disorders (peripheral and axial arthropathy), dermatologic disorders (erythema nodosum and pyoderma gangrenosum), ophthalmologic disorders (episcleritis and uveitis), primary sclerosing cholangitis, nephrolithiasis, and thromboembolic events.

The aim of this study was to conduct a systematic literature review and meta-analysis of risk of EIC in patients with CD, UC, and IBD combined. Only population-based studies were assessed to provide estimates based on the occurrence of events in unselected patient populations representing the whole spectrum of disease extent and severity.

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METHODS

Literature search

To identify population-based papers on risk of EIC in patients with IBD, we conducted a systematic MEDLINE search (January 1966 to January 2009) using the MESH headings "inflammatory bowel disease/epidemiology" combined with a free text search on the following words: extra-intestinal/extra-colonic cancer OR neoplasia OR adenocarcinoma OR carcinoma OR malignancy OR tumor. The search was limited to items with abstracts only and studies on humans. In addition, abstracts available on CD-ROM from international conferences, the American Digestive Disease Week (2005–2009), and the United European Gastroenterology Week (2005–2008) were searched. Lastly, reference lists of included papers were studied to disclose additional literature on the topic.

Inclusion and exclusion criteria

To be included in the meta-analysis, studies had to be population based (i.e., including all pediatric and adult cases in a given geographic area in a given period of time) and CD and/or UC had to be diagnosed according to well-defined criteria (11). Furthermore, papers had to be generally available, contain information on the total number of patients followed, exact number of EICs occurring in the cohort during follow-up vs. expected number of EICs in a matched background population, and/or rates of observed to expected EIC cases with 95% confidence intervals (CIs). Studies that only contained information on cumulative cancer risk, studies representing subpopulations or selected populations (e.g., general practitioner or hospital databases, health insurance databases, hospitalization-based patient populations, pediatric cohorts, and referral center populations), reviews, case reports, editorials, and letters to the editor were excluded.

Data collection

The two first researchers conducted the search and extraction of the data separately. In case of discrepancy, consensus was made through a discussion with the senior researcher.

A total of 308 papers were identified, of which 8 (12–19) fulfilled the inclusion criteria. The study by Katsanos *et al.* (16) was a collaborative study from the EC-IBD (European Collaborative group of Inflammatory Bowel Disease) including seven European countries and Israel, and data were treated country by country when possible. For the purpose of calculating risk of hematological disorders, the population-based part of a study by Askling *et al.* (20), which provided further follow-up on the Swedish cohorts (13,15,19,21), was used.

Included papers were reviewed in detail to abstract data on author, country, calendar year of publication, calendar period of inclusion and observation, number of patients studied, median/mean follow-up, number of EICs observed in the cohort, expected numbers of EIC in a matched background population, and/or observed to expected cancer rates with 95% CIs.

Statistical analysis

Pooled risk estimates (standardized incidence ratios (SIRs), observed/expected) with 95% CIs for EIC were calculated using the STATA meta-analysis program (Stata Corporation, College Station, TX; www.stata.com). According to the test for heterogeneity (significance at 5% level), either a fixed or a random effects model was applied. A significance level of 5% was chosen. In case of reported zero incidence, the Haldane correction was used (22).

RESULTS

In all, eight papers fulfilled the inclusion criteria and reported on EIC in patients with IBD ($n=5$), (12,13,16–18) CD ($n=6$), (12–14,17–19) or UC ($n=5$) (12,13,15,17,18) (**Table 1**).

The EC-IBD study (representing eight countries) and the Ekbom study reported on the overall risk of EIC in IBD (13,16) resulting in a pooled SIR of 1.10 (95% CI 0.96–1.27; **Figure 1**). Four papers reported on overall EIC in patients with either CD (13,14) or UC (13,15), resulting in pooled SIRs of 1.13 (95% CI 0.89–1.40) and 1.04 (95% CI 0.92–1.16), respectively.

