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Malignancies Associated With Inflammatory Bowel Diseases

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Abstract:
MALIGNANCIES ASSOCIATED WITH INFLAMMATORY BOWEL DISEASES. Nicole G. Jawitz, Deborah D. Proctor. Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT.

Inflammatory Bowel Diseases (IBD), specifically Crohn's disease and ulcerative colitis, have been associated with numerous intestinal and extra-intestinal malignancies. Recent studies have suggested use of immunomodulator therapies has increased risks of malignancies, including melanoma, non-epithelial skin cancers, cervical cancer, and bladder and urinary tract cancers. The question regarding how biologic agents, which became a mainstay therapy of IBD in the early 2000s, have influenced malignancy risk among patients with IBD has yet to be definitely answered.

The aims of this study were to characterize prevalence of comorbid malignancies among hospitalized patients with IBD and how it has changed over the past decade, to develop a sense of the chronology by which malignancies present in IBD patients relative to the general population, and to identify malignancies that are less well defined in the context of IBD. The overall hypothesis of this work is that the prevalence of co-diagnosed malignancies among hospitalized patients with IBD has changed significantly over the study period.

This is a cross-sectional analysis characterizing the comorbid malignancies of hospitalized patients, with and without IBD, across the United States at two time points, spanning nearly a decade. Using the Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (HCUP-NIS) database years 2002 and 2003, and 2010 and 2011, the absolute and percent prevalence of malignancies were calculated for patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess rate of change of prevalence in patients with IBD relative to patients without IBD.

There was no difference in prevalence of colon cancer among IBD patients in 2010-2011 compared to 2002-2003, across all age groups. Both anorectal and colon cancer rates were increased among patients with IBD compared to those without. There was an increase in the co-diagnosis of Non-Hodgkin lymphoma and IBD in the 58-67 year old age group in 2010-2011 compared to 2002-2003. Cervical cancer prevalence was increased among 38-47 year old women with IBD, and non-epithelial skin cancers were increased among older IBD patients. There were no statistical differences in rates of Hodgkin lymphoma, leukemia, melanoma, pancreatic and bladder cancers between patients with or without IBD.

Substantial changes in the prevalence of several types of cancers among hospitalized patients with IBD have occurred in the study time period. There continues to be an increased risk of colon, anal, and rectal cancers. The prevalence of bladder cancer, pancreatic cancer, melanoma, Hodgkin lymphoma, and leukemias among hospitalized patients with IBD has not significantly increased among IBD patients in the study period. Thyroid cancers, non-epithelial skin cancers, non-Hodgkin lymphoma, and cervical cancer rates were increased among IBD patients relative to the general population. Further investigation into these associations is warranted.

Acknowledgements

First and foremost, I would like to thank Dr. Deborah Proctor. This thesis would not have been possible without her mentorship and guidance, and her eternally positive attitude. She has greatly influenced me not only in the realm of research, but also in the world of clinical medicine: I have observed first hand how incredibly compassionate and extremely competent she is as a clinician, and how successful she has been as a leader in academic gastroenterology. Dr. Proctor has truly been the most formative clinician in the shaping my own medical career so far, and for that I am forever grateful – thank you.

Thank you to Dr. Fred Gorelick and the Internal Medicine Department Thesis Committee for reviewing this work, as well as to Yale University School of Medicine, as an institution, for giving me the incredible opportunity and every mechanism of support to conduct this research.

Lastly, to my family – my husband, Oliver, my parents, Rose and George, and my brother, David – whose concerns for my well-being, success, and happiness have been unwavering and unconditional, thank you.

Introduction

Inflammatory bowel diseases (IBD), comprised of Crohn's disease and ulcerative colitis, are chronic, relapsing and remitting conditions primarily characterized by cycles of intestinal mucosal inflammation due to defects of barrier function and inappropriate immunologic activation.[1,2]

For incompletely understood reasons, likely at least partially related to the overuse of antibiotics over the past decade, the prevalence of Crohn's disease and ulcerative colitis has risen. Between 2000 and 2013, Crohn's disease rates increased from 214 to 236 per 100,000, while ulcerative colitis rates increased from 235 to 248 per 100,000.[3]

Although all-cause mortality is significantly increased among patients with IBD compared to the general population, with a standardized mortality ratio of 1.45 for Crohn's disease and 1.21 for ulcerative colitis, over the past 15 years, all-cause mortality, as well as mortality related to colorectal cancers, digestive neoplasms, and infectious diseases, has decreased.[4] As a result, patients with IBD now expectedly incur longer durations of disease, making understanding and clearly defining the long-term complications of IBD has increasingly important. Of particular interest is the characterization of malignancies that patients with IBD may be at a higher risk of developing, relative to the general population.

It has been very well documented that patients with long-standing IBD have an increased risk for developing colorectal cancers, there have been growing concerns that IBD patients may also be at risk of developing other malignancies. Liver and intrahepatic

bile duct malignancies, for example, have been loosely associated with IBD, with a borderline increased risk reported by several European studies.[5,6]

Associations between IBD and extra-intestinal malignancies have also been reported in the literature:

Papillary thyroid carcinoma, for instance, was reported at a higher rate in Crohn's disease patients, with diagnosis occurring at a significantly younger age when compared to the general population.[6] A 2013 study from the University of Utah reported a 3-5 fold increase in pancreatic cancer in IBD patients in Utah relative to the general US population,[7] although the overall risk of pancreatic cancer in IBD is not well defined. The incidence of cervical dysplasia and neoplasia among women with IBD, independent of infection with human papilloma virus, was reported to be 3 times higher relative to the general population.[8] Renal malignancies have been loosely associated with IBD, with a recent study suggesting that Crohn's disease patients, particularly those with a complex phenotype, had an increased incidence of renal cell carcinoma.[9]

Furthermore, there have been specific concerns regarding how the risk for developing malignancies among IBD patients has changed, particularly as the management of IBD has evolved over the past decade.

Many studies have also reported IBD patients receiving thiopurine therapies are at increased risk for both melanoma and squamous cell cancers.[10] Women with IBD were reported to be at an even higher risk of developing high-grade cervical lesions or cervical neoplasia when on immunosuppressive medications.[11] Azathioprine use among IBD patients has been associated with a higher risk of bladder cancer and an increased incidence of urinary tract cancers.[12] In an examination of a large cohort of IBD patients

within the Swedish Cancer Registry, however, there was no significant overall increase in the standardized incidence ratio for urinary tract cancers among IBD patients.[13]

Additionally, there have been concerns regarding the development of rare lymphoproliferative disorders, as associated with the use of biologic agents. Several studies have suggested increased incidence of rare leukemias and lymphomas among IBD patients on these therapies. However, the most recent meta-analysis examining this question concluded there was no substantial evidence to suggest an increased risk of malignancy in patients on anti-TNFα therapies.[12,13]

In addition to defining the malignancy risks inherent to the pathology of IBD, it has become important to define the modifications to the malignancy risk profile of IBD patients over the past decade due to our changing therapies and management of IBD. There are few studies that examine the overall risk of malignancies in patients with IBD in this manner, and, to our knowledge, there have not been any large cohort studies characterizing malignancies among IBD patients in the United States.

The question regarding how biologics have influenced malignancy risk among IBD patients has yet to be definitely answered. To broadly address how these agents may have affected the malignancies faced by IBD patients, the prevalence of co-morbid cancer diagnoses among a large cohort of hospitalized IBD patients was determined, at a two time points: 2002-2003 and 2010-2011. These time points were chosen relative to the Federal Drug Administration approval of infliximab for use in Crohn's disease in 1998, followed by approval of adalimumab in 2005, using the assumption that biologic use was minimal in 2002-2003.

The results of this cross-sectional analysis characterizing the comorbid malignancies of hospitalized patients across the United States with IBD at two time points, spanning nearly a decade are presented in this thesis, assessing the initial hypothesis that the prevalence of co-diagnosed malignancies among hospitalized patients with IBD has changed significantly.

Three specific aims of this study were:

1) To characterize prevalence of comorbid malignancies among hospitalized patients with IBD and how it changed over the study period

2) To develop a sense of the chronology by which malignancies presented in IBD patients relative to the general population

3) To identify malignancies that were less well defined in the context of IBD, and that would warrant clinician attention and further investigation

For clarity, this thesis will be presented in several parts, with separate results and discussions for each category of malignancy, followed by a comprehensive discussion.

Materials and Methods

Database:

The Healthcare Cost and Utilization Project - Nationwide Inpatient Sample (HCUP-NIS) database was examined in the years 2002, 2003, 2010, and 2011. This is an administrative dataset developed through a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality. The HCUP-NIS captures all-payer inpatient hospitalization data from participating hospitals across the United States. In the years examined, approximately 1000 hospitals across between 35 to 46 states contributed data. In each of the years analyzed, de-identified information from ~8 million inpatient admission stays is provided. Collectively, this data is intended to represent a 20% stratified sample of all nationwide inpatient admissions for any given year.

Study Design:

The years 2002 and 2003 were chosen as the earlier, reference time point for this study for several reasons. As infliximab, the first anti-TNFα agent, was approved by the FDA for use in moderate to severe Crohn's disease in 1998, with adalimumab approved in 2005, biologic therapies were relatively novel in 2002-2003. Therefore, for the purposes of this study, use of these therapies was assumed to be minimal among IBD patients in 2002-2003. Secondly, although HCUP-NIS data is available from 1998 through 2015, there have been multiple changes to database structure within this timespan. The most uniformity in data elements and the statistical sampling scheme used to make national estimates was between the years 2002 and 2011, which was therefore chosen as the endpoint of this study.

Using standard International Classification of Diseases, 9th revision (ICD-9) conventions, patients were identified as having IBD if their hospitalization record carried any diagnosis code of ulcerative colitis (555.0 – 555.9) or Crohn's disease (556.0 – 555.9). The IBD patient population examined represents individuals hospitalized both for disease-related and disease-independent causes. Patients younger than age 18 at the time of admission were excluded from analysis. Patients who did not carry any diagnosis of IBD were included in the reference group, the hospitalized "general population", for each year of analysis.

Both the hospitalized IBD patient population and general population were further stratified into 7 cohorts, based on age: 18-27 year olds, 28-37 year olds, 38-47 year olds, 48-57 year olds, 58-67 year olds, 68-77 year olds, and those age 78 and older. For each cohort, patients were identified as having a co-diagnosed malignancy using single-level, Clinical Classifications Software diagnosis (DXCCS) codes. DXCCS codes are pre-defined clusters of ICD-9 codes, a subset of which represent specific groups of malignancies. The frequency of carrying a diagnosis of malignancy was calculated for each cohort of patients, both with and without IBD. In the calculation of frequencies for gender specific malignancies, specifically cervical cancer, patients of the opposite sex were excluded. A percent prevalence of malignancy was also calculated for each age cohort in the general population and IBD groups of both 2002-2003 and 2010-2011.

Based on this data, four points of statistical comparison were made between:

1) The 2002-2003 hospitalized IBD population and the 2010-2011 hospitalized IBD population. This analysis was performed to determine what the relative

change in risk of a malignancy was among IBD patients at these two time points.

