Increased Lifetime Risk of Intestinal Complications and Extraintestinal Manifestations in Crohn's Disease and Ulcerative Colitis

Gary R. Lichtenstein, MD,[1] Ahva Shahabi, MPH, PhD,[2] Seth A. Seabury, PhD,[3] Darius N. Lakdawalla, PhD,[4] Oliver Díaz Espinosa, PhD,[5] Sarah Green, BA,[2] Michelle Brauer, BS,[2] and Robert N. Baldassano, MD[6]

[1]Department of Medicine, Center for Inflammatory Bowel Disease, Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

[2]Health Policy and Economics, Precision Health Economics, Los Angeles, California

[3]Pharmaceutical and Health Economics, Leonard D. Schaeffer Center for Health Policy & Economics, University of Southern California, Los Angeles, California

[4]Pharmaceutical and Regulatory Innovation, Leonard D. Schaeffer Center for Health Policy & Economics, University of Southern California, Los Angeles, California

[5]Advanced Modelling Team, Precision Health Economics, Los Angeles, California

[6]Center for Pediatric Inflammatory Bowel Disease, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Corresponding author:
Dr Gary R. Lichtenstein
Raymond and Ruth Perelman School of Medicine of the University of Pennsylvania
Perelman Center for Advanced Medicine
Hospital of the University of Pennsylvania
Gastroenterology Division
Department of Internal Medicine
7th Floor South Pavilion, Room 753
3400 Civic Center Boulevard
Philadelphia, PA 19104-4283
Tel: (215) 349-8222
Fax: (215) 349-5915
E-mail: Gary.Lichtenstein@pennmedicine.upenn.edu

Keywords
Inflammatory bowel disease, lifetime disease burden, comorbidities, intestinal complications, extraintestinal manifestations

Abstract: Patients with Crohn's disease (CD) or ulcerative colitis (UC) have high morbidity rates owing to debilitating intestinal complications and extraintestinal manifestations (EIMs). We retrospectively identified patients in the Truven MarketScan databases with an incident CD or UC diagnosis from January 2008 to September 2015 to quantify the incremental lifetime risk of experiencing an intestinal complication or EIM after CD or UC diagnosis. Seven intestinal complications and 13 categories of EIMs by site were identified, and lifetime risk of experiencing an intestinal complication or EIM from age at CD or UC diagnosis to end of life was estimated using parametric models. Results were compared with controls' propensity score matched by age, sex, health plan, and pre-index Charlson Comorbidity Index. The CD or UC incremental risk was calculated using the difference in rates between CD or UC patients and matched controls. A total of 34,692 CD patients and 48,196 UC patients with 1:1 matched controls were included. CD and UC patients had an increased lifetime risk of intestinal complications, which varied across ages, inflammatory bowel disease (IBD) types, and categories of intestinal complications and EIMs. CD and UC patients aged 0 to 11 years had the highest incremental lifetime risk for all 7 intestinal complications and the majority of EIMs, with blood EIMs associated with the highest incremental risk (CD: 32%; UC: 21%). CD and UC patients of all ages have a higher lifetime risk of experiencing intestinal complications and EIMs than patients without CD or UC. When evaluating the burden of disease on patients with IBD, it is important to include the burden of these intestinal complications and EIMs in the assessment.

Patients with inflammatory bowel disease (IBD) face a lifetime of repeated disease flare-ups with both intestinal and extraintestinal symptoms. IBD consists of Crohn's disease (CD) and ulcerative colitis (UC). With approximately 70,000 new IBD cases diagnosed in the United States per year and most patients diagnosed before age 35 years,[1] treating IBD symptoms that affect multiple organs is important for improving quality of life throughout adulthood. Prompt diagnosis and appropriate treatment are crucial for reducing symptoms as well as the burden of the disease on the patient and health care system. Lifetime total cost estimates for prevalent populations incurred by patients with CD or UC are $498 billion and $377 billion, respectively, in the United States.[2] The clinical challenge of addressing IBD-related conditions is identifying patients who are most likely to experience an IBD-related condition in the future.

Intestinal and extraintestinal symptoms related to IBD are classified as either complications or manifestations of the disease, which can be a consequence of the disease activity (eg, iron-deficiency anemia), related to medical and surgical treatments (eg, malabsorption owing to loss of function, removal of diseased bowel areas that can lead to osteoporosis), or both. The European Crohn's and Colitis Organisation (ECCO) has defined extraintestinal manifestation (EIM) as "an inflammatory pathology in a patient with IBD that is located outside the gut and for which the pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."[3] EIMs can arise from the underlying physiologic basis of IBD (eg, conditions associated with joints, skin, and eyes), which sometimes can be mitigated by treating IBD.[4] Having at least 1 EIM has been associated with a higher likelihood of having another EIM in the future.[5] An estimated 25% to 40% of IBD patients have EIMs; therefore, these patients' quality of life and health status can continuously deteriorate without proper management and vigilant care over their lifetimes.[4,6-9]

Many of the complications and manifestations that affect IBD patients have also been observed in the general population; however, a comparison of lifetime risks to determine incremental risk and disease burden for patients is lacking. Although many studies report associated intestinal complications and EIMs as well as general prevalence rates for IBD,[4,5,10,11] relatively few studies have computed the incremental risks of developing these complications faced by IBD patients, and none have assessed these incremental risks over a lifetime.[12,13] A better understanding of the incremental lifetime risks from the age at diagnosis for IBD patients is important for capturing the lifetime disease burden and informing age-appropriate treatment decisions.

Table 1. Intestinal Complications and Manifestations Associated With CD and UC

Complication or Manifestation	CD or UC Patients Affected	Pediatric, Adult, or Both
Fistulas or abscesses (penetrating disease)[7,16,17]	CD	Both
Strictures (nonpenetrating disease)[7,16,17]	Both	Both
Severe GI bleeding or hemorrhage[16,17]	Both	Both
Toxic megacolon[16,17]	UC	Both
Perforation of the bowel[7,17]	Both	Both
Small bowel cancer[7]	Both	Adult
Colorectal cancer[4,5,18]	Both	Adult

CD, Crohn's disease; GI, gastrointestinal; UC, ulcerative colitis.

To fill this research gap, we evaluated the incremental lifetime risk of developing intestinal complications and EIMs among patients with CD or UC. We accomplished this for specific age groups and for a number of intestinal complications and EIMs, and in each case we compared these risks with individuals who do not have IBD. Using a cohort developed from administrative claims data, we were able to project the incremental lifetime risk of each intestinal complication and EIM following an IBD diagnosis.