Table 1. Population-based literature on extra-intestinal cancer occurrence in patients with inflammatory bowel disease

Author, country	Calendar period (publication year)	No. of patients	Mean/median follow-up (years)	Diagnosis
Ekbom *et al.*, Sweden[a] (13)	1965–1984 (1990)	4,776	—	IBD, CD, UC
Persson *et al.*, Sweden[a] (19)	1958–1989 (1994)	1,251	—	CD
Karlen *et al.*, Sweden[a] (15)	1955–1989 (1999)	1,547	16.5	UC
Palli *et al.*, Italy (18)	1978–1997 (2000)	920	11	IBD, CD, UC
Loftus *et al.*, Minnesota, USA (17)	1950–1993 (2000)	454	14.6[b]	IBD, CD, UC
Bernstein *et al.*, Canada (12)	1984–1997 (2001)	5,529	7.4[b]	IBD, CD, UC
Jess *et al.*, Denmark (14)	1962–1997 (2003)	374	17	CD
Katsanos *et al.*, EC-IBD (16)	1991–2004 (2007)	2,201	10.3	IBD

CD, Crohn's disease; EC-IBD, European collaborative group of inflammatory bowel disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]As regards hematological disorders, these cohort studies were followed up by Askling *et al.* (20).
[b]Calculated as the number of person-years of observation divided by the number of patients in the cohort.

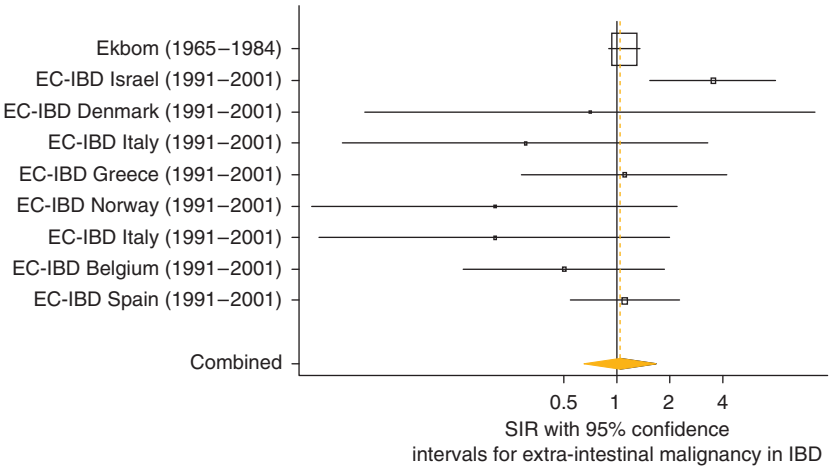

Figure 1. Individual and combined standardized incidence ratios (SIRs) with 95% confidence intervals for extra-intestinal cancer occurrence in inflammatory bowel disease: a meta-analysis of population-based cohort studies. The size of the boxes is proportional to the weight (1/s.e.) of each study.

Table 2. Risk of extra-intestinal cancer in patients with Crohn's disease: meta-analysis of population-based cohort studies