2) The 2002-2003 hospitalized general population and the 2010-2011 general population.
3) The 2002-2003 IBD compared to the 2002-2003 general population.
4) The 2010-2011 IBD compared to the 2010-2011 general population

To consolidate these statistical comparisons, prevalence rate ratio was calculated for each age demographic when possible, using the following equation:

$$\boldsymbol{Prevalence\ Rate\ Ratio} = \frac{\dfrac{\boldsymbol{Percent\ Prevalence\ of\ malignancy\ among\ IBD\ patients\ in\ 2010-2011}}{\boldsymbol{Percent\ \ prevalence\ of\ malignancy\ among\ IBD\ population\ in\ 2002-2003}}}{\dfrac{\boldsymbol{Percent\ prevalence\ of\ malignancy\ among\ the\ general\ population\ 2010-2011}}{\boldsymbol{Percent\ prevalence\ of\ malignancy\ among\ the\ general\ population\ in\ 2002-2003}}}$$

This represents the relative change in prevalence of a malignancy among an age-matched IBD patient cohort relative to the change in prevalence among patients without IBD between 2002-2003 and 2010-2011.

Statistical Methods:

In all analyses, national estimates were derived using appropriate weighting at the individual patient discharge, hospital, and stratum levels, as indicated by HCUP –NIS weighting protocol. The standard errors of all reported estimates are less than 30%. Estimates with standard errors greater than 30% are not reportable by HCUP-NIS standards. Chi-squared analyses were performed to assess statistical significance, which was achieved at a pre-determined p-value < 0.05. All statistical analyses were performed with SPSS Statistics, version 22 (IBM).

Attestation of Work:

Dr. Deborah Proctor and I both contributed to the overall project design, as well data interpretation, and the final written text of this thesis. I was independently responsible for data collection, statistical analyses, and the formatting of tables and figures.

Colon Cancers:

Results:

In general, the prevalence of colon cancer among hospitalized patients without IBD across age-matched cohorts has increased slightly from 2002-2003 to 2010-2011, with prevalence increasing with age (Figure 1a). When comparing the 2002-2003 general population and 2010-2011 general population cohorts, there were statistically significant differences detected in the prevalence of colon cancer in the 28-37, 38-47, 48-57, and 58-67 year old groups. Increases were from 0.09% to 0.13%, $p = 0.001$; 0.4% to 0.6%, $p= 0.001$; 1.0% to 1.1%, $p = 0.001$; and 1.7% to 1.6%, $p = 0.026$, respectively (Table 1).

Among hospitalized patients with IBD, the percent prevalence of colon cancer was similar between age-matched cohorts in 2002-2003 and 2010-2011, with slightly higher rates reported in all age groups of 2010-2011 (Figure 1b). These differences, however, were not statistically significant.

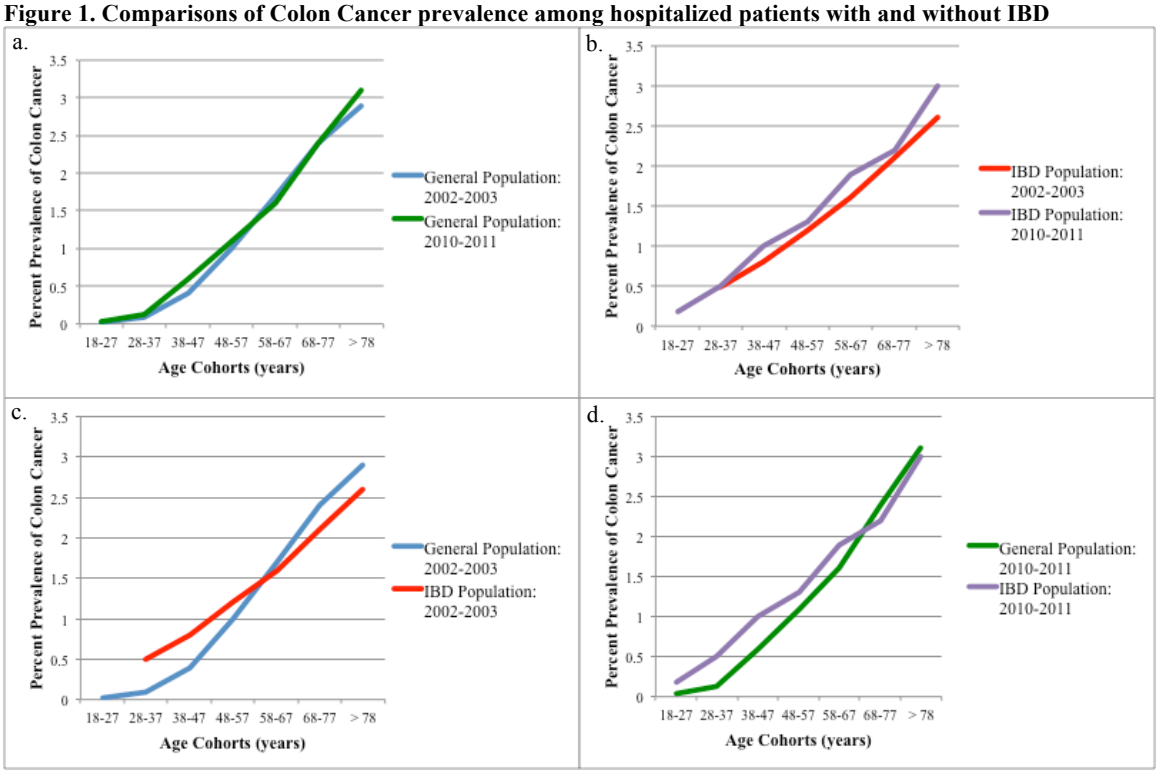
When comparing the IBD cohort with age-matched general population in 2002-2003, there was a significantly higher prevalence of colon cancer reported in IBD patients aged 28-37 and 38-47 (Figure 1c). These rates were 0.49% in patients with IBD compared to 0.09% in the general hospitalized population, and 0.8% in IBD versus 0.4% in the general population, respectively (Table 1). At a crossover point around age 50, however, the diagnosis of colon cancer became more prevalent in the hospitalized general population compared to the hospitalized IBD population (Figure 1c). Likewise, the prevalence of colon cancer in 2010-2011 IBD cohorts was higher than in the age-matched population in younger cohorts.

Table 1. Prevalence of Colon Cancer Among Hospitalized Patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Colon Cancer			General Population with Colon Cancer			Percent Prevalence of Colon Cancer				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27		126 ± 35		1659 ± 145	1903 ± 157	0.146	0.02%		0.03%	0.18%	
28-37	297 ± 43	445 ± 63	0.822	7144 ± 399	9398 ± 522	<0.001	0.09%	0.49%	0.13%	0.51%	0.72
38-47	541 ± 76	853 ± 94	0.242	29796 ± 1276	35362 ± 1663	<0.001	0.4%	0.8%	0.6%	1%	0.83
48-57	751 ± 82	1355 ± 130	0.296	76720 ± 3086	98646 ± 3630	<0.001	1%	1.2%	1.1%	1.3%	0.98
58-67	779 ± 82	1779 ± 140	0.198	137516 ± 4940	161892 ± 5588	0.026	1.7%	1.6%	1.6%	1.9%	1.26
68-77	987 ± 87	1690 ± 129	0.689	251509 ± 8363	237044 ± 7440	0.528	2.4%	2.1%	2.4%	2.2%	1.05
> 78	997 ± 88	2026 ± 137	0.098	361509 ± 12032	392792 ± 12843	<0.001	2.9%	2.6%	3.1%	3%	1.08

Comparisons of absolute and percent prevalence of colon cancer among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of colon cancer prevalence among IBD patients relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients.

Figure 1. Comparisons of Colon Cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of colon cancer among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, stratified by age. Colon cancer prevalence was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011, the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011.

The crossover point where rates of colon cancer were higher in the general population as compared to the IBD population occurred in the older, 68-78 year age group (Figure 1d). The prevalence rate ratios for all age groups were close to 1, with the exception of the 58-67 year olds, where it was 1.26 (Table 1).

Discussion:

The prevalence of colon cancer among patients with IBD did not decrease with time as expected. There were no significant changes in the prevalence of colon cancer among hospitalized patients with IBD in 2010-2011 compared to 2002-2003. Furthermore, the overall prevalence ratio analysis with ratios close to 1 suggests that the rate of change in prevalence between 2002-2003 and 2010-2011 in the IBD and general population cohorts were similar. Therefore, it is most likely that the small, non-statistically significant increases in the prevalence of colon cancer reflect non-specific changes in surveillance and overall management of colon cancers.

There are several possible explanations for these findings:

Firstly, there was likely an increased awareness and stringent adherence to colon cancer screening guidelines during the study period, resulting in more diagnoses of colon cancer, and therefore an increased prevalence among all hospitalized patients. This is supported by the finding that the prevalence of colon cancer is higher in the hospitalized general population in 2010-2011 compared to prior. Furthermore, as patients with IBD are known to be at increased risk for developing colon cancer, at baseline they have more frequent surveillance, with higher sensitivity modalities including chromoendoscopy[15], beginning at an earlier age. This would result in higher detection of malignancies relative to the general population. As expected, this data demonstrated that rates of colon cancer were higher among patients with IBD, especially earlier age groups. This was consistent with literature suggesting that patients with IBD of greater than 8 years duration were at ~0.5-1% increased risk of colon cancer annually, compared to the overall population, whose lifetime risk of colorectal cancers were 4.4-4.7%.[16]

Secondly, over the examined time period, there was likely an overall improvement in the standard of care for patients who developed colon cancer. With better prognosis and decreased mortality, there would expectedly be a non-specific, cumulative increase in colon cancer prevalence. One indication this is occurring is the increased prevalence seen among the older cohorts of the general population in 2010-2011 compared to prior.

Lastly, colon cancer develops over the span of decades. Therefore, although the data does not demonstrate any substantial decrease in the prevalence of colon cancer, it is possible the study time period is simply too short to identify effects on mortality.

Cancer of Rectum and Anus:

Results:

The prevalence of rectal and anal cancers in younger cohorts of hospitalized IBD patients was not reportable due to limited number of cases. In the 38-47 age group and older cohorts, the prevalence of rectal and anal cancers was comparable between 2002-2003 and 2010-2011 IBD cohorts (Figure 2b). The only statistically significant difference was detected among 68-77 year olds, where prevalence of cancers of the rectum or anus was reported at 0.5% in 2002-2003 compared to 0.8% in 2010-2011 ($p=0.044$).

In 2002-2003, the peak prevalence of cancers of the rectum and anus among hospitalized IBD patients was reported within the 48-57 year old age bracket, whereas in 2010-2011 peak prevalence was reached among 58-67 year olds. The magnitude of the peak was the same in 2010-2011 as in 2002-2003, at 0.9%. While there was a steady decrease in prevalence of rectal and anal cancers in 2002-2003 in older age groups, rates in 2010-2011 remained at 0.8%-0.9% in the 48-57, 58-67, and 68-77 year olds, before dropping to 0.4% in the 78 and up age group (Table 2).