Materials and Methods

Study Population

Individuals in the study population were identified using data from the Truven Health MarketScan Commercial, Claims, and Encounters database and Medicare Supplemental database (Truven Health Analytics, now IBM Watson Health) from January 2008 to September 2015. The study included CD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 555.x) and UC (ICD-9-CM 556.x) patients with a minimum of 1 year of continuous observation before and after diagnosis. Patients were included if they had a CD or UC diagnosis, defined as having 1 or more inpatient claims or 2 or more outpatient claims with a qualifying ICD-9-CM code for CD or UC and with service dates at least 30 days apart but not more than 365 days apart. The index date was assigned as the date of the first claim with a qualifying diagnosis.

All cases were defined as incident cases, with no CD or UC diagnosis codes on claims with service dates in the 365-day pre-index period. Patients were assigned to

Table 2. Extraintestinal Complications and Manifestations Associated With CD and UC

Affected Organ or Site	Complication or Manifestation	CD or UC Patients Affected	Pediatric, Adult, or Both
Blood	Thrombocytosis, anemia of chronic disease, autoimmune hemolytic anemia, and thrombophilia; iron-deficiency anemia and vitamin B12 deficiency may occur as local disease complications[4,5,7-9,11,19]	Both	Both
Eye	Uveitis, panuveitis, vasculitis, episcleritis, scleritis, keratopathy, pain, loss of vision, conjunctivitis, and iritis[4,5,7-11,19]	Both	Both
Physical or mental health	Weight loss with delayed development and growth, malnutrition, and emotional distress may occur as a local disease complication or as a result of medical and surgical treatments[7-9,20]	Both	Both
Joint	Enteropathic arthropathy (spondyloarthropathy such as sacroiliitis and ankylosing spondylitis), peripheral arthritis, and arthralgia[4,5,7-11,19]	Both	Both
Hepato-pancreatobiliary	Primary sclerosing cholangitis, liver disease, choledocholithiasis, cholelithiasis, autoimmune hepatitis, and pancreatitis[4,5,7-11,19]	Both	Both
Bone	Avascular necrosis (osteonecrosis); osteopenia and osteoporosis may occur as local disease complications or as a result of medical and surgical treatments[4,5,7,8,10,11,19]	Both	Both
Pulmonary	Pulmonary vasculitis, fibrosing alveolitis, chronic bronchitis, bronchiolitis or bronchiectasis, acute laryngotracheitis or tracheal stenosis, bronchiolitis obliterans organizing pneumonia, and pleuritis or serositis may occur as a result of medical and surgical treatments[4,5,7,8,11]	Both	Both
Mucocutaneous	Erythema nodosum and pyoderma gangrenosum, Sweet syndrome, aphthous stomatitis, cheilitis, stomatitis, aphthae, skin tags, acrodermatitis enteropathica, and psoriasis; enterocutaneous fistulas may occur as a local disease complication[4,5,7-11,19]	Both	Both
Neurologic	Multiple sclerosis, optic neuritis, peripheral neuropathies, and sensorineural hearing loss[4,5,8,10,11,19]	Both	Both
Kidney	Amyloidosis, glomerulonephritis, enterovesical fistula, ureteral obstruction, and urinary tract infection; nephrolithiasis and tubulointerstitial nephritis may occur as a result of medical and surgical treatments[4,5,7-11,19]	Both	Both
Immunologic[a]	Hemophagocytic lymphohistiocytosis[6,21]	Both	Both; higher in pediatric
Cardiac	Pericarditis, perimyocarditis, cardiomyopathy, and endocarditis[10,11,19,20]	Both	Both
Cancer	Lymphoma and leukemia[6,9,19,22]	Both	Both

[a]Included in search based on clinical guidance.

CD, Crohn's disease; UC, ulcerative colitis.

mutually exclusive CD or UC cohorts based on the types of diagnosis codes on the index date and follow-up period. Patients with multiple instances of ICD-9-CM codes for CD and UC were assigned to the condition that appeared most often in the data (eg, a patient with 3 qualifying diagnoses of CD and 1 diagnosis of UC was considered a CD case). Patients with an equal number of qualifying CD and UC diagnosis codes throughout their follow-up history were excluded, an approach similar to one used in a previous study.[14] The pre-index period was also used to assess baseline comorbidities using the Charlson Comorbidity Index, calculated using a previously published and validated algorithm.[15]

To identify the incremental lifetime risk factor for IBD patients as well as the difference in risk between IBD patients and general population controls, we matched IBD patients separately to demographically similar controls without CD or UC diagnosis. To improve the chances of finding the best match for each IBD patient, individuals without an IBD diagnosis were randomly preselected from the data (with a 10:1 ratio of controls to IBD cases) and assigned an index date matching an identified case. Controls who met the same qualifying continuous enrollment criteria as IBD patients were identified and entered the matching process. The selected qualifying controls left for each case were propensity score–matched (1:1, nearest

Table 3. Study Population Baseline Characteristics

	CD Patients n=34,692		Matched Controls (Without CD or UC) n=34,692		UC Patients n=48,196		Matched Controls (Without CD or UC) n=48,196	
Age, years	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0-11	870	2.51	863	2.49	358	0.74	317	0.66
12-17	1915	5.52	1854	5.34	1103	2.29	1064	2.21
18-29	4300	12.39	4293	12.37	4326	8.98	4243	8.80
30-39	4787	13.80	4799	13.83	6256	12.98	6305	13.08
40-49	6335	18.26	6340	18.28	9250	19.19	9239	19.17
50-59	7651	22.05	7639	22.02	11,885	24.66	11,900	24.69
60-64	3469	10.00	3518	10.14	5385	11.17	5463	11.33
65-69	1720	4.96	1735	5.00	2843	5.90	2913	6.04
≥70	3645	10.51	3651	10.52	6790	14.09	6752	14.01
Female	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	19,514	56.25	19,512	56.24	26,681	55.36	26,566	55.12
Charlson Comorbidity Index	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0	25,597	73.78	25,645	73.92	35,269	73.18	35,265	73.17
1	4300	12.39	4328	12.48	5584	11.59	5634	11.69
2	2876	8.29	2895	8.34	4128	8.57	4103	8.51
≥3	1919	5.53	1824	5.26	3215	6.67	3194	6.63
Health plan type	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
PPO	21,033	60.63	21,128	60.90	28,312	58.74	28,425	58.98
HMO	4755	13.71	4773	13.76	7050	14.63	7110	14.75
Other	8904	25.67	8791	25.34	12,834	26.63	12,661	26.27
Follow-up time in the data, years	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	2.89	1.47	3.04	1.54	2.91	1.47	3.06	1.53

CD, Crohn's disease; HMO, health maintenance organization; PPO, preferred provider organization; SD, standard deviation; UC, ulcerative colitis.

neighbor within specified calipers, without replacement) to each IBD patient based on age, sex, health plan type, and pre-index Charlson Comorbidity Index.