Organ	No. of studies	Lowest SIR	95% CI	Highest SIR	95% CI	Pooled SIR	95% CI
Upper gastrointestinal tract	2	0.56	0.01–3.12	3.05	1.67–5.11	2.87	1.66–4.96[a]
Stomach	3	1.44	0.43–4.80	2.56	0.94–5.56	2.05	1.06–3.97[a]
Liver and biliary system	3	1.40	0.20–0.50	5.22	0.96–28.5	2.47	0.95–6.46
Pancreas	2	0		0.70	0.00–3.70	0.51	0.06–4.57
Respiratory tract	3	0.80	0.20–2.40	2.35	0.63–6.02	1.41	0.95–2.10
Lung	4	0.90	0.20–2.70	2.94	0.79–7.53	1.82	1.18–2.81[a]
Breast	5	0.58	0.21–1.27	1.23	0.14–4.43	0.85	0.60–1.21
Cervix uteri	2	0.69	0.09–5.26	2.25	0.27–8.13	1.38	0.38–5.10
Corpus uteri	4	0.50	0.12–2.09	1.30	0.20–4.70	0.84	0.36–1.96
Ovarium	3	0.63	0.15–2.64	1.38	0.28–4.03	1.01	0.42–2.39
Prostate and testis	2	0.40	0.05–1.45	0.67	0.02–3.73	0.47	0.11–1.92
Prostate	2	0.65	0.30–1.40	1.10	0.30–2.80	0.77	0.41–1.45
Kidney	2	0.52	0.01–2.92	1.02	0.31–3.34	0.92	0.31–2.76
Urinary bladder	3	1.30	0.51–3.30	2.74	0.31–9.89	2.03	1.14–3.63[a]
Melanoma	3	1.06	0.32–3.50	2.03	0.42–5.93	1.35	0.65–2.82
Skin (squamous)	3	1.53	0.19–5.52	5.50	2.0–11.9	2.35	1.43–3.86[a]
Brain	4	0.50	0.00–2.80	1.71	0.47–4.37	1.25	0.52–3.02
Thyroid gland	2	2.85	0.59–13.7	5.56	0.14–30.98	3.38	0.87–13.14
Hematopoietic system	2[b]	1.15	0.8–1.70	2.50	0.28–9.0	1.19	0.83–1.71
Lymphoma	3[b]	1.28	0.8–1.70	2.40	1.17–4.97	1.42	0.95–2.12
Leukemia	3[b]	1.09	0.4–2.5	1.43	0.04–7.97	0.99	0.50–1.99

CI, confidence interval; SIR, standardized incidence ratio.
[a]Confidence interval excluding 1.0 ($P<0.05$).
[b]One of these studies (Askling *et al.* (20)) was based on two cohorts (13,19).

Organ-specific extra-intestinal cancer risk

CD. In CD, a significantly increased risk of cancer of the upper gastrointestinal tract (SIR 2.87, 95% CI 1.66–4.96), the stomach *per se* (SIR 2.05, 95% CI 1.06–3.97), the urinary bladder (SIR 2.03, 95% CI 1.14–3.63), and the skin (squamous) (SIR 2.35, 95% CI 1.43–3.86) was observed (**Table 2**). In addition, a significantly increased risk of pulmonary cancer was found (SIR 1.82, 95% CI 1.18–2.81; **Figure 2**), leading to a tendency toward an increased risk of overall

Table 3. Risk of extra-intestinal cancer in patients with ulcerative colitis: meta-analysis of population-based cohort studies

Organ	No. of studies	Lowest SIR	95% CI	Highest SIR	95% CI	Pooled SIR	95% CI
Stomach	3	0.3	0.00–1.50	1.02	0.36–2.84	0.73	0.31–1.70
Liver and biliary system	3	1.3	0.50–2.70	3.96	1.05–14.9	2.58	1.58–4.22[a]
Pancreas	2	0.60	0.10–1.80	0.87	0.27–2.83	0.75	0.30–1.87
Respiratory tract	3	0.23	0.03–0.83	0.82	0.50–1.34	0.67	0.45–1.01
Lung	3	0.28	0.03–1.02	0.50	0.20–1.20	0.39	0.20–0.74[a]
Breast	4	0.70	0.30–1.20	1.44	0.53–3.13	1.04	0.78–1.40
Cervix uteri	2	1.08	0.25–4.62	1.70	0.50–4.30	1.45	0.61–3.44
Corpus uteri	3	0.24	0.03–1.77	1.50	0.50–3.20	1.12	0.54–2.32
Ovarium	3	0.50	0.10–1.70	1.20	0.20–3.40	0.87	0.40–1.88
Prostate	4	0.70	0.30–1.50	1.96	0.53–5.02	1.14	0.85–1.52
Kidney	2	0.30	0.00–1.80	0.80	0.25–2.58	0.71	0.24–2.13
Urinary bladder	3	0.40	0.10–1.60	0.67	0.24–1.85	0.55	0.26–1.16
Melanoma	3	1.11	0.40–3.13	3.95	0.79–11.53	1.56	0.80–3.05
Skin (squamous)	3	0.59	0.07–2.14	2.70	1.0–5.90	1.68	0.90–3.12
Hematopoietic system	2[b]	1.17	0.9–1.6	2.70	1.16–5.33	1. 64	0.74–3.68
Lymphoma	2[b]	0.84	0.5–1.3	1.03	0.47–2.24	0.89	0.59–1.33
Non-Hodgkin's lymphoma	3[b]	0.00	0–6.4	1.8	0.20–6.5	1.12	0.67–1.87
Leukemia	3[b]	1.02	0.37–2.86	2.32	1.40–3.70	2.00	1.31–3.06

CI, confidence interval; SIR, standardized incidence ratio.
[a]Confidence interval excluding 1.0 ($P<0.05$).
[b]One of these studies (Askling *et al.* (20)) was based on two cohorts (13,15).