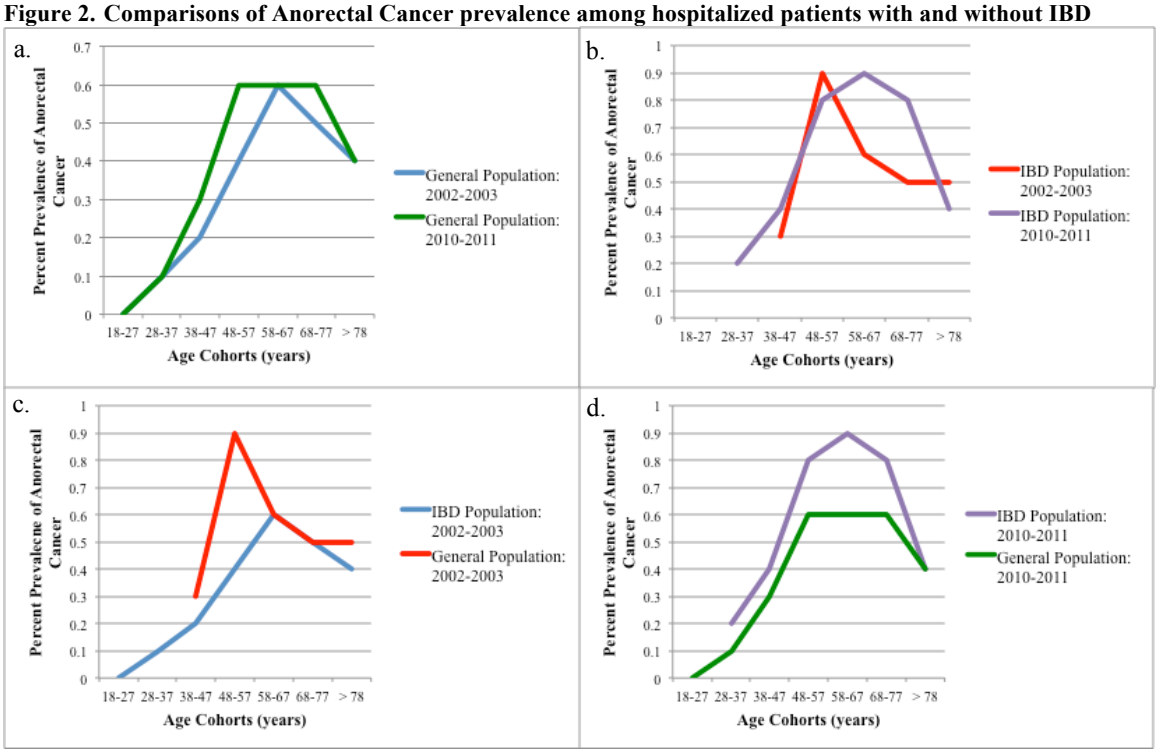
In comparing the hospitalized general population of 2002-2003 to that of 2010-2011, statistically increased rates of anorectal cancers were detected across all age groups, except those aged 78 and older (Figure 2a). This was most apparent in the 48-57 year old cohort, where 0.4% of patients had anorectal cancers in 2002-2003 compared to 0.6% in 2010-2011. The peak prevalence of anorectal cancers within the general population of both 2002-2003 and 2010-2011 was the same, at 0.6%, reported among different age cohorts: the 58-67 year olds in 2002-2003 and the 48-57 year olds in 2010-2011.

Table 2. Prevalence of Anorectal Cancers Among Hospitalized Patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Anorectal Cancer			General Population with Anorectal Cancer			Percent Prevalence of Anorectal Cancer				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				795 ± 124	1271 ± 166	0.005	0%		0%		
28-37	86 ± 28	155 ± 42	0.583	4085 ± 301	5812 ± 474	<0.001	0.1%		0.1%	0.2%	
38-47	224 ± 45	349 ± 63	0.458	16461 ± 961	21653 ± 1313	<0.001	0.2%	0.3%	0.3%	0.4%	0.89
48-57	543 ± 94	814 ± 89	0.787	35101 ± 1715	55870 ± 2609	<0.001	0.4%	0.9%	0.6%	0.8%	0.59
58-67	285 ± 47	787 ± 87	0.061	45924 ± 1959	63089 ± 2808	0.001	0.6%	0.6%	0.6%	0.9%	1.50
68-77	247 ± 45	615 ± 69	0.044	56529 ± 2106	59279 ± 2381	0.001	0.5%	0.5%	0.6%	0.8%	1.33
> 78	185 ± 35	298 ± 42	0.75	53214 ± 1874	55585 ± 2044	0.514	0.4%	0.5%	0.4%	0.4%	0.80

Comparisons of absolute and percent prevalence of anorectal cancers among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of anorectal cancer prevalence among IBD patients relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients.

Figure 2. Comparisons of Anorectal Cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of anorectal cancers among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of anorectal cancers was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

In general, the rates of anal and rectal cancers were higher among the IBD population compared to age-matched cohorts of the general population (Figure 2c). In 2002-2003, rates of anorectal cancer were higher among the IBD population until the 58-67 age bracket, where it reached the same prevalence as in the general population, with a

prevalence rate ratio of 1.5. In 2010-2011, the prevalence among IBD patients was higher than among the general population in all but the 78 and older cohort (Figure 2d).

Discussion:

As expected, in all age groups the prevalence of anorectal cancers among IBD patients was higher than among the general population in both 2002-2003 and 2010-2011. Among hospitalized IBD patients, the prevalence of anorectal cancers did not change across the study time points, reaching the same peak prevalence.

The overall prevalence trend among hospitalized IBD patients, however, did change. First, there was an overall slightly higher prevalence of anorectal cancers in older groups. Although this dataset is not equipped to directly assess how or why prevalence has changed, the latter finding may suggest that patients with anorectal cancers incurred a lower mortality rate in 2010-2011 compared to prior. This is further supported by the data reflecting: 1) a higher prevalence of anorectal cancers in the hospitalized general population in 2010-2011 compared to prior, and 2) an similar increase in prevalence among IBD patients compared to age-matched groups of the general population.

The second change in prevalence trend was that peak prevalence of anorectal cancers shifted to a later cohort among IBD patients while it moved to an earlier point among the general population. It is likely increased surveillance and diagnosis contributed to the early shift in the general population. However, this does not explain the later peak within the IBD cohort. Furthermore, the prevalence ratio analysis demonstrated a 1.5 time faster rate of change in prevalence of anorectal cancers among IBD patients aged 58-67 compared to the age-matched general population, supports the idea that an

IBD specific factor at least partially responsible for the increased prevalence. One possible explanation is that changing management of IBD has affected the time course over which patients develop anorectal cancers, with a later onset. A recent study suggests that IBD patients exhibit higher rates of anal dysplasia compared with the general population, unrelated to immunosuppressive use,[17] which could contribute to the finding of increased rates of anal cancer. Yet unpublished expert opinion has also indicated 6-mercaptopurine use may be associated with increased rates of anal cancer.[18] These findings may both partially explain the increased prevalence of anal cancer among IBD patients. However, to ultimately define how changes in IBD management have affected the epidemiology of anorectal cancers would require controlling for both duration of disease and the medications taken by patients, which is not available in the HCUP-NIS.

The data, overall, suggests anorectal cancers continue to be a class of malignancies that IBD patients are at a significantly increased risk for developing. Despite the changes in management of IBD, the cumulative risk of having anorectal cancer as a patient with IBD appears largely unchanged. However, changing management of IBD may have affected the time course over which patients with IBD develop anorectal cancers, which bears further investigation.

Cancer of Liver and Intrahepatic Bile Ducts:

Results:

Across all age groups of hospitalized IBD patients in 2002-2003, the prevalence of cancers of the liver and intrahepatic bile ducts was not reportable due to low number of reported cases. In 2010-2011, the frequency of IBD patients with co-diagnosis of cancer of liver or intrahepatic bile ducts was large enough to calculate prevalence in several age groups. Overall, there was a narrow range of prevalence, from 0.2% in those aged 38-47 years old, to a peak of 0.4% in the 58-67 year old cohort (Table 3). In contrast, 58-67 year old patients with IBD in 2002-2003 had a statistically significantly lower prevalence of intrahepatic bile duct and liver cancers, at 0.2% ($p = 0.001$).

When comparing hospitalized patients without a diagnosis of IBD in 2002-2003 versus 2010-2011, there were similar rates of liver and intrahepatic bile duct malignancies among younger patients. However, in the 48-57 age bracket and above, there were increased rates of these malignancies in 2010-2011 compared to 2002-2003 (Figure 3a).

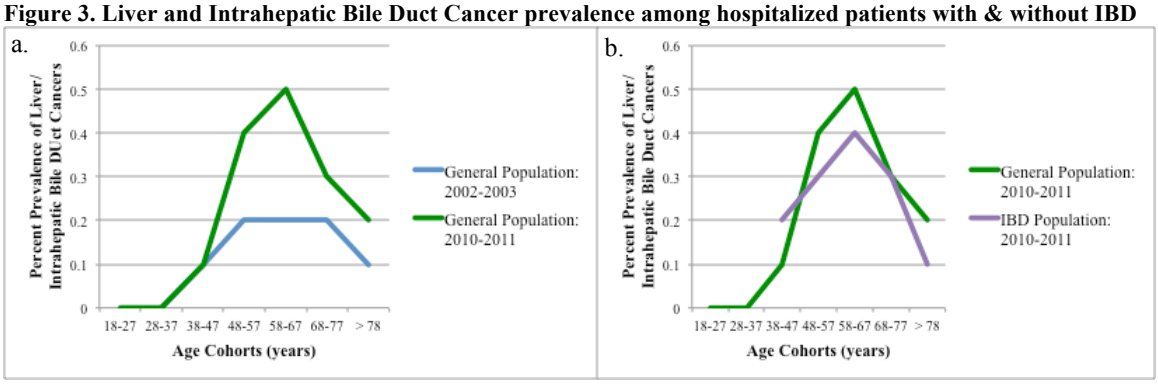
In 2002-2003, the peak prevalence of these malignancies in the general population was 0.2%, in the 48-57 year old demographic. This prevalence remained stable in all older age groups. In 2010-2011, however, the highest prevalence of hepatic and intrahepatic bile duct malignancies was 0.5%, with this peak reported among the older cohort of 58-67 year olds. The prevalence of these malignancies decreased steadily in older age brackets. As a result, the greatest difference in rates of hepatic and intrahepatic bile duct cancers was recorded in the 58-67 year cohort, with 0.2% of the general

Table 3.
Prevalence of Liver and Intrahepatic Bile Duct Cancers Among Hospitalized Patients, 2002-2003 & 2010-2011

Age Cohorts (years)	Patients with IBD and Liver/Intrahepatic Bile Duct Cancers			General Population with Liver/Intrahepatic Bile Duct Cancers			Percent Prevalence of Liver/Intrahepatic Bile Duct Cancers				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				691 ± 158	885 ± 125	0.3	0%		0%		
28-37				1630 ± 185	1793 ± 175	0.25	0%		0%		
38-47		186 ± 48		6594 ± 582	6663 ± 560	0.183	0.1%		0.1%	0.2%	
48-57		305 ± 49		17351 ± 1503	38327 ± 2788	<0.001	0.2%		0.4%	0.3%	
58-67	78 ± 21	379 ± 54	0.001	18150 ± 1524	45460 ± 3148	<0.001	0.2%	0.2%	0.5%	0.4%	0.8
68-77		250 ± 44		20406 ± 1258	31634 ± 1862	<0.001	0.2%		0.3%	0.3%	
> 78		75 ± 20		13193 ± 657	20931 ± 956	<0.001	0.1%		0.2%	0.1%	

Comparisons of absolute and percent prevalence of liver and intrahepatic bile duct cancers among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of these cancers among IBD patients relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 3. Liver and Intrahepatic Bile Duct Cancer prevalence among hospitalized patients with & without IBD



Graphical representations of the prevalence of liver and intrahepatic bile duct cancers among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalences of liver and intrahepatic bile duct cancers were compared between general populations of 2002-2003 and 2010-2011 (a) and the general population and the IBD population in 2010-2011 (b).

population carrying this diagnosis in 2002-2003 compared to 0.5% in 2010-2011 (p=0.001).