Using age at diagnosis, we pooled overlapping samples of patients over the years of available data, thus maximizing the data for each age group, and constructed a data set from which we could perform the analysis by age groups. The populations for analysis were stratified into specific age groups as follows: 0 to 11 years, 12 to 17 years, 18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 64 years, 65 to 69 years, and 70 years and older.

Identifying Complications and Manifestations Associated With Inflammatory Bowel Disease

Intestinal complications and EIMs among IBD patients were identified based on the literature and clinical insights. To determine the list of conditions to include in the study, we performed a targeted literature review in PubMed, Google, and Google Scholar using a combination of the following terms: complications, intestinal, extraintestinal manifestations, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pediatric, and adult. The resulting list of conditions was established by the gastroenterologists working on this study (Dr Gary R. Lichtenstein and

Table 4. Incremental Lifetime Risk of Intestinal Complications for CD Patients Compared With Patients Without Inflammatory Bowel Disease

Age, years	Fistula or Abscess	Stricture	Bleeding	Colorectal Cancer
Incremental lifetime risk for a CD patient				
0-11	+45%	+30%	+22%	+1%
12-17	+35%	+29%	+19%	+1%
18-29	+29%	+27%	+16%	+1%
30-39	+22%	+25%	+13%	+1%
40-49	+16%	+23%	+9%	+1%
50-59	+11%	+19%	+6%	+1%
60-64	+7%	+16%	+3%	+0%
65-69	+6%	+14%	+1%	+0%
≥70	+4%	+11%	+0%	+0%
Lifetime risk for a person without CD or UC (from the age of CD diagnosis of their matched CD patient)				
0-11	2%	1%	8%	0%
12-17	3%	1%	10%	1%
18-29	3%	1%	11%	1%
30-39	3%	2%	12%	2%
40-49	3%	2%	13%	2%
50-59	3%	3%	14%	3%
60-64	3%	4%	14%	4%
65-69	3%	5%	14%	5%
≥70	2%	5%	13%	5%

Lists of intestinal complications and extraintestinal manifestation categories are separately ordered based on descending values of incremental risk for a CD patient diagnosed at 0 to 11 years of age. Toxic megacolon, bowel perforation, small bowel cancer, immunologic, and cardiac complications were not shown owing to small sample size.

CD, Crohn's disease; UC, ulcerative colitis.

Dr Robert N. Baldassano). The final comprehensive list of conditions used in the study consists of 7 separate intestinal complications (strictures, severe intestinal bleeding or hemorrhage, toxic megacolon, perforation of the bowel, small bowel cancer, colorectal cancer, fistulas or abscesses) and 13 groups of EIMs (blood, bone, cancer, cardiac, eye, hepatopancreatobiliary, immunologic, kidney, joint, mucocutaneous, neurologic, physical or mental health, pulmonary) (Tables 1 and 2).[4-11,16-22]

Using the list of intestinal complications and EIMs and associated ICD-9-CM codes, patients were flagged if they had any of the intestinal complications or EIMs. Patients were required to have at least 2 diagnoses for any of the EIMs of the specific organ site after the index date in order to be flagged as having an EIM of that specific body site. Having at least 2 claims ensured greater accuracy by reducing the likelihood of including patients who might have received a claim for a tentative diagnosis that was later ruled out. A previous study also implemented a multiclaim definition to improve accuracy,[12] although that study was able to use at least 5 claims owing to longer follow-up of a population-based database.

For patients who were identified as having an intestinal complication or EIM, the duration of time from IBD diagnosis to the date of the first diagnosis of each intestinal complication or EIM was determined. To reduce bias, we excluded patients who had a diagnosis of the complication at least 12 months prior to the index date. Although it is possible for IBD patients to be diagnosed with an intestinal complication or EIM before their IBD diagnosis,[5] excluding these patients from the analysis would reduce the chances of a risk estimate bias, which can occur if these patients are more likely to have an undiagnosed IBD for a longer duration and thus have a biased index date.

For the EIMs, we evaluated the risk of being diagnosed with at least 1 EIM in the specific body site. For example, a patient flagged with 3 ocular EIMs and 1 bone EIM after IBD diagnosis was identified as having both an ocular EIM (using the service date of the first claim as the incident occurrence) and a bone EIM (using the same strategy). In the analysis, lifetime risk was evaluated separately for each EIM organ category.

Statistical Analysis

To calculate the lifetime risk of complications, parametric models were used to extrapolate the limited data of our study population, from age of IBD diagnosis to a specific intestinal complication or EIM or to censoring or death. For each intestinal complication or EIM category, separate parametric models were created to determine risk factors. To determine the best-fitting model for the data, different variations of flexible parametric survival models were evaluated. Based on visual inspections of the data fit with various distributions, the parametric model with the Weibull distribution provided the best fit for extrapolation of survival curves. Categories for age at diagnosis were included as the only covariate in the model to capture the lifetime risk by age group. For each intestinal complication or EIM assessed, a survival curve was built for each age group, which was then used to average the probability of having a complication over a lifetime distribution, based on the time from and age at IBD diagnosis. To estimate the lifetime risk, mortality probabilities were incorporated in the models to account for risk of death as a person ages using US Life Tables for the general US population.[23] Survival curves were then extrapolated using the parameters from the data to determine the risk

Table 5. Incremental Lifetime Risk of Extraintestinal Manifestations for CD Patients Compared With Patients Without Inflammatory Bowel Disease