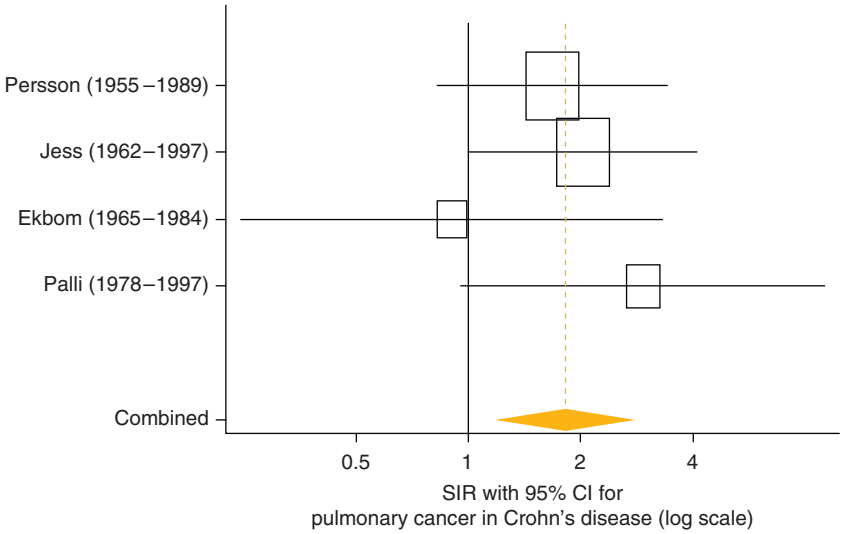

Figure 2. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for pulmonary cancer in Crohn's disease: a meta-analysis of population-based cohort studies. The size of the boxes is proportional to the weight (1/s.e.) of each study.

cancer of the respiratory tract (SIR 1.41, 95% CI 0.95–2.10). Furthermore, a borderline significantly increased risk of cancer of the liver–biliary system (SIR 2.47, 95% CI 0.95–6.46) and of lymphoma (SIR 1.42, 95% CI 0.95–2.12) was observed, whereas no cancers occurred with significantly reduced frequency (**Table 2**).

Ulcerative colitis. On the basis of four population-based studies, patients with UC were found to have a lower risk of lung cancer (SIR 0.39, 95% CI 0.20–0.74; **Figure 3**) and overall cancer of the respiratory tract (SIR 0. 67, 95% CI 0.45–1.01) when compared with the background population (**Table 3**).