As there were very few patients with IBD who also carried a diagnosis of hepatic and intrahepatic bile duct malignancy, comparisons between patients with IBD and those without cannot be made. In the only reportable point of comparison in 2002-2003, the 58-67 age cohort, the percent prevalence of hepatic and intrahepatic bile duct cancers was 0.2% in both the hospitalized population with and without IBD. In all reportable age groups in 2010-2011, patients with IBD had rates of liver and intrahepatic bile duct cancers that were roughly 0.1% lower than in the overall hospitalized population without

IBD. These were non-statistically significant differences, and the only prevalence rate ratio that could be calculated, for the 58-67 year olds, was 0.8 (Table 3).

Discussion:

Due to low number of patients in 2002-2003 with co-diagnoses of IBD and liver and intrahepatic bile duct malignancies, our data is inconclusive with respect to how the prevalence of these malignancies has changed among IBD patients in the study timeframe.

Although among 58-67 year old patients with IBD there was a significant increase in the prevalence of these malignancies in 2010-2011 compared to 2002-2003, at 0.5% versus 0.2%, respectively, the same change in percent prevalence was seen in the general population, in same demographic. Additionally, prevalence rate ratio in this age group was 0.8. This means the change in prevalence of liver and intrahepatic bile duct cancers among IBD patients from 2002-2003 to 2010-2011 was 20% slower than the rate of change among the general population, though this not a significant different. Therefore, the increase in prevalence among the 58-67 year old cohort was likely related to universal increases in awareness, screening, diagnosis, and outpatient care, rather than IBD specific pathology or management. Although previously reported studies demonstrated a borderline significance in the development of cancers of the liver and intrahepatic bile ducts, this was not supported by our data. Overall, this data suggests that there have been no significant changes to the risk of IBD patients developing hepatic and intrahepatic bile duct cancers.

Hodgkin Lymphoma:

Results:

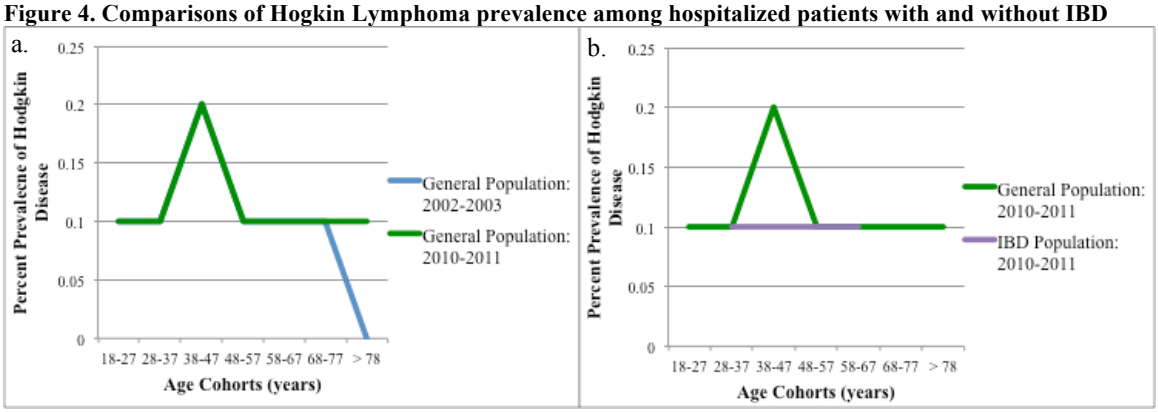
Across all age groups in 2002-2003, there were very few patients carrying co-diagnoses of both IBD and Hodgkin lymphoma, below the threshold of reporting. In 2010-2011 there was an increase in the frequency of IBD patients with Hodgkin lymphoma: in the 28-37, 38-47, and 48-57 year old age brackets, 0.1% of patients carried both diagnoses (Table 4).

Table 4. Prevalence of Hodgkin Lymphoma Among Hospitalized Patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Hodgkin Disease			General Population with Hodgkin Disease			Percent Prevalence of Renal Cancers			
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011
18-27				7249 ± 879	7789 ± 617	0.48	0.1%		0.1%	
28-37		93 ± 25		10483 ± 735	9210 ± 646	0.36	0.1%		0.1%	0.1%
38-47		90 ± 26		11792 ± 732	11111 ± 704	0.327	0.2%		0.2%	0.1%
48-57		120 ± 36		10994 ± 583	12903 ± 684	0.998	0.1%		0.1%	0.1%
58-67		131 ± 44		8150 ± 452	11588 ± 579	0.005	0.1%		0.1%	0.1%
68-77				7544 ± 409	8545 ± 404	0.001	0.1%		0.1%	
> 78				5558 ± 290	6679 ± 340	0.005	0.0%		0.1%	

Comparisons of absolute and percent prevalence of Hodgkin lymphoma among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of Hodgkin lymphoma among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 4. Comparisons of Hogkin Lymphoma prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of Hodgkin lymphoma among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. The prevalence of Hodgkin lymphoma was compared between general populations of 2002-2003 and 2010-2011 (a) and the general population and the IBD population in 2010-2011 (b).

In all age cohorts of the 2002-2003 hospitalized general population the prevalence of Hodgkin lymphoma was 0.1%; the exception was within the 38-47 year old cohort,

where prevalence reached 0.2%. There was no change in the prevalence of Hodgkin lymphoma among the hospitalized general population in 2010-2011: point prevalence of Hodgkin lymphoma continued to be 0.1% in most age groups, with peak prevalence of 0.2% achieved in the 38-47 age demographic (p=0.327). The overall prevalence trend also mirrored that of 2002-2003. Although the percent prevalence in all cohorts was comparable, statistically, there were significant differences detected when comparing rates among the 58-67, 68-77, and age 78 and up cohorts, with p =0.005, 0.001, and p=0.005, respectively (Table 4).

Discussion:

Based on this limited data, it is impossible to make comparisons between the prevalence of co-morbid diagnoses of IBD and Hodgkin lymphoma between 2002-2003 and 2010-2011. However, as rates of Hodgkin lymphoma among patients with and without IBD were similar in 2010-2011, it is unlikely there were substantial changes to the risk of developing Hodgkin lymphoma as a patient with IBD.

Non-Hodgkin Lymphoma:

Results:

The prevalence of Non-Hodgkin lymphoma was significantly higher among hospitalized IBD patients in 2010-2011 compared to 2002-2003 in most age brackets (Figure 5b). Prevalence rose from 0.2% to 0.5%, $p<0.001$ in the 38-47 age group, from 0.3% to 0.6%, $p=0.044$ in the 48-57 age group, 0.7% to 1.1%, $p=0.022$ in the 58-67 age group, 0.8% to 1.3%, $p=0.029$ in the 68-77 age group, and 0.7% to 1.1%, $p =0.024$ in the 78 and up age group (Table 5). Overall, in 2010-2011, the prevalence of Non-Hodgkin lymphoma in hospitalized IBD patients approached that of the general hospitalized population. Peak prevalence in both groups was 1.3% in the 68-77 year old cohort.

In 2002-2003, the highest prevalence of Non-Hodgkin lymphoma in the general population was reported in the 68-77 year age group, at 1%. Co-diagnosis of Non-Hodgkin lymphoma among hospitalized patients with IBD was significantly lower in all age groups, with a peak prevalence of 0.8% in the 68-77 year age group (Table 5, Figure 5c). In 2010-2011, overall, the prevalence of Non-Hodgkin lymphoma diagnosis in the hospitalized general population increased relative to 2002-2003. The peak prevalence was 1.3%, in the 68-77 year-old cohort, compared to 1.0% prior (Figure 5d).

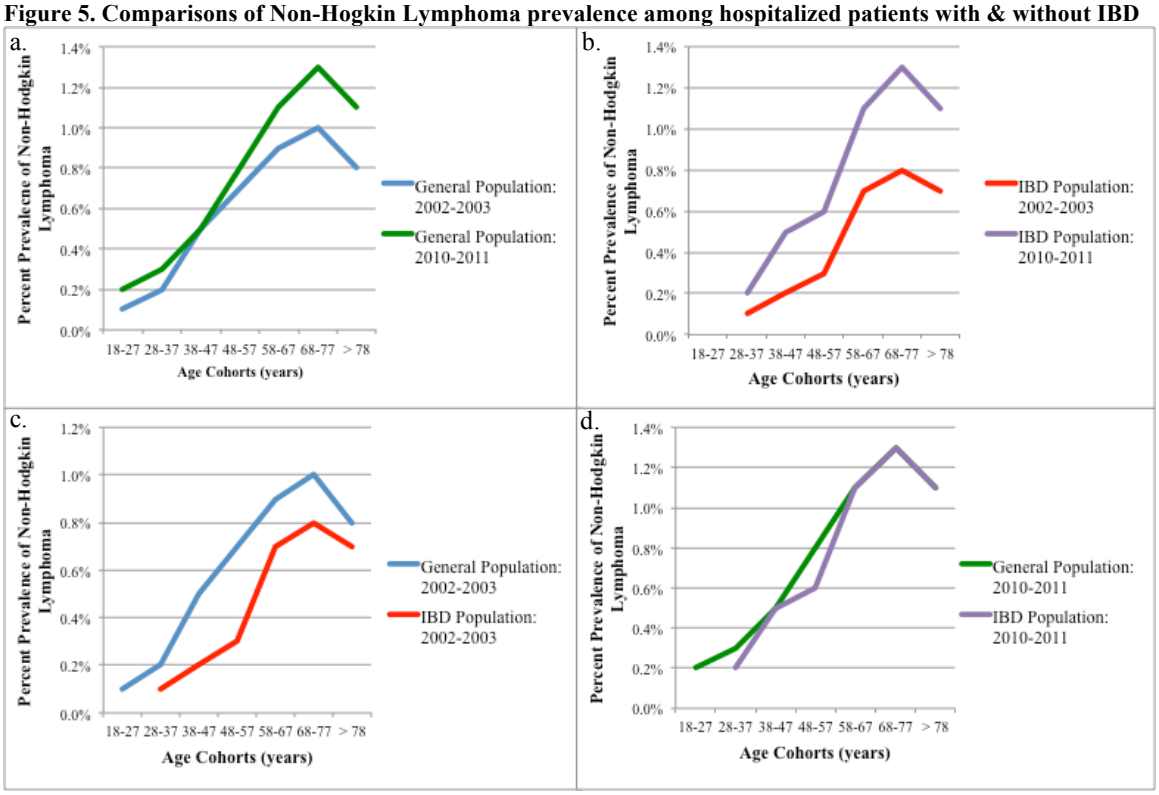
Prevalence rate ratios ranged from 1.14 in the 78 and older cohort to 2.5 in the 38-47 year olds. Notably, the ratio was 1.75 among the 48-57 year olds (Table 5).