Age, years	Blood	Physical or Mental Health	Muco-cutane-ous	Eye	Joint	Genito-urinary	Hepato-pancreato-biliary	Cancer	Bone	Pulmo-nary	Neuro-logic
Incremental lifetime risk for a CD patient											
0-11	+32%	+31%	+24%	+22%	+17%	+15%	+12%	+9%	+6%	+1%	+3%
12-17	+32%	+27%	+20%	+19%	+14%	+14%	+12%	+11%	+8%	+2%	+5%
18-29	+31%	+25%	+17%	+17%	+13%	+14%	+12%	+12%	+9%	+2%	+6%
30-39	+29%	+22%	+14%	+15%	+11%	+13%	+11%	+13%	+11%	+3%	+7%
40-49	+26%	+19%	+11%	+12%	+9%	+12%	+10%	+13%	+11%	+4%	+9%
50-59	+23%	+15%	+8%	+9%	+8%	+10%	+9%	+12%	+11%	+5%	+10%
60-64	+19%	+12%	+5%	+6%	+7%	+8%	+8%	+9%	+9%	+5%	+10%
65-69	+16%	+10%	+4%	+5%	+7%	+7%	+8%	+8%	+8%	+5%	+9%
≥70	+14%	+8%	+3%	+4%	+6%	+6%	+7%	+7%	+6%	+5%	+8%
Lifetime risk for a person without CD or UC (from the age of CD diagnosis of their matched CD patient)											
0-11	6%	59%	11%	17%	59%	11%	12%	7%	1%	1%	2%
12-17	8%	61%	11%	19%	66%	12%	14%	11%	3%	1%	3%
18-29	10%	61%	11%	20%	69%	13%	16%	15%	4%	2%	4%
30-39	12%	61%	11%	21%	73%	14%	17%	21%	6%	3%	6%
40-49	15%	60%	11%	21%	76%	15%	18%	28%	9%	5%	9%
50-59	17%	57%	10%	21%	76%	15%	18%	35%	12%	8%	13%
60-64	19%	53%	9%	19%	75%	15%	18%	41%	17%	12%	17%
65-69	20%	50%	8%	18%	74%	14%	17%	43%	19%	14%	19%
≥70	20%	46%	7%	17%	72%	13%	16%	44%	22%	17%	21%

Lists of intestinal complications and extraintestinal manifestation categories are separately ordered based on descending values of incremental risk for a CD patient diagnosed at 0 to 11 years of age. Toxic megacolon, bowel perforation, small bowel cancer, immunologic, and cardiac complications were not shown owing to small sample size.

CD, Crohn's disease; UC, ulcerative colitis.

of experiencing an intestinal complication or EIM as a person ages until death. Technical details underlying the methodology used to estimate lifetime risk of complication by age can be found in the technical documentation (see Supplementary Material at www.gastroenterology-andhepatology.net).

Results

Patient Population

Characteristics of the CD and UC populations with their 1:1 propensity score–matched controls are shown in Table 3. A total of 34,692 incident CD patients and their 34,692 matched controls and 48,196 incident UC patients and their 48,196 matched controls were included. No statistically significant differences (P<.05) were observed in matched characteristics between the CD or UC populations and their matched controls, as was expected if matching is successful. Approximately 3 years of follow-up were used in the analysis and for extrapolation of survival curves.

Incremental Lifetime Risks for Crohn's Disease Patients

The incremental risks of experiencing an intestinal complication or EIM for a CD patient and for an individual without IBD by age group are shown in Tables 4 and 5. Among intestinal complications, CD patients diagnosed at younger ages faced the highest incremental lifetime risk, with the highest risk for fistula or abscess among those diagnosed with CD at 0 to 11 years of age (45% increased lifetime risk compared with patients without IBD). Overall, the incremental risk of an intestinal complication was inversely related to increasing age at CD diagnosis. The incremental risk for having a stricture remained at greater than 10% among all age groups. The risk of colorectal cancer for patients 60 years of age

Table 6. Incremental Lifetime Risk of Intestinal Complications for UC Patients Compared With Patients Without Inflammatory Bowel Disease

Age, years	Bleeding	Stricture	Perforation	Colorectal Cancer
Incremental lifetime risk for a UC patient				
0-11	+44%	+7%	+7%	+1%
12-17	+38%	+8%	+7%	+1%
18-29	+33%	+8%	+7%	+1%
30-39	+27%	+9%	+6%	+2%
40-49	+21%	+10%	+6%	+1%
50-59	+15%	+10%	+5%	+1%
60-64	+9%	+10%	+4%	+1%
65-69	+7%	+10%	+4%	+1%
≥70	+5%	+10%	+3%	+0%
Lifetime risk for a person without CD or UC				
0-11	7%	0%	2%	0%
12-17	9%	0%	2%	1%
18-29	11%	0%	2%	1%
30-39	12%	0%	2%	2%
40-49	14%	0%	3%	2%
50-59	15%	0%	3%	3%
60-64	15%	0%	3%	4%
65-69	15%	0%	2%	4%
≥70	14%	0%	2%	5%

Lists of intestinal complications and extraintestinal manifestation categories are separately ordered based on descending values of incremental risk for a UC patient diagnosed at 0 to 11 years of age. Toxic megacolon, bowel perforation, small bowel cancer, immunologic, and cardiac complications were not shown owing to small sample size.

CD, Crohn's disease; UC, ulcerative colitis.

or older was the same as for patients without IBD (ie, 0% incremental risk when compared with controls) and slightly higher (increase of 1% in risk) for IBD patients younger than 60 years of age.

When comparing all intestinal complications and EIMs across age groups, CD patients had a higher lifetime risk than patients without CD at all ages. Specifically across categories, blood EIMs topped the list and remained at greater than 10% increased risk at all ages compared with controls (0-11 years: 32%; ≥70 years: 14%), followed by physical or mental health (0-11 years: 31%; ≥70 years: 8%). For all other categories, CD patients had a greater than 10% incremental risk of eye, joint (with the exception of patients 40-49 years, who had a 9% incremental risk), genitourinary, and hepatopancreatobiliary complications among those younger than 50 years, compared with controls. The incremental risk of extraintestinal cancers and bone, pulmonary, and neurologic EIMs rose with increasing CD diagnosis age and leveled out or lowered following age 50 years; this trend of increasing risk with age was also seen among matched controls, although it was lower in magnitude.

The average total and incremental lifetime risk of intestinal complications or EIMs for a CD patient is shown in Figure 1. In the matched-control population, lifetime risk was highest for physical or mental health EIMs (0-11 years: 59%; ≥70 years: 46%) and joint EIMs (0-11 years: 59%; ≥70 years: 72%) compared with other categories of EIMs (Table 5).

Incremental Lifetime Risks for Ulcerative Colitis Patients

Among intestinal complications, UC patients diagnosed at younger ages faced the highest incremental lifetime risk of intestinal bleeding and perforation (0-11 years: 44% and 7%, respectively; Table 6). However, the incremental risk of strictures was higher for patients 40 years of age or older, compared with younger patients (10% vs <10% increased risk). The risk of colorectal cancer in patients 60 years of age or older was less than that seen in patients without IBD and slightly higher (increase of 1%-2% in risk) for IBD patients younger than 60 years of age.