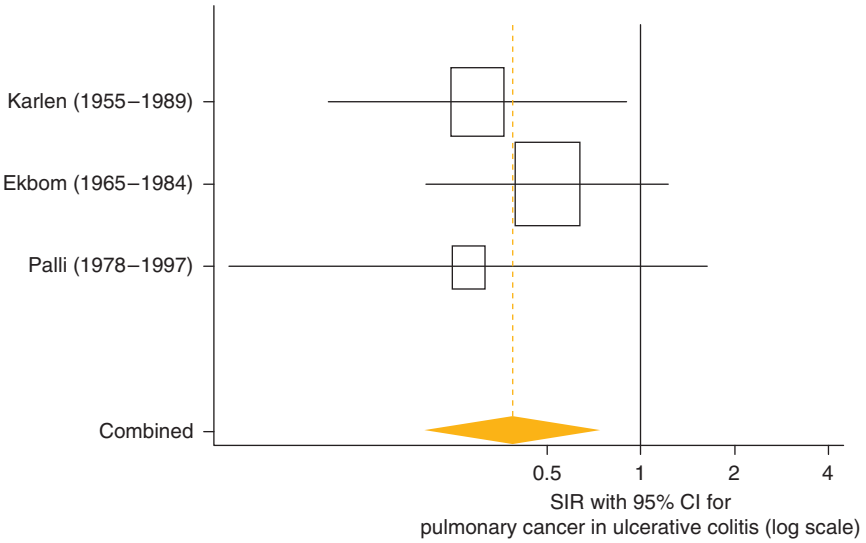

Figure 3. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for pulmonary cancer in ulcerative colitis: a meta-analysis of population-based cohort studies. The size of the boxes is proportional to the weight (1/s.e.) of each study.

Table 4. Risk of extra-intestinal cancer in patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease combined): meta-analysis of population-based cohort studies

Organ	No. of studies	Lowest SIR	95% CI	Highest SIR	95% CI	Pooled SIR	95% CI
Stomach	3	0.66	0.18–1.68	1.16	0.53–2.54	1.04	0.68–1.59
Liver and biliary system	2	1.30	0.60–2.60	4.38	1.54–12.4	1.94	1.07–3.54[a]
Pancreas	3	0.51	0.16–1.63	1.57	0.18–5.69	0.66	0.33–1.35
Respiratory tract	3	0.58	0.21–1.25	1.06	0.76–1.48	0.64	0.40–1.05
Lung	2	0.60	0.30–1.20	0.71	0.26–1.55	0.64	0.37–1.11
Breast	3	0.70	040–1.10	1.38	0.59–2.72	0.91	0.69–1.19
Cervix uteri	2	0.91	0.28–2.97	1.30	0.50–2.70	1.15	0.58–2.29
Corpus uteri	2	0.37	0.12–1.18	1.40	0.60–2.80	0.93	0.49–1.75
Ovarium	2	0.70	0.20–1.70	0.82	0.3–2.05	0.77	0.38–1.54
Prostate	3	0.86	0.57–1.28	2.13	0.69–4.97	1.16	0.88–1.52
Kidney	2	0.89	0.39–2.06	1.30	0.60–2.50	1.11	0.64–1.90
Urinary bladder	3	0.89	0.24–2.28	1.10	0.50–2.0	0.99	0.63–1.54
Melanoma	3	0.70	0.20–1.80	3.06	0.62–8.94	1.17	0.66–2.08
Skin (squamous)	2	0.72	0.15–2.11	2.20	1.10–3.90	1.79	1.01–3.16[a]
Brain	2	0.43	0.06–3.15	1.30	0.60–2.50	1.15	0.59–2.24
Hematopoietic system	2	1.0	0.50–1.60	2.65	1.27–4.88	1.60	0.62–4.16
Lymphoma	2	1.0	0.50–1.90	1.52	0.90–2.57	1.30	0.86–1.96
Non-Hodgkin's lymphoma	2	1.0	0.03–5.60	1.43	0.16–5.16	1.28	0.30–5.45
Leukemia	3	0.80	0.20–2.0	1.67	0.19–6.02	0.95	0.52–1.72

CI, confidence interval; SIR, standardized incidence ratio.
[a]Confidence interval excluding 1.0 ($P<0.05$).

On the other hand, the risk of cancer of the liver and biliary system was significantly increased (SIR 2.58, 95% CI 1.58–4.22) as was the risk of leukemia (SIR 2.00, 95% CI 1.31–3.06). Furthermore, a trend toward an increased risk of squamous cell carcinoma was observed (SIR 1.68, 95% CI 0.90–3.12; **Table 3**).

Inflammatory bowel disease. Three studies provided data on organ-specific EIC in CD and UC combined, revealing a significantly increased risk of cancer of the liver–biliary system (SIR 1.94, 95% CI 1.07- 3.54) and of squamous cell carcinoma (SIR 1.79, 95% CI 1.01–3.16; **Table 4**).