Table 5. Prevalence of Non-Hodgkin Lymphoma Among Hospitalized Patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Non-Hodgkin Lymphoma			General Population with Non-Hodgkin Lymphoma			Percent Prevalence of Non-Hodgkin Lymphoma				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				8853 ± 826	11610 ± 923	0.006	0.1%		0.2%		
28-37	63 ± 18	172 ± 40	0.08	16852 ± 1356	18796 ± 1340	0.066	0.2%	0.1%	0.3%	0.2%	1.33
38-47	114 ± 26	398 ± 79	< 0.001	34638 ± 2383	35089 ± 2023	0.048	0.5%	0.2%	0.5%	0.5%	2.50
48-57	222 ± 53	603 ± 90	0.044	55246 ± 3371	75306 ± 4189	0.009	0.7%	0.3%	0.8%	0.6%	1.75
58-67	321 ± 61	999 ± 120	0.022	76533 ± 3795	114132 ± 5616	<0.001	0.9%	0.7%	1.1%	1.1%	1.29
68-77	386 ± 65	957 ± 100	0.029	102884 ± 4161	127817 ± 5079	<0.001	1.0%	0.8%	1.3%	1.3%	1.25
> 78	276 ± 42	712 ± 71	0.024	95809 ± 3664	142871 ± 5173	<0.001	0.8%	0.7%	1.1%	1.1%	1.14

Comparisons of absolute and percent prevalence of Non-Hodgkin lymphoma among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of Non-Hodgkin lymphoma among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 5. Comparisons of Non-Hogkin Lymphoma prevalence among hospitalized patients with & without IBD



Graphical representations of the prevalence of Non-Hodgkin lymphoma among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of Non-Hodgkin lymphoma was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Discussion:

There was an increased prevalence of IBD patients with Non-Hodgkin lymphoma in 2010-2011 relative to 2002-2003, with prevalence among 2010-2011 IBD patients approaching that of general population. Based on this finding, it is not likely that IBD patients are at increased risk of developing Non-Hodgkin lymphoma relative to the general population. However, the substantial increase in prevalence compared to 2002-2003 is significant. There was a disproportionate rise in lymphoma rates among IBD patients relative to rise in the general population.

Furthermore, the prevalence ratios of 2.5 and 1.75 in the 38-47 and 48-57 age demographics, respectively, suggested a 150% and 75% faster increase in prevalence of Non-Hodgkin lymphoma among IBD patients, relative to rate of increase among the age-matched general population. This proportion of the change of prevalence can be thought of as independently attributable to IBD rather than the universal improvements in diagnosis, outpatient care, or the overall management of Non-Hodgkin lymphoma, which also contributes to longevity and hence elevating prevalence.

One potential independent factor leading to increased prevalence of Non-Hodgkin lymphoma among IBD patients is the utilization of anti-TNFα therapies in treating IBD. Many studies have suggested a link between these agents and the development of rare, lymphoproliferative disorders, and while this study does not examine the direct association between biologic use and lymphomas, it does suggest IBD patients have incurred higher rates of lymphomas than prior. Further investigation of this association is warranted.

Leukemias:

Results:

In the younger age groups (18-27, 28-37, and 38-47), there were few hospitalized patients with IBD carrying a co-diagnosis of leukemia in 2002-2003; these figures were below the reporting threshold. In older age groups, the prevalence of leukemia ranged from 0.3% to 0.6%, with a peak prevalence in the 68-77 year age group. Comparatively, the prevalence of leukemia in the 58-67 year IBD cohort in 2010-2011 was significantly higher at 0.9% ($p = 0.000$). The overall the percent prevalence of IBD patients with leukemia in 2010-2011 was higher compared to rates in 2002-2003, however these differences were not statistically significant (Figure 6b, Table 6).

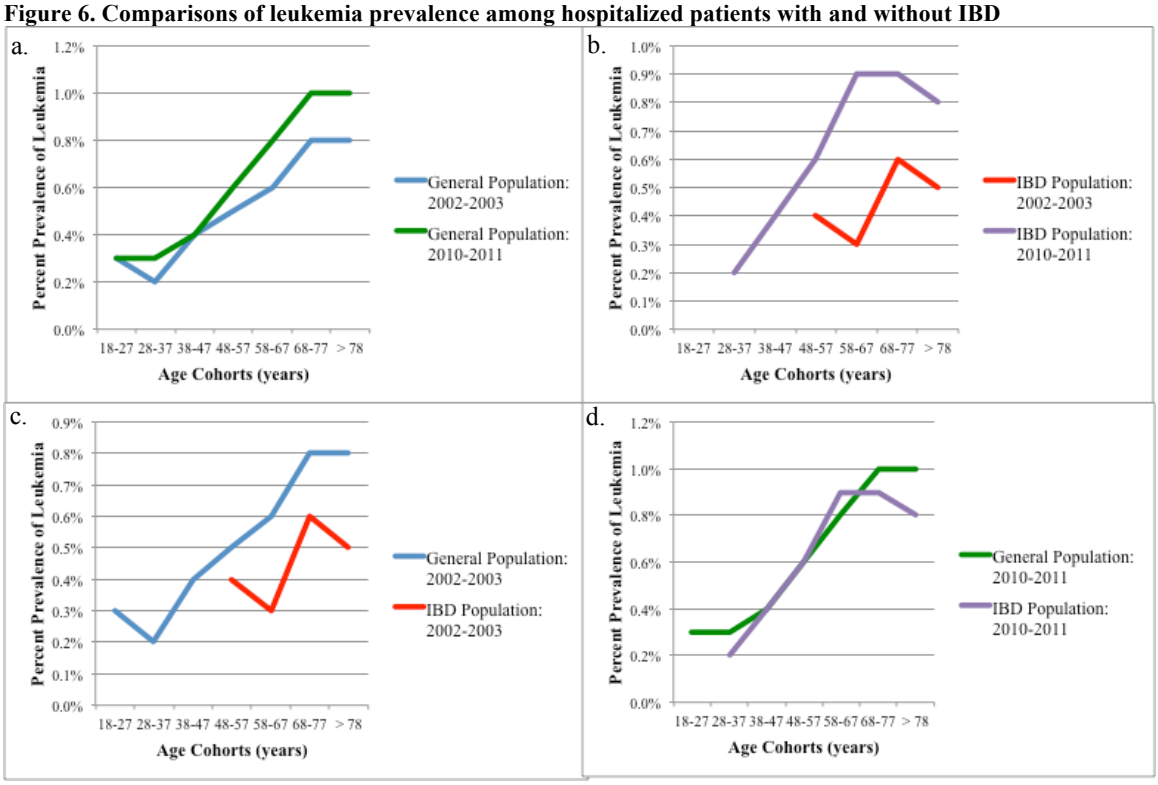
In the 2002-2003 hospitalized general population, the prevalence of leukemia ranged from 0.2% to 0.8%, trending upwards with age. The prevalence of leukemia in the 2010-2011 general population was similar to the prevalence in 2002-2003, especially among younger patients (Figure 6a). However, leukemia was more prevalent in older cohorts (58-67, 68-77, and 78 and up) in 2010-2011 compared to 2002-2003, with rates approaching 1.0% versus 0.8% prior ($p =0.000$ in all three groups). Prevalence rate ratios could not be calculated for the younger age cohorts, due to limited sample size. In reportable groups, the ratio ranged from 1.2 in the 68-77 year cohort, to 2.25 among the 58-67 year olds (Table 6).

Table 6. Prevalence of leukemias among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Leukemia			General Population with Leukemia			Percent Prevalence of Leukemia				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27		200 ± 50		18307 ± 2534	20883 ± 1771	0.306	0.3%		0.3%		
28-37		171 ± 49		17499 ± 2131	20737 ± 1700	0.085	0.2%		0.3%	0.2%	
38-47		311 ± 65		26019 ± 2983	28250 ± 2158	0.078	0.4%		0.4%	0.4%	
48-57	244 ± 57	588 ± 86	0.113	36992 ± 3689	51668 ± 3747	0.073	0.5%	0.4%	0.6%	0.6%	1.25
58-67	130 ± 31	826 ± 113	<0.001	51744 ± 3455	80195 ± 4892	<0.001	0.6%	0.3%	0.8%	0.9%	2.25
68-77	286 ± 49	667 ± 77	0.075	79211 ± 3371	97625 ± 4053	<0.001	0.8%	0.6%	1.0%	0.9%	1.2
> 78	211 ± 39	540 ± 64	0.067	92515 ± 3080	124560 ± 4182	<0.001	0.8%	0.5%	1.0%	0.8%	1.28

Absolute and percent prevalence of leukemias among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of leukemias among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients.

Figure 6. Comparisons of leukemia prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of leukemia among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of leukemia was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Discussion:

Overall, rates of leukemia among IBD patients were similar in 2002-2003 and 2010-2011. The exception demonstrated by the data was an increase in the co-diagnosis of leukemia and IBD in the 58-67 year old age group in 2010-2011, which was statistically significant. The prevalence rate ratio of 2.25 for this age group indicates a significantly higher rate of change in the prevalence among IBD patients from 2002-2003 to 2010-2011, compared to the rate of change among the general population. Although this dataset was not intended to explain changes in prevalence, this prevalence ratio analysis strongly suggests an IBD-specific factor is responsible for the increased prevalence. Given the similar prevalence in the general population among younger groups in both 2002-2003 and 2010-2011, but increased prevalence among older groups, there was likely an improvement in mortality rates associated with leukemia in the study time period. This, however, does not fully explain the increased prevalence of leukemia among the 58-67 year olds. One potential explanation could be that biologic use among IBD patients has increased lymphoma rates, however this study cannot assess this association. As in all other age groups there does not appear to be a significant increase in lymphoma prevalence between 2002-2003 and 2010-2011, it is unlikely this is the case.

Overall, it appears that prevalence of leukemia among IBD patients is comparable to that of the general population.

Cancer of Pancreas:

Results:

As expected, patients with IBD in younger age groups very rarely carried a co-diagnosis of pancreatic cancer. In 2002-2003, there was a 0.2% prevalence of pancreatic cancer in hospitalized patients with IBD age 58-67; this rate did not change in older groups. In comparison, in 2010-2011, a higher peak prevalence of pancreatic cancer was reported among IBD patients, at 0.4% in the 58-67 year old group (Figure 7b). However, this difference was not statistically significant ($p = 0.139$). Although a statistically increased rate of pancreatic cancer was reported in 68-77 year old IBD patients in 2010-2011 compared to 2002-2003 ($p=0.044$), the percent prevalence was comparable at 0.2% in 2002-2003 versus 0.3% in 2010-2011 (Table 7).

Although the percent prevalence of pancreatic cancer in the hospitalized general population was comparable in the younger age groups of 2002-2003 compared to 2010-2011, there was a statistically significant difference reported in the 28-37 and 38-47 year age groups ($p= 0.030$, $p=0.010$). There was also a difference in the percent prevalence of pancreatic cancer in the older age groups: in 2002-2003 the prevalence of pancreatic cancers in the general population trended to a peak of 0.4% among the 58-67 year old and 68-77 year old cohorts. In 2010-2011, although the peak prevalence occurred in same 58-67 year age bracket, the rate of pancreatic cancer was higher, at 0.7% ($p=0.000$).