For all intestinal complications and EIMs, UC patients had a higher risk than their non-UC counterparts at all ages. As with CD patients, blood (hematologic) conditions were the EIM with the highest incremental risk among youngest UC patients (0-11 years: 21%; ≥70 years: 4%), followed by conditions of the eye (0-11 years: 18%; ≥70 years: 5%), physical or mental health (0-11 years: 14%; ≥70 years: 6%), and hepatopancreatobiliary complication (0-11 years: 12%; ≥70 years: 3%). Following with less than 10% incremental risk starting at pediatric ages and decreasing into adulthood were mucocutaneous and joint complications and extraintestinal cancers (with cancer risk increasing slightly but then decreasing at age 50 years or older). Among UC patients, the incremental risk of bone, neurologic, genitourinary, and pulmonary complications or EIMs rose with increasing UC diagnosis age, although most decreased slightly toward the oldest ages.

The average total and incremental lifetime risks of intestinal complications and EIMs for a UC patient are shown in Figure 2. In the matched-control population, lifetime risk was highest for physical or mental health EIMs (0-11 years: 60%; ≥70 years: 46%) and joint EIMs (0-11 years: 60%; ≥70 years: 72%) compared with other categories of EIMs (Table 7).

Table 7. Incremental Lifetime Risk of Extraintestinal Manifestations for UC Patients Compared With Patients Without Inflammatory Bowel Disease

Age, years	Blood	Eye	Physical or Mental Health	Hepato-pancreato-biliary	Muco-cutane-ous	Joint	Cancer	Bone	Neuro-logic	Genito-urinary	Pulmo-nary
Incremental lifetime risk for a UC patient											
0-11	+21%	+18%	+14%	+12%	+8%	+8%	+6%	+3%	+2%	+2%	+0%
12-17	+20%	+17%	+13%	+11%	+8%	+7%	+7%	+4%	+3%	+2%	+0%
18-29	+19%	+16%	+11%	+9%	+8%	+7%	+8%	+5%	+3%	+2%	+1%
30-39	+17%	+15%	+10%	+8%	+8%	+7%	+8%	+6%	+4%	+2%	+1%
40-49	+14%	+13%	+9%	+7%	+7%	+6%	+8%	+7%	+5%	+3%	+1%
50-59	+11%	+10%	+8%	+5%	+6%	+6%	+7%	+7%	+5%	+3%	+1%
60-64	+8%	+8%	+7%	+4%	+6%	+6%	+5%	+7%	+5%	+3%	+1%
65-69	+6%	+6%	+6%	+3%	+5%	+6%	+5%	+6%	+5%	+3%	+1%
≥70	+4%	+5%	+6%	+3%	+4%	+6%	+4%	+6%	+4%	+3%	+0%
Lifetime risk for a person without CD or UC											
0-11	6%	13%	60%	16%	10%	60%	8%	2%	2%	15%	0%
12-17	9%	15%	61%	17%	10%	66%	13%	3%	4%	17%	1%
18-29	10%	16%	62%	18%	10%	70%	17%	4%	5%	17%	2%
30-39	13%	17%	62%	18%	10%	74%	24%	6%	7%	18%	3%
40-49	15%	18%	60%	19%	10%	76%	31%	9%	11%	18%	5%
50-59	17%	18%	57%	18%	9%	77%	38%	12%	15%	18%	8%
60-64	19%	17%	53%	17%	8%	76%	43%	16%	19%	16%	12%
65-69	19%	17%	50%	16%	7%	74%	45%	18%	21%	15%	14%
≥70	19%	16%	46%	15%	6%	72%	45%	20%	23%	14%	16%

Lists of intestinal complications and extraintestinal manifestation categories are separately ordered based on descending values of incremental risk for a UC patient diagnosed at 0 to 11 years of age. Toxic megacolon, bowel perforation, small bowel cancer, immunologic, and cardiac complications were not shown owing to small sample size.

CD, Crohn's disease; UC, ulcerative colitis.

Discussion

Results of this study are consistent with the findings that CD and UC patients have an increased lifetime risk for all intestinal complications and EIMs compared with the general population.[4,5,10,11] Published data further quantifying the differences in EIMs between IBD and non-IBD patients are sparse, and additional research is needed. Previous studies have reported the proportions of patients experiencing specific complications and manifestations rather than the lifetime risk or likelihood of experiencing the intestinal complication or EIM after IBD diagnosis.[4,5,8-10,21] Although they are useful for understanding the percentage of IBD patients who experience the intestinal complication or EIM, proportion estimates fail to provide clinical insight into which patients may be at highest risk for specific conditions.

The current study improves our understanding of the magnitude of increased risk for EIMs at different stages of the disease, providing valuable information that can be used to inform the optimal multidisciplinary treatment of individuals with IBD. For example, knowing that adult patients are at higher risk for intestinal complications or EIMs than younger IBD patients or patients without IBD can help clinicians maintain proper vigilance, determine potential follow-up, and administer appropriate treatment to prevent other diseases or, at a minimum, mitigate disease severity and progression.

Lifetime risk differs substantially and depends on the age at diagnosis for patients with IBD. In this study, we found that most intestinal complications and EIMs with the highest incremental lifetime risk were seen in the younger populations and decreased with increasing age. Based on the pathophysiology of IBD, the occurrence