DISCUSSION

The present meta-analysis on EIC in patients with IBD, which is based on population-based studies only, revealed that despite a nonsignificantly increased overall risk for EIC among IBD patients, CD patients were at increased risk of upper gastrointestinal, lung, urinary bladder, and squamous skin cancer, and potentially also of liver–biliary cancer and lymphoma. On the other hand, UC patients had an increased risk of liver–biliary cancer and leukemia, which was counterweighted by a decreased risk of lung cancer.

The primary strength of this study was the assessment of unselected patient cohorts on the basis of strict inclusion and exclusion criteria, hence minimizing the risk of selection bias and thereby assuring the external validity of results. This allows generalization to the general IBD population and thereby to newly diagnosed patients with a yet-unknown disease course. To our knowledge, only one previous meta-analysis on risk of EIC in patients with IBD has been published—by von de Roon (8)—which includes both studies from referral centers and population-based studies reporting on the risk of EIC in CD only. In contrast to population-based studies, studies from tertiary referral centers may be biased because of referral of patients for both IBD and the extra-intestinal malignancy in question or because of an overrepresentation of severely ill IBD patients with a potentially higher risk of complications than the average patients—hence providing inappropriately elevated risk estimates. A second strength was the use of cancer diagnoses, which may be assumed to be of greater validity and to be more consistently reported than other kinds of diagnoses, including cause-of-death diagnoses.

A potential limitation was the identification of only a few studies reporting on overall EIC risk in IBD, CD, or UC, and hence limiting the interpretation of the overall risk estimates. On the other hand, organ-specific cancer reporting was fairly detailed in most studies. Another potential limitation to be considered was the risk of detection bias related to a greater awareness of other diseases among patients frequently visiting a physician, which could potentially lead to the detection of a falsely high frequency of cancers among IBD patients. However, such a limitation would imply that cancers found in excess were mild non-fatal types, which would normally not lead to detection in the general population, and furthermore, results would be expected to be the same for CD and UC patients, which was not the case.

The overall risk of EIC among IBD patients corresponded to that of the general population. However, assessing CD and UC in combination may be of limited relevance, considering the different organ-specific EIC patterns in the two disease subtypes. For CD patients *per se*, the *overall* risk of EIC was slightly but nonsignificantly increased, whereas in UC patients the risk was close to unity. Although these estimates were based on few studies, they may to some extent reflect the more detailed organ-specific estimates discussed below.

Patients with CD were found to be at increased risk of a number of EICs. First, an increased risk of upper gastrointestinal cancer, including stomach cancer, was observed, which may be directly related to the presence of CD in these organs. Patients have been suggested to have an increased risk of small and large bowel cancer (2) because of ongoing inflammation, and the same mechanisms may be hypothesized to lead to development of upper gastrointestinal cancer. However, to evaluate this hypothesis, there is a need for studies specifically assessing the association between localization of CD and upper gastrointestinal cancer occurrence in sufficiently large patient samples.

In addition, CD patients were at increased risk of pulmonary and urinary bladder cancer. These findings are most likely explained by the high prevalence of smokers among CD patients (23,24). Tobacco smoking is known not only to affect pulmonary health but also to have a causal role in the development of a number of other cancer types, including urinary bladder cancer (23). Hence, the present observations are further good reasons for encouraging CD patients to quit smoking.

On the other hand, the observation of an increased risk of squamous skin cancer among patients with CD could potentially be a key example of detection bias of a fairly mild cancer type in patients seen regularly by a physician. Alternatively, skin manifestations of IBD may be hypothesized to explain the finding, but the observed risk of skin cancer was not as pronounced in UC patients as in CD patients. A third potential explanation is the use of immunosuppressive agents, which has been reported to cause increased skin photosensitivity and potentially also non-melanoma skin cancer (25). A study on renal transplanted immunosuppressed patients has shown that 6-thioguanine (the active metabolite of azathioprine) incorporates in the DNA of skin cells, leading to photosensibility to ultraviolet A radiation and subsequent lesions of DNA (25,26). These observations could potentially explain the increased risk of skin cancer in CD patients—especially when differences in skin cancer risk in CD and UC patients were paralleled by differences in treatment strategies. However, the studies included in the present meta-analysis covered a long time span and not all patients may be assumed to have received such treatments.