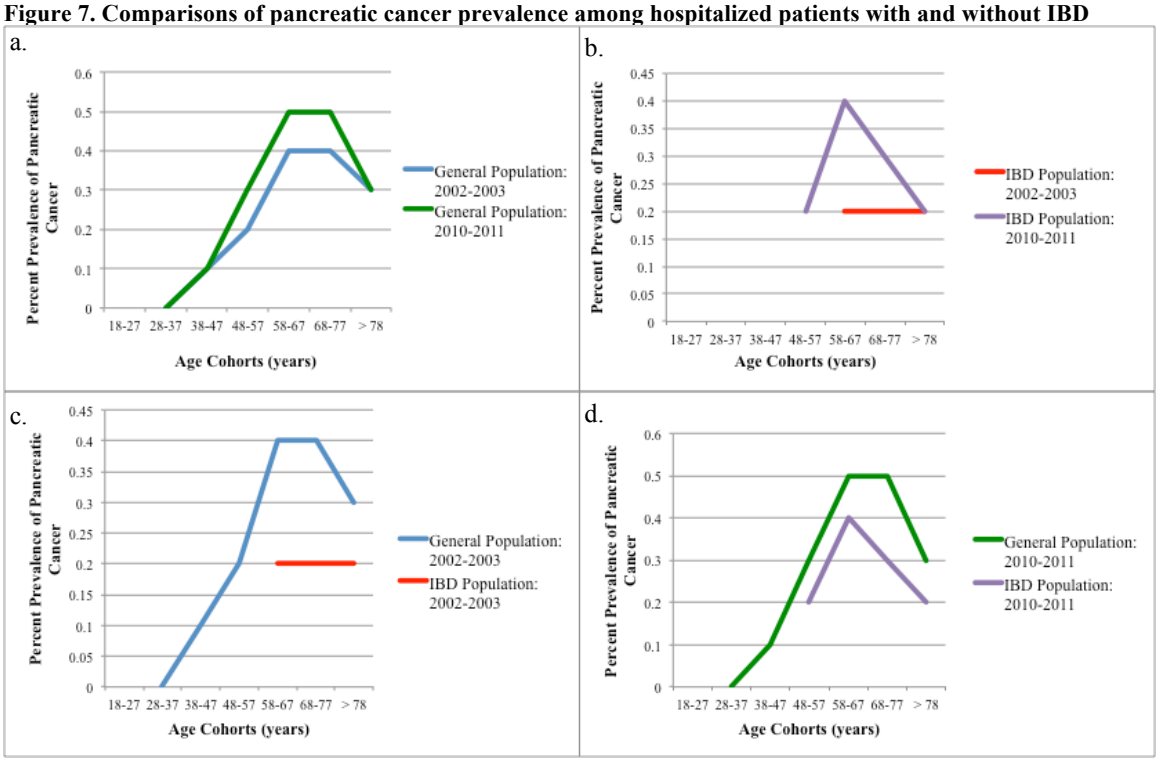
In general, the rate of pancreatic cancers among patients with IBD was lower than among patients without IBD in all age groups of 2002-2003 and 2010-2011 (Figure 7b). In 2010-2011, the prevalence of pancreatic cancer reached peak magnitude in the 58-67 year age bracket in the both the general population (0.7%) and IBD population (0.4%).

Table 7. Prevalence of pancreatic cancer among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Pancreatic Cancer			General Population with Pancreatic Cancer			Percent Prevalence of Pancreatic Cancer				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				194 ± 54	359 ± 99	0.094					
28-37				1165 ± 143	1554 ± 174	0.03	0.0%		0.0%		
38-47				6890 ± 493	7480 ± 498	0.01	0.1%		0.1%		
48-57		216 ± 49		18653 ± 1103	28526 ± 1601	<0.001	0.2%		0.3%	0.2%	
58-67	119 ± 32	366 ± 60	0.139	29358 ± 1458	49444 ± 2672	<0.001	0.4%	0.2%	0.5%	0.4%	1.6
68-77	82 ± 24	262 ± 44	0.044	39254 ± 1754	51361 ± 2570	<0.001	0.4%	0.2%	0.5%	0.3%	1.2
> 78	82 ± 23	154 ± 33	0.828	32834 ± 1346	44072 ± 1859	<0.001	0.3%	0.2%	0.3%	0.2%	1

Absolute and percent prevalence of pancreatic cancer among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of pancreatic cancer among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 7. Comparisons of pancreatic cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of pancreatic cancer among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of pancreatic cancer was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Comparatively, there was a non-significant difference in prevalence of pancreatic cancer in the 58-67 year cohort of 2002-2003, with 0.2% of IBD patients and 0.4% of all other patients having pancreatic cancer. In this cohort, the prevalence rate ratio was 1.6. For the older cohorts, the ratio was near 1 (Table 7).

Discussion:

Although there were statistically significant changes in rates of pancreatic cancer among the general population, there were no changes in the prevalence of pancreatic cancer among hospitalized IBD patients in 2002-2003 and 2010-2011. Furthermore, the prevalence ratio analysis indicates no change in the rate of change among IBD patients relative to rate of change in prevalence among in the general population.

Despite literature suggesting that pancreatitis and pancreatic insufficiency occur more frequently in patients with IBD compared to rest of the population, this data suggests pancreatic cancer is less likely a concern inherent to the natural pathology of IBD. It is also unlikely that the risk of developing pancreatic cancer has been substantially modified as a result of evolving IBD management.

Melanoma:

Results:

Overall there were more patients among the hospitalized general population with melanoma in 2010-2011 compared to in 2002-2003 (Figure 8a). While prevalence of melanoma was stably low at ~0.1% in the 18-27 and 28-37 year old groups (p=0.462 and p=0.512, respectively), there was a statistically significant increase in melanoma rates among patients aged 38-47, with rates of 0.16% compared to 0.2%, p =0.035.

In 2002-2003, a stable peak prevalence of melanoma among hospitalized patients without IBD was reached, at 0.3%; this occurred in the 58-67 year old cohort. The prevalence of melanoma decreased to 0.2% in the oldest age cohort. In contrast, in 2010-2011, there was no clear peak prevalence achieved. Rates of melanoma were highest, however, among the 68-77 year olds, at 0.6%, significantly higher than the 0.3% of 68-77 year old patients with melanoma in 2002-2003 (p = 0.000) (Table 8).

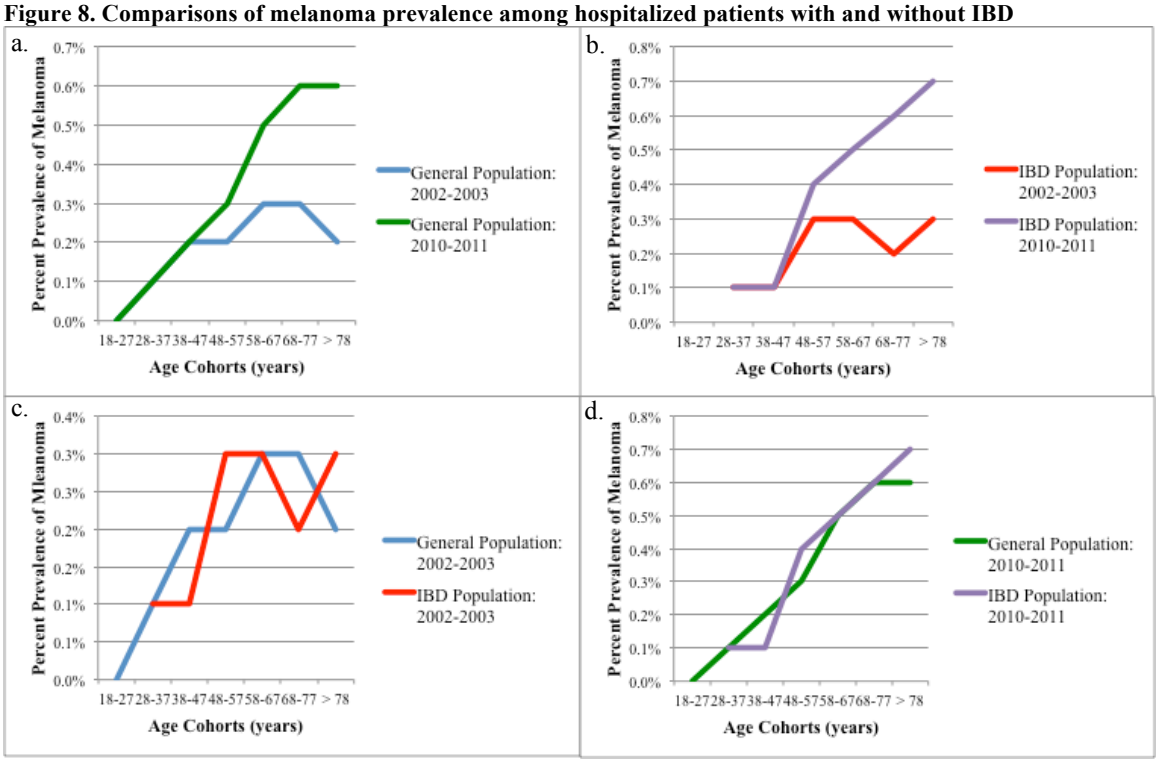
Very few patients with IBD in the 18-27, 28-37, and 38-47 year old cohorts carried a co-diagnosis of melanoma. In 2002-2003, the rate of melanoma among the 38-47 year old hospitalized patients with IBD were not reportable; in 2010-2011 the rate in this age cohort was 0.1%. In all other age groups, the prevalence of melanoma among hospitalized patients with IBD was higher in 2010-2011 than in 2002-2003 (Figure 8b). In 48-57 year olds the percent prevalence of melanoma was 0.3% in 2002-2003, and was recorded at the same rate in older groups.

Table 8. Prevalence of melanoma among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Melanoma			General Population with Melanoma			Percent Prevalence of Melanoma				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				1597 ± 240	1756 ± 143	0.462	0.0%		0.0%		
28-37	61 ± 22	99 ± 27	0.777	5854 ± 740	6034 ± 440	0.512	0.1%	0.1%	0.1%	0.1%	1.00
38-47	63 ± 22	132 ± 27	0.232	11989 ± 1016	12803 ± 855	0.035	0.2%	0.1%	0.2%	0.1%	1.00
48-57	173 ± 39	367 ± 46	0.291	19132 ± 1313	28751 ± 1631	<0.001	0.2%	0.3%	0.3%	0.4%	0.89
58-67	124 ± 25	438 ± 56	0.012	22699 ± 1331	46473 ± 2364	<0.001	0.3%	0.3%	0.5%	0.5%	1.00
68-77	111 ± 24	488 ± 61	<0.001	30861 ± 1491	55096 ± 2490	<0.001	0.3%	0.2%	0.6%	0.6%	1.50
> 78	99 ± 24	448 ± 54	<0.001	29426 ± 1295	72215 ± 3070	<0.001	0.2%	0.3%	0.6%	0.7%	0.78

Absolute and percent prevalence of melanoma among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of melanoma among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 8. Comparisons of melanoma prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of melanoma among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of melanoma was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

In 2010-2011, however, there was an upward trend in prevalence of melanoma, reaching a maximum of 0.7% in patients aged 78 and older (Figure 8d). The prevalence of melanoma among hospitalized patients with IBD as well as the hospitalized general

population was comparable in 2002-2003, with rates around 0.2-0.3% (Figure 8c). In 2010-2011, IBD patients had similar rates of melanoma when compared to all other hospitalized patients. Prevalence rate ratios were near 1 in all age groups except 68-77 year olds, where the ratio was 1.5 (Table 8).

Discussion:

Overall, there were more patients among the hospitalized general population with melanoma in 2010-2011 compared to in 2002-2003, and major differences in prevalence trend between these two time points. While a peak prevalence of melanoma was achieved in 2002-2003, prevalence continued to rise in all age groups, without peaking, in 2010-2011. The prevalence of melanoma among hospitalized patients with IBD was also higher in 2010-2011 than in 2002-2003.

An increase in surveillance and diagnosis of melanoma has undoubtedly contributed to the increasing prevalence among all hospitalized patients. Therapies in the treatment of melanoma have also changed dramatically over the past decade. With the introduction of CTLA-4 and PD-1 inhibitors, as well as a host of monoclonal antibody therapies, the overall prognosis for patients with melanoma is improved.[21,22]

Although melanoma rates among hospitalized IBD patients have increased, the prevalence of melanoma was comparable to that of the hospitalized general population in both 2002-2003 and 2010-2011. This, taken together with prevalence rate ratios near 1, suggesting a similar rate of change in prevalence among IBD patients compared to the general population, indicates melanoma prevalence has not changed significantly over the study time period. Although the dataset does not have enough granularity to directly

assess the direct association of immunomodulatory therapies on melanoma risk, the data suggests it is unlikely that either the intrinsic pathology of IBD or changes in the management of IBD have increased the risks of developing melanoma among IBD patients.