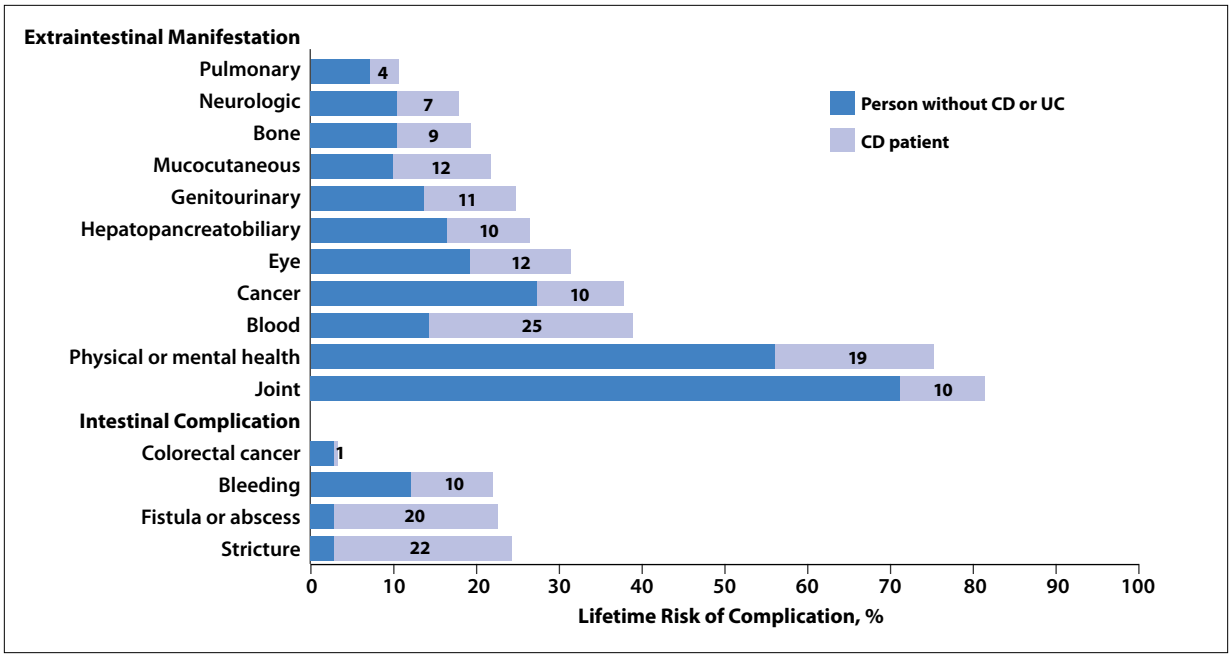

Figure 1. Average lifetime risk of complications and manifestations for a Crohn's disease (CD) patient vs a person without CD or ulcerative colitis (UC). Categories for intestinal complications and extraintestinal manifestations are ordered by ascending total lifetime risk for a CD patient.

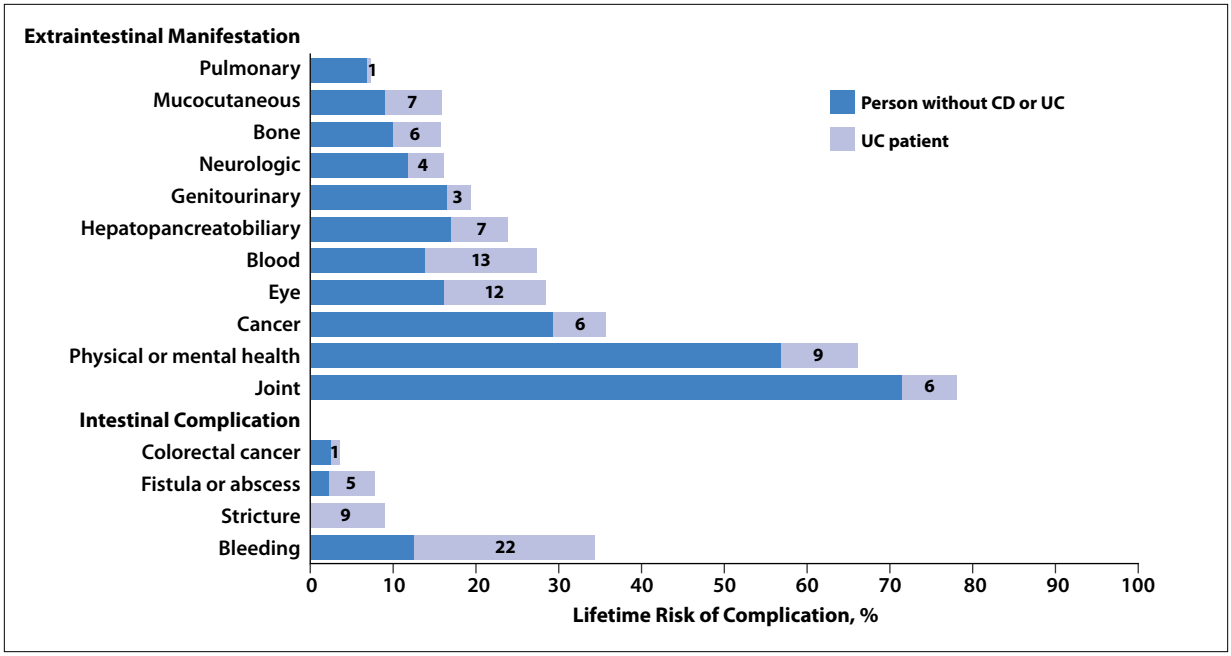

Figure 2. Average lifetime risk of complications and manifestations for an ulcerative colitis (UC) patient vs a person without UC or Crohn's disease (CD). Categories for intestinal complications and extraintestinal manifestations are ordered by ascending total lifetime risk for a UC patient.

of intestinal complications, blood EIMs, and physical or mental health EIMs would generally be expected to correlate with levels of IBD activity; thus, it would be reasonable to observe similar risk patterns in these categories of intestinal complications and EIMs, as demonstrated in our analysis.

Lifetime risk estimates also varied according to IBD type. For the youngest age group (0-11 years), incremental

lifetime risk estimates differed between CD and UC, with fistulas or abscesses and blood EIMs showing the highest estimates for CD patients, and intestinal bleeding and blood EIMs the highest for UC patients. Pediatric IBD patients generally have a more severe disease pathway[8,24] and, on average, live more years with their IBD, which may raise their potential for experiencing complications. In a separate analysis, the average patient was estimated to accrue an additional $416,352 or $195,799 in health care costs in their lifetime for CD and UC diagnoses, respectively.[2] Patients diagnosed at a younger age accrued higher incremental costs than patients who received their diagnosis later in life. The higher risk of intestinal complications and EIMs in these younger patients found in this analysis may explain the increase in estimated lifetime total health care costs.