Patients with UC—and to some extent also patients with CD—were found to be at an increased risk of cancer of the liver and biliary system. This observation may be related to the relatively frequent occurrence of primary sclerosing cholangitis in patients with IBD, affecting up to 5% of patients with UC and up to 3.6% of patients with CD (27,28). Patients with primary sclerosing cholangitis are known to have a lifetime risk of developing cholangiocarcinoma of 10–15% (29).

Patients with UC had, in contrast to patients with CD, a decreased risk of lung cancer, potentially explained by the low frequency of smokers among patients with UC (24,30,31). It is reassuring for patients that although onset of UC may be related to cessation of smoking (hence discouraging this action), in the long run patients are protected against smoking-related diseases, as also suggested in studies of mortality from cardiovascular disease in patients with UC (32).

Lastly, a significantly increased risk of leukemia was observed among patients with UC, whereas in patients with CD, the risk of lymphoma was borderline-significantly increased. The study by Askling *et al.*—based partly on the follow-up of two Swedish cohort studies—revealed that the increased risk of leukemia in UC was mainly explained by an excess risk of myeloid leukemia, whereas the marginally increased risk of lymphoma in CD was due to both Hodgkin's and non-Hodgkin's lymphomas (20). Another recent study by Lewis *et al.* from 2005 (33), based on IBD cases from the General Practice Research Database in the United Kingdom, found no excess risk of lymphomas in either CD (RR 1.39, 95% CI 0.5–2.40) or UC (RR 1.11, 95% CI 0.51–2.19), but results may potentially be biased toward the null owing to a selection of milder cases (as opposed to what is observed in tertiary referral

center studies). The role of the disease itself vs. the role of treatment in the development of hematological disorders has formerly been discussed (17,34) and still needs further exploration. Future studies will have to assess the occurrence of hematological cancers in patients treated according to recently introduced guidelines and compare these findings with cancer occurrence in patients with the same spectrum of disease severity but without exposure to treatment with biologics. The present results based on unselected patient materials will probably serve as the best source of comparison in this regard.

In conclusion, our meta-analysis of population-based cohort studies revealed that CD patients are at a higher risk of developing EIC than UC patients, whose risk is similar to that of the background population. CD patients are at increased risk of developing upper gastrointestinal cancer, lung, urinary bladder, and squamous cell cancer when compared with the background population, whereas UC patients are at an increased risk of developing liver–biliary cancer and leukemia counterweighted by a decreased risk of lung cancer. The present results are assumed to provide a fairly valid and generalizable picture of the occurrence of EIC in IBD and suggest a causal role of extra-intestinal manifestations of disease as well as of smoking.

CONFLICT OF INTEREST

Guarantor of the article: Tine Jess, MD.

Specific author contributions: The study was initiated by Tine Jess. Natalia Pedersen, Dana Duricova, and Margarita Elkjaer performed the literature search and selected the papers to be included in the meta-analysis. Natalia Pedersen, Dana Duricova, and Tine Jess performed the statistical analyses. Natalia Pedersen drafted the manuscript, which was critically revised by all coauthors. All authors approved the final version of the manuscript.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The risk of intestinal cancer in inflammatory bowel disease (IBD) has been analyzed thoroughly, presumably because of the fact that IBD primarily affects the small and large intestine.
- ✓ The risk of extra-intestinal cancer (EIC) in patients with IBD remains uncertain, despite knowledge of a relatively high frequency of extra-intestinal manifestations among patients with Crohn's disease (CD) and ulcerative colitis (UC).

WHAT IS NEW HERE

- ✓ This is to our knowledge the first meta-analysis assessing the risk of overall and site-specific EIC in patients with CD and UC based exclusively on population-based studies.
- ✓ We observed a higher overall risk of developing EIC among patients with CD than among patients with UC, whose risk was similar to that of the background population.
- ✓ More specifically, CD patients were at an increased risk of developing upper gastrointestinal cancer, lung, urinary bladder, and squamous cell cancer.
- ✓ On the other hand, UC patients had an increased risk of developing liver–biliary cancer and leukemia counterweighted by a decreased risk of lung cancer.

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