Non-epithelial Skin Cancers:

Results:

In hospitalized patients without IBD of all age groups, the overall prevalence of non-epithelial skin cancers – defined as basal cell, Merkle cell, and squamous cell carcinomas, as well as carcinoma *in situ*, was higher in 2010-2011 compared to 2002-2003 (Figure 9b). In the 2002-2003 general population, prevalence of non-epithelial skin cancers rose to 0.7% in the group of patients 78 years old and greater. Comparatively, in the 2010-2011 general population, non-epithelial skin cancer rates approached 1.7%.

In 2002-2003, the frequency of non-epithelial skin cancer diagnoses among the hospitalized general population and patients with IBD are comparable (Figure 9a). The highest prevalence of non-epithelial skin cancers in IBD patients was 0.6%, in the 68-77 year demographic; the prevalence among the general population for this same group was also 0.6%. The only statistically significant difference in the prevalence of non-epithelial skin cancers between patients with IBD and the general hospitalized population in 2002-2003 was among 48-57 year olds. In this cohort, 0.4% IBD patients carried a diagnosis of non-epithelial skin cancer compared to 0.2% of the general population.

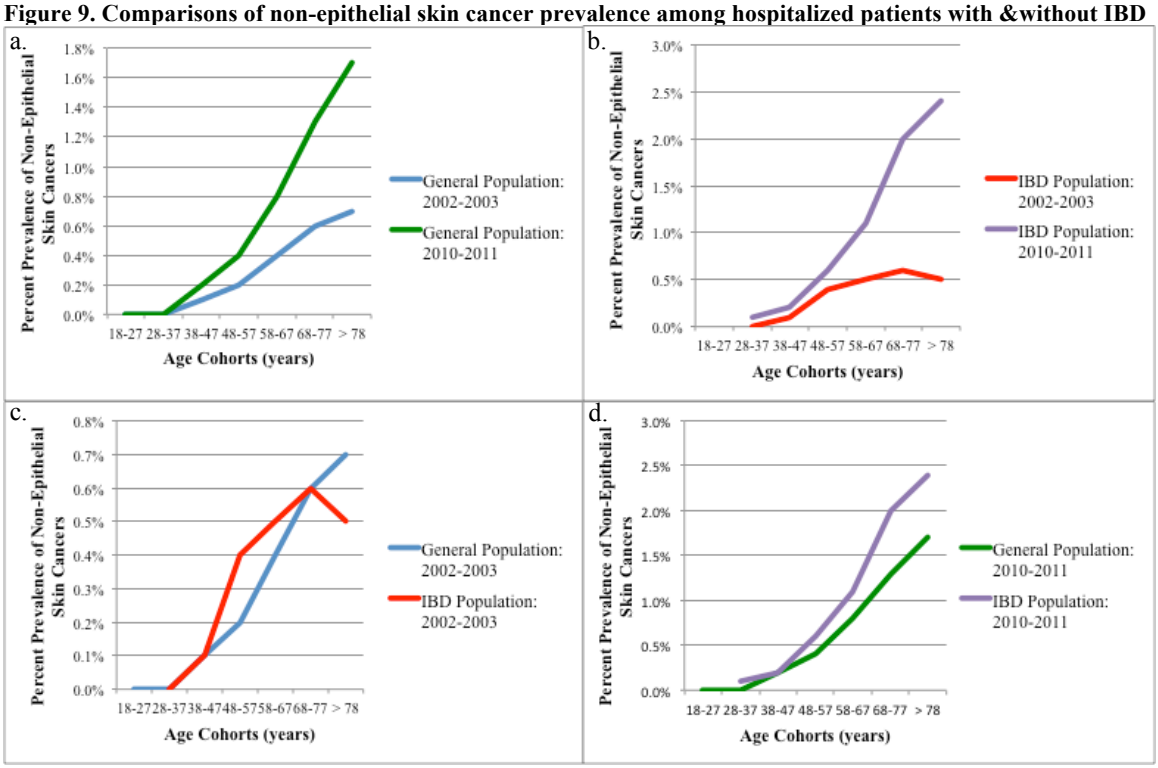
In all age groups of 2010-2011, the frequency of non-epithelial skin cancers in IBD patients was higher compared to the general population (0.6% versus 0.4% in the 48-57 year cohort; 1.1% versus 0.5% in the 58-67 cohort; 2% versus 0.6% among the 68-77 year olds) (Figure 9d). The prevalence of non-epithelial skin cancers among patients with IBD approached 2.4% in the 78-year and older cohort, while the prevalence was 0.5% in the age-matched 2002-2003 cohort (Table 9, Figure 9c).

Table 9. Prevalence of non-epithelial skin cancers among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Non-epithelial Skin Cancers			General Population with Non-epithelial Skin Cancers			Percent Prevalence of Non-epithelial Skin Cancers				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				524 ± 68	742 ± 80	0.016	0.0%		0.0%		
28-37		96 ± 27		2194 ± 158	3027 ± 198	<0.001	0.0%	0.0%	0.0%	0.1%	
38-47	75 ± 21	154 ± 29	0.149	7501 ± 394	10656 ± 638	<0.001	0.1%	0.1%	0.2%	0.2%	1.00
48-57	224 ± 38	625 ± 77	0.003	17990 ± 949	39059 ± 1854	<0.001	0.2%	0.4%	0.4%	0.6%	0.75
58-67	231 ± 39	1070 ± 103	<0.001	31815 ± 1581	82432 ± 4058	<0.001	0.4%	0.5%	0.8%	1.1%	1.10
68-77	386 ± 40	1505 ± 123	<0.001	57859 ± 2813	126076 ± 6135	<0.001	0.6%	0.6%	1.3%	2.0%	1.54
> 78	195 ± 33	1610 ± 139	<0.001	82398 ± 3609	216002 ± 10381	<0.001	0.7%	0.5%	1.7%	2.4%	1.98

Absolute and percent prevalence of non-epithelial skin cancers among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of non-epithelial skin cancers among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 9. Comparisons of non-epithelial skin cancer prevalence among hospitalized patients with &without IBD



Graphical representations of the prevalence of non-epithelial skin cancers among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of non-epithelial skin cancer was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

The ratio of prevalence ratios was only significantly increased in the 68-77 and 78 and up cohorts, where ratios were 1.54 and 1.98, respectively (Table 9). Otherwise the rate of change of prevalence of non-epithelial skin cancers was comparable between the IBD and general population cohorts between 2002-2003 and 2010-2011.

Discussion:

The overall prevalence of non-epithelial skin cancers in hospitalized patients of all age groups is higher in 2010-2011 compared to 2002-2003. In all age-matched cohorts, the frequency of non-epithelial skin cancers in IBD patients was higher compared to the 2010-2011 general population. In 2002-2003, the frequency of non-epithelial skin cancer diagnoses among hospitalized general population and patients with IBD are comparable. Exception of 48-57 year age group, in which 0.4% IBD patients carried a diagnosis of non-epithelial skin cancer, compared to 0.2% of the general population.

As with most other cancers, there is likely increased detection in 2010-2011 compared to prior. However for increased diagnosis to be the only cause of the increase in prevalence, we would expect the rate of increase among IBD patients to be proportional to increase in the general population. This is not the case. The rate of change between prevalence in the 2002-2003 versus 2010-2011 general population is less than rate of change for IBD. Furthermore, the prevalence ratio analyses for the 68-77 and 78 and older cohorts suggests a 54% and 98% increased rate of change in prevalence among IBD patients relative to the change among the general population. This indicates that while perhaps there may be non-specific reasons related to universal changes in practice and expected mortality, the increased rates of non-epithelial skin cancers among IBD patients may be associated with an additional factor related to the pathology of IBD or the way we are manage our patients with IBD.

One potential contributing factor is the use of immunomodulator therapies such as azathioprine and anti-TNFα agents. While our study cannot directly assess these

associations, it does support the theory that IBD patients are at increased risk for developing non-epithelial skin cancers, emphasizing the importance of routine skin exams and increased awareness of these cancers among IBD patients.

Cervical Cancer:

The prevalence of cervical cancer was significantly increased in 2010-2011 among most age groups of IBD patients, compared to in 2002-2003 (Figure 10b). In both 2002-2003 and 2010-2011 there was a similar trend in prevalence trend across age groups. In 2002-2003, prevalence peaked in the 48-57 and 68-77 age brackets, at 0.5%. In 2010-2011, the prevalence peaked among the 38-47 year olds at 1% and the 68-77 year olds, at 0.8% (Table 10).

Cervical cancer prevalence among the general population was also significantly increased in most age groups of 2010-2011 compared to prior (Figure 10a). The distribution of prevalence across age groups was unchanged, with peak prevalence reported among the 38-47 year olds.

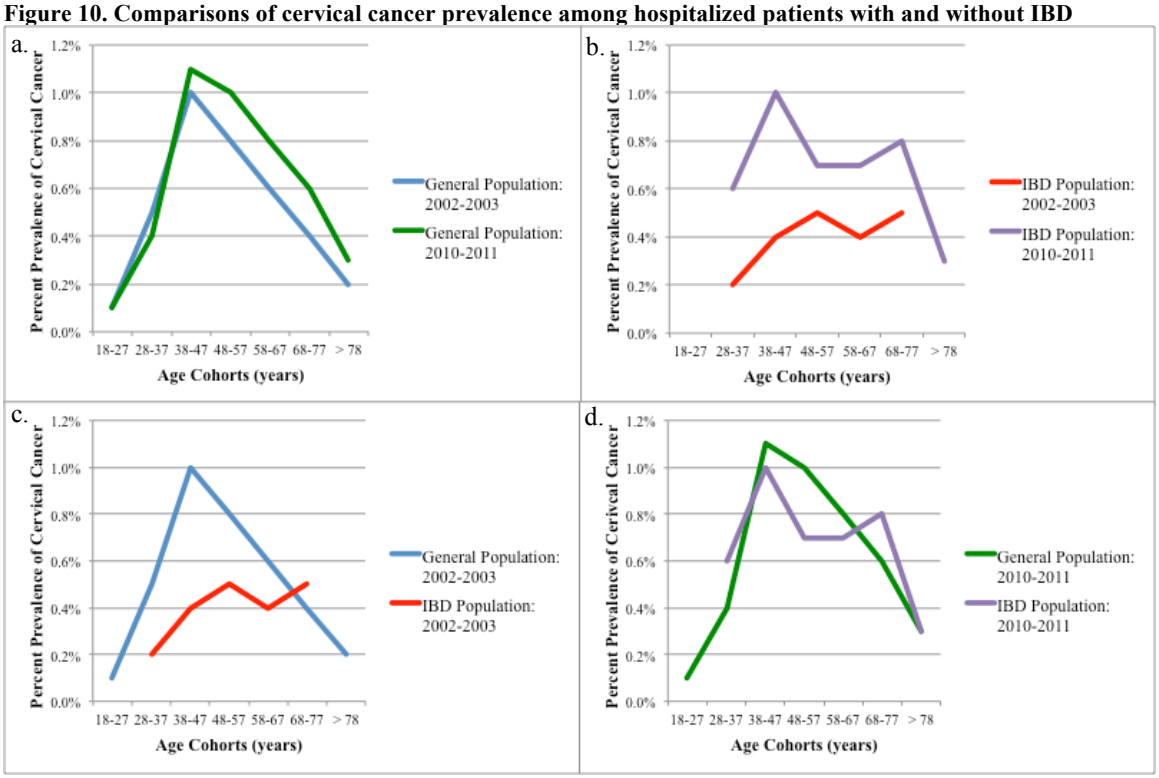
In 2002-2003, cervical cancer rates were significantly lower among IBD population compared to the general population (in all age groups) (Figure 10c). In 2010-2011, prevalence of cervical cancer was similar across age-matched groups of patients with and without IBD (Figure 10d). The prevalence rate ratio was most notable among the 28-37 year olds, where the rate ratio was 3.75 (Table 10). Among 38-47 year olds, the prevalence rate ratio was 2.27, and was otherwise near 1 for other reportable groups.