The lifetime risk of physical or mental health and joint EIMs remains high in patients without IBD throughout their lives, with increased risk of developing a joint EIM among older patients (Tables 5 and 7). In a previous retrospective claims analysis of IBD patients, those patients treated with gut-targeted biologic therapy experienced more EIMs than those treated with broader biologic therapies.[25] The authors hypothesized that EIMs may be associated with more systemic inflammation, which targeted biologics bypass in the treatment of IBD.[25] Systemic therapies for IBD may have contributed to the numerical difference in EIMs reported. In this study, the average lifetime risk of developing a joint EIM was generally the greatest among all EIM categories in both IBD and non-IBD patients; this may be because of the inclusion of arthralgia as a joint manifestation. The roles of ustekinumab (Stelara, Janssen) and Janus kinase inhibitors in EIM management have not been adequately established, and comparative trials are needed to define recommended treatment strategies.[26]

The nature of the association between EIMs in IBD vs non-IBD populations is poorly understood. Although an in-depth discussion of potential mechanisms of EIMs was beyond the scope of this study, several theories on the pathogenesis of EIMs have been reported. Hedin and colleagues described 2 main mechanisms that are not mutually exclusive and may contribute to different EIMs.[3] The first mechanism involves an extension of immune responses from the intestine, including ectopic expression of gut-specific chemokines and adhesion molecules, T-cell trafficking driven by nonspecific adhesion molecules, microbial antigen translocation and/or cross-reactivity, and circulating antibodies. The second mechanism involves independent inflammatory events that lead to EIMs, including a shift in inflammatory tone to favor the development of EIMs, systemic changes in innate immune function, gut microbiota, and altered hematopoiesis.

Limitations

Several study design considerations may limit the interpretation and generalizability of our findings. First, we did not assess the risk of having additional complications after patients experience their first complication. Our study evaluated the risks independent of the number of types of conditions patients may experience during their lifetimes, although patients who do have at least 1 complication may have an increased risk of having another later in their life. Second, by using US Life Tables for the general US population, our model may underestimate the true mortality rates for IBD patients. Results of our targeted literature search indicated that there was no consensus on mortality rates for IBD patients differing from that of the average person. In some studies, CD or UC patients had increased risk of mortality,[27-29] possibly resulting from these EIMs,[30] yet in others there was no difference.[27,28,31] In our analysis, we assumed that the mortality rate of CD or UC patients matched that of the average person. Third, since we evaluated categories of EIMs, the overall risk should not be applied to each separate disease within the group; patients may experience one specific condition more frequently than another in the same category.

Conclusion

This study demonstrates that patients with CD and UC experience increased lifetime risk of intestinal complications that varies by age, type of IBD, and category of intestinal complication and EIM. Additional research is needed to examine the nature of the association between EIMs and IBD, including the role of inflammation and immune-mediated response in the pathogenesis of EIMs. Some current IBD therapies, as well as innovative therapies that effectively alleviate CD and UC symptoms, may help reduce the potential occurrence of other related comorbidities. Although this study did not assess the impact of current treatment on the lifetime risk of complications and EIMs, future studies evaluating the burden of CD and UC should consider the impact of treatment in patients of all ages during their lifetimes.

Acknowledgments

The authors received editorial support in the preparation of this report from Precision Health Economics and Peloton Advantage, LLC, an OPEN Health company, sponsored by Bristol Myers Squibb. The authors, however, directed and are fully responsible for all content and editorial decisions for this report.

Specific Author Contributions

Dr Lichtenstein, Dr Shahabi, Dr Seabury, Dr Lakdawalla, Ms Green, and Dr Baldassano conceptualized the research

project. Dr Shahabi, Dr Seabury, Dr Lakdawalla, Dr Díaz Espinosa, and Ms Brauer received medical writing assistance with academic inputs from all authors. All authors contributed to data collection and data interpretation, as well as provided critiques of the manuscript. All authors also gave approval of the final draft of the manuscript. All authors had full access to all of the data.

Financial Support

This study was supported by Bristol Myers Squibb, Princeton, New Jersey. Dr Seabury acknowledges partial support from an unrestricted departmental grant to the Department of Ophthalmology at the University of Southern California.

Potential Competing Interests

Dr Lichtenstein has served as a consultant for AbbVie, Actavis, Celgene Corporation/Bristol Myers Squibb, Ferring, Hospira, Janssen, Lilly, Luitpold/American Regent, Merck, Pfizer, Prometheus, Romark, Salix/Valeant, Santarus, Shire, Takeda, and UCB; and has received grant/research support from Celgene Corporation and Bristol Myers Squibb to conduct this study. Dr Shahabi has served as an employee of Precision Health Economics (PHE). Dr Díaz Espinosa, Ms Green, and Ms Brauer have served as employees of PHE, a research consultancy that received financial support from Celgene Corporation and Bristol Myers Squibb to conduct this study. Dr Seabury has served as a consultant for PHE. Dr Lakdawalla has served as a consulting scientific advisor for PHE and has been an investor in Precision Medicine Group, the parent company of PHE. Dr Baldassano has received grant/research support from Celgene Corporation and Bristol Myers Squibb to conduct this study.

Data Sharing

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

References

1. Crohn's & Colitis Foundation of America. The facts about inflammatory bowel diseases. https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf. Published November 2014. Accessed December 23, 2021.
2. Lichtenstein GR, Shahabi A, Seabury SA, et al. Lifetime economic burden of Crohn's disease and ulcerative colitis by age at diagnosis. *Clin Gastroenterol Hepatol*. 2020;18(4):889-897.e10.
3. Hedin CRH, Vavricka SR, Stagg AJ, et al. The pathogenesis of extraintestinal manifestations: implications for IBD research, diagnosis, and therapy. *J Crohns Colitis*. 2019;13(5):541-554.
4. Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol*. 2013;10(10):585-595.
5. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2011;7(4):235-241.
6. Ashworth LA, Billett A, Mitchell P, Nuti F, Siegel C, Bousvaros A. Lymphoma risk in children and young adults with inflammatory bowel disease: analysis of a large single-center cohort. *Inflamm Bowel Dis*. 2012;18(5):838-843.
7. Diefenbach KA, Breuer CK. Pediatric inflammatory bowel disease. *World J Gastroenterol*. 2006;12(20):3204-3212.
8. Mamula P, Markowitz JE, Baldassano RN. Inflammatory bowel disease in early childhood and adolescence: special considerations. *Gastroenterol Clin North Am*. 2003;32(3):967-995, viii.
9. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.
10. Ardizzone S, Puttini PS, Cassinotti A, Porro GB. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis*. 2008;40(suppl 2):S253-S259.
11. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. *World J Gastroenterol*. 2006;12(30):4819-4831.
12. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2001;96(4):1116-1122.
13. Card TR, Langan SM, Chu TPC. Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported. *Dig Dis Sci*. 2016;61(9):2619-2626.
14. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med*. 2008;50(11):1261-1272.
15. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
16. Arora G, Singh G, Vadhavkar S, et al. Incidence and risk of intestinal and extra-intestinal complications in Medicaid patients with inflammatory bowel disease: a 5-year population-based study. *Dig Dis Sci*. 2010;55(6):1689-1695.
17. Crohn's & Colitis Foundation of America. Fact sheet: about Crohn's disease and ulcerative colitis. https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/IBDoverview.pdf. Published June 2018. Accessed December 23, 2021.
18. Lichtenstein GR. Reduction of colorectal cancer risk in patients with Crohn's disease. *Rev Gastroenterol Disord*. 2002;2(suppl 2):S16-S24.
19. Jose FA, Heyman MB. Extraintestinal manifestations of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2008;46(2):124-133.
20. Mamula P, Markowitz JE, Baldassano RN, eds. *Pediatric Inflammatory Bowel Disease.* 2nd ed. New York, NY: Springer; 2013. http://dx.doi.org/10.1007/978-1-4614-5061-0. Accessed December 23, 2021.
21. Biank VF, Sheth MK, Talano J, et al. Association of Crohn's disease, thiopurines, and primary Epstein-Barr virus infection with hemophagocytic lymphohistiocytosis. *J Pediatr*. 2011;159(5):808-812.
22. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13(5):847-858.e4.
23. Arias E, Heron M, Xu J. United States Life Tables, 2012. *Natl Vital Stat Rep*. 2016;65(8):1-65.
24. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology*. 2008;135(4):1106-1113.
25. Dubinsky MC, Cross RK, Sandborn WJ, et al. Extraintestinal manifestations in vedolizumab and anti-TNF-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(9):1876-1882.
26. Greuter T, Rieder F, Kucharzik T, et al. Emerging treatment options for extraintestinal manifestations in IBD. *Gut*. 2021;70(4):796-802.
27. Caini S, Bagnoli S, Palli D, et al. Total and cancer mortality in a cohort of ulcerative colitis and Crohn's disease patients: the Florence inflammatory bowel disease study, 1978-2010. *Dig Liver Dis*. 2016;48(10):1162-1167.
28. Bewtra M, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. *Inflamm Bowel Dis*. 2013;19(3):599-613.
29. Card T, Hubbard R, Logan RFA. Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology*. 2003;125(6):1583-1590.
30. Kassam Z, Belga S, Roifman I, et al. Inflammatory bowel disease cause-specific mortality: a primer for clinicians. *Inflamm Bowel Dis*. 2014;20(12):2483-2492.
31. 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(3):609-617.

Supplementary Material

Technical Documentation Estimating Lifetime Risk of Complications

Lifetime Complication Risk Estimates

We estimated the probability of developing a complication during the lifetime of an individual diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) and their matched controls who were not affected by CD or UC. These individuals were used to estimate the distribution of time at which a complication occurs after their index date.

We considered data only from individuals who had no history of the specific complication we assessed before they were diagnosed with CD or UC. For each disease group, we grouped data by whether they came from a case (UC or CD) or a matched control. Using survival techniques, we built a parametric model for the distribution of time from diagnosis to time at which the complication appears. Because we successfully matched cases and controls using demographic characteristics, the age of diagnosis was included as the only covariate in the models to estimate the risk based on age at diagnosis.

Expression for Probability of Developing a Complication After Crohn's Disease or Ulcerative Colitis Diagnosis

Suppose that an individual was diagnosed with CD (similarly for UC) at age x with no prior history of complications. For a given complication a, we used T_x^a to denote the time after the diagnosis at which complication a appears. Under these assumptions, the probability that complication a occurs is given by $P[T_x^a < \infty]$.

We built a parametric model for the survival distribution

$$S_x^a(t) := P[T_x^a > t | T_x^a < \infty]$$

We then used standard US Life Tables to estimate mortality. For an individual of age x, the distribution

$$F_x(t) = P[T_x \le t]$$

and survival function S_x of their time of death T_x are related by

$$S_x(t) = 1 - F_x(t)$$

Assuming that the time at which the complication occurs is independent of the time of mortality, a conditioning argument gives

$$P[T_x^a < \infty] = \mathrm{E}\left[\mathrm{P}[T_x^a < \infty | T_x]\right] = E[P[T_x^a < T_x | T_x]] = E[1 - S_x^a(T_x)]$$

As the survival function S_x^a, the cumulative hazard function H_x^a and hazard function h_x^a of the t time T_x^a at which complication a occurs are related by the expressions

$$S_x^a(t) = \exp(-H_x^a(t))$$

$$H_x^a(t) = \int_0^t h_x^a(s)ds$$

From this, it can be deduced that the risk (r_x^a) of experiencing complication a for an individual diagnosed with CD or UC at age x (age x at index date for matched controls) is given by

$$r_x^a := P[T_x^a < \infty] = E[F_x^a(T_x)] = \int_0^\infty h_x^a(t) S_x^a(t) S_x(t) dt$$

The terms S_x^a and h_x^a are estimated using a parametric model of the form

$$h_x^a(t) = h_a(t) \exp(\beta_0 + \beta_1 x)$$

Parametric Estimate for Survival Function of Time of Complication

Parametric models allow for extrapolation of survival curves beyond the data range of the data set. Therefore, we evaluated these models to determine which would be the best fit for our data. The Weibull distribution has a simple expression and is flexible enough to accommodate a great variety of shapes. Based on visual inspection of the model fit that was determined by plotting a Kaplan-Meier curve and applying parametric models on top of the curve, we confirmed that the Weibull distribution best fits our data.

Data to build this model were used from CD and UC patients with their matched controls who had no history of the complication assessed before the time of diagnosis. Data from individuals who did not develop a complication after time of diagnosis were censored.

For each disease (CD or UC) and for each complication a, we built a Weibull-type parametric model to estimate the survival function

$$S_x^a(t) = P[T_x^a > t | T_x^a < \infty]$$

The general model for $S_x^a(t)$ is given by

$$S_x^a(t) = \exp\left(-t^k \exp(-b_{0a} - b_{1a}x)\right)$$

$$h_x^a(t) = kt^{k-1} \exp(-b_{0a} - b_{1a}x)$$

where x is the age of an individual at the time of diagnosis for CD or UC and k, b_{0a}, and b_{1a} are parameters to be estimated. The survival function for mortality $S_x(t)$ is estimated directly from US Life Tables by interpolation of times between integer values. The lifetime risk was calculated from the extrapolation of the parameters measured from the data using survival techniques assuming the Weibull distribution. The risk of complication $r_x^a = P[T_x^a < \infty]$ was then computed by numerical integration over the time interval $[0,\infty]$.