Table 10. Prevalence of cervical cancer among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Cervical Cancer			General Population with Cervical Cancer			Percent Prevalence of Cervical Cancer				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				7845 ± 483	5506 ± 306	<0.001	0.1%		0.1%		
28-37	93 ± 22	300 ± 45	0.002	26541 ± 1244	22914 ± 1014	0.063	0.5%	0.2%	0.4%	0.6%	3.75
38-47	155 ± 32	516 ± 64	<0.001	41205 ± 2045	40232 ± 1804	0.004	1.0%	0.4%	1.1%	1.0%	2.27
48-57	173 ± 40	436 ± 59	0.074	33082 ± 1729	45127 ± 1918	<0.001	0.8%	0.5%	1.0%	0.7%	1.12
58-67	103 ± 23	369 ± 50	0.026	24644 ± 1210	38939 ± 1547	<0.001	0.6%	0.4%	0.8%	0.7%	1.31
68-77	127 ± 26	320 ± 50	0.065	22197 ± 932	28527 ± 1090	<0.001	0.4%	0.5%	0.6%	0.8%	1.07
> 78		144 ± 29		18516 ± 790	24506 ± 914	<0.001	0.2%		0.3%	0.3%	

Absolute and percent prevalence of cervical cancer among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of cervical cancer among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 10. Comparisons of cervical cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of cervical cancer among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of cervical cancer was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Discussion:

Rates of cervical cancer increased in general population and IBD population in 2010-2011, most likely related to the increased screening and diagnosis.

The prevalence trend for IBD patients in 2010-2011 was also significantly different from the general population in that it demonstrated two peak prevalences. The first peak, among the 38-47 year old IBD patients, is likely partially due to increased screening and diagnosis. However, the prevalence rate ratio of 2.27 – meaning the rate of change of cervical cancer prevalence among IBD patients was 127% faster than the rate of change among the age-matched general population – suggests other factors have contributed.

The second peak among the 68-77 year old IBD patients, was not seen among the general population. The explanation for this is unclear. In 2002-2003 there also appears to be a small peak in this age group, raising the question of whether the IBD alone is a risk factor for cervical cancer. Additionally, it is possible that changing management of IBD has played a role in the increased prevalence, although this is less likely, given the prevalence rate ratio of approximately 1.

Whether or not these changes in prevalence are related to biologic use or infection with human papilloma virus is unknown, and cannot be assessed with this database. While further investigation should be undertaken, given other studies correlating cervical cancer with IBD and these findings, it would be prudent to emphasize the importance of gynecologic exams for all women with IBD.

Cancer of Bladder:

Results:

Among hospitalized patients with IBD in 2002-2003, the prevalence of bladder cancers increased from 0.2% in the 48-57 year demographic to 1.0% in the oldest cohort. In 2010-2011, it rose steadily to 1.4% in the oldest group. Other than in the group of patients age 78 and older where the difference in prevalence was statistically significant ($p=0.019$), the rates of bladder cancer were comparable between age-matched cohorts in 2002-2003 and 2010-2011 (Figure 11b).

In the general population the prevalence of bladder cancer was comparable in age-matched groups of 2002-2003 and 2010-2011 until the 48-57 year age bracket (Figure 11a). In this group, the prevalence in 2002-2003 was 0.2% - the same prevalence of in the matched cohort of IBD patients – but rose to 0.3% in 2010-2011 ($p=0.001$). While the maximum prevalence of bladder cancer among the general population in 2002-2003 was 1.1% the peak prevalence of bladder cancer rose to 1.5% in 2010-2011; this was point of greatest difference, $p<0.001$.

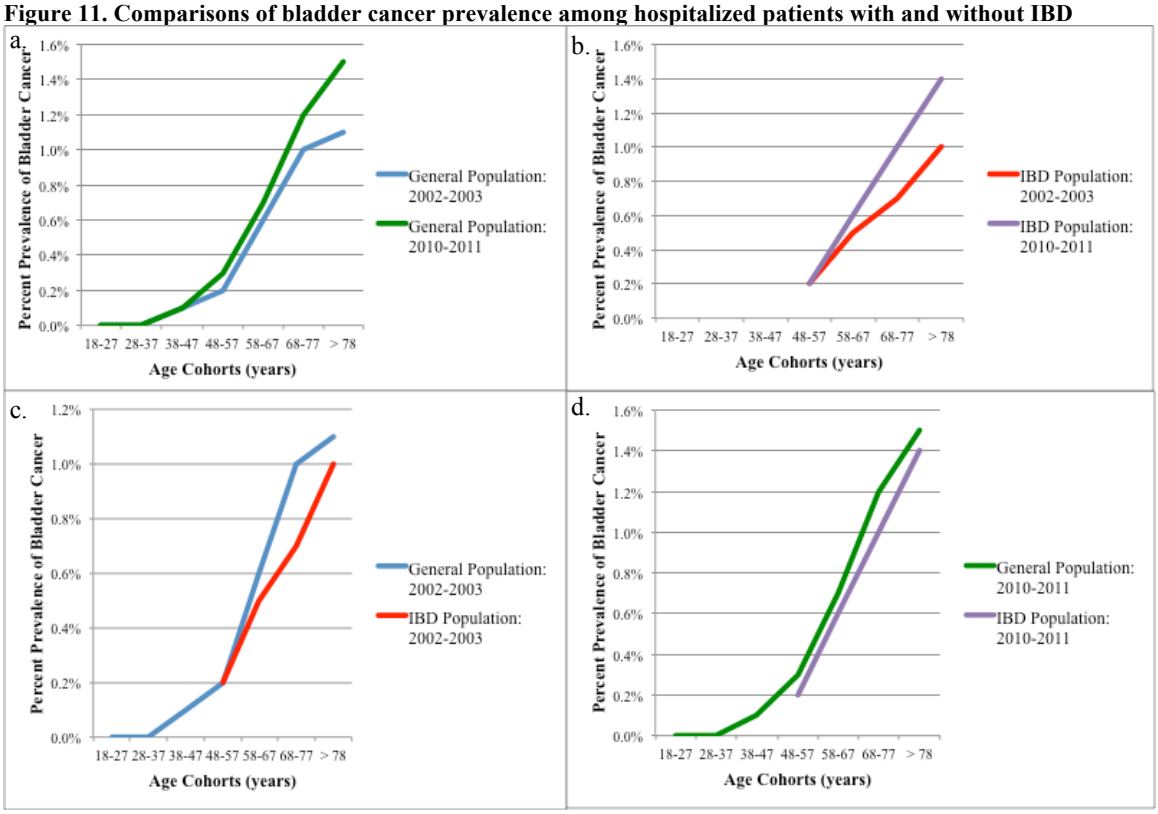
The rates of bladder cancer among patients with IBD and the general population were comparable among all reportable age groups in 2002-2003 (Figure 11c). In most cases, the percent prevalence was slightly lower in the IBD population, although this was not statistically significant. In 2010-2011 rates of bladder cancer continued to be slightly lower in all age-matched groups of the IBD population compared to the general population (Figure 11d). The prevalence rate ratios of all the older cohorts were near 1. (Table 11).

Table 11. Prevalence of bladder cancer among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Bladder Cancer			General Population with Bladder Cancer			Percent Prevalence of Bladder Cancer				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				174 ± 43	325 ± 78	0.054	0.0%		0.0%		
28-37				1102 ± 118	1193 ± 132	0.353	0.0%		0.0%		
38-47				5872 ± 445	5652 ± 416	0.369	0.1%		0.1%		
48-57	106 ± 28	160 ± 39	0.907	18601 ± 979	25978 ± 1333	0.001	0.2%	0.2%	0.3%	0.2%	0.67
58-67	217 ± 46	524 ± 62	0.403	48602 ± 2125	66265 ± 3071	0.006	0.6%	0.5%	0.7%	0.6%	1.03
68-77	333 ± 58	763 ± 85	0.082	102918 ± 3954	121287 ± 4739	<0.001	1.0%	0.7%	1.2%	1.0%	1.19
> 78	391 ± 52	980 ± 98	0.019	136880 ± 4840	195371 ± 7183	<0.001	1.1%	1.0%	1.5%	1.4%	1.03

Absolute and percent prevalence of bladder cancer among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of bladder cancer among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 11. Comparisons of bladder cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of bladder cancer among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of bladder cancer was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Discussion:

Other than the significantly increased prevalence of bladder cancer among IBD patients aged 78 and older, there were no substantial differences in the rates of bladder cancer between other age-matched cohorts of 2002-2003 compared to 2010-2011. Coupled with the findings of increases in bladder cancer prevalence among the general population and that bladder cancer rates among IBD patients were lower than within the general population, it is unlikely this class of malignancy is intrinsically concerning to the innate pathology of IBD.

Although the percent prevalence of bladder cancer was increased in all groups, prevalence rate ratio near 1, particularly in the 78 and older group, indicates the rate of change of prevalence among IBD patients from 2002-2003 to 2010-2011 was identical to that of the general population. This, too, supports the idea that the changes to the management of IBD in the study time period have not substantially changed bladder cancer risk. The increased prevalence of bladder cancer demonstrated by this data is ultimately most likely associated with non-specific factors such as changes in smoking rates, increased diagnosis, diagnosis at earlier stages, and improved prognosis with better treatments.

Cancer of Kidney and Renal Pelvis:

Results:

The prevalence of malignancies of the kidney and renal pelvis was similar in 2002-2003 compared to 2010-2011 among younger IBD patients (Figure 12b). There were very few patients younger than 37 years old with both IBD and renal malignancies. In all reportable groups, percent prevalence was ~0.1% lower in 2002-2003 compared to 2010-2011, until the 58-67 age group. These differences were not statistically significant. Peak prevalence of renal malignancies was 0.6% in the 58-67 year age group in 2002-2003, a non-significant difference compared to the 0.8% prevalence in 2010-2011 ($p=0.188$). In 2010-2011 the peak prevalence of renal malignancies increased to 0.9%, reported in the older 68-77 year age group. Among this cohort in 2002-2003, prevalence was 0.6% ($p=0.010$).

There were statistically significant differences in the prevalence of renal malignancies in all age groups of 2002-2003 versus 2010-2011 of the general population, although percent prevalence was similar (Figure 12a). Rates of these malignancies were ~0.1% lower in 2002-2003 compared to 2010-2011, until the 48-57 year age group. None of these differences were statistically significant. In 2002-2003, the prevalence peaked in the 58-67 age bracket at 0.6%, and was reported at the same rate in older groups. The peak prevalence within the 2010-2011 general population was higher than in 2002-2003, at 1.0%, and reported in the older 68-77 year old cohort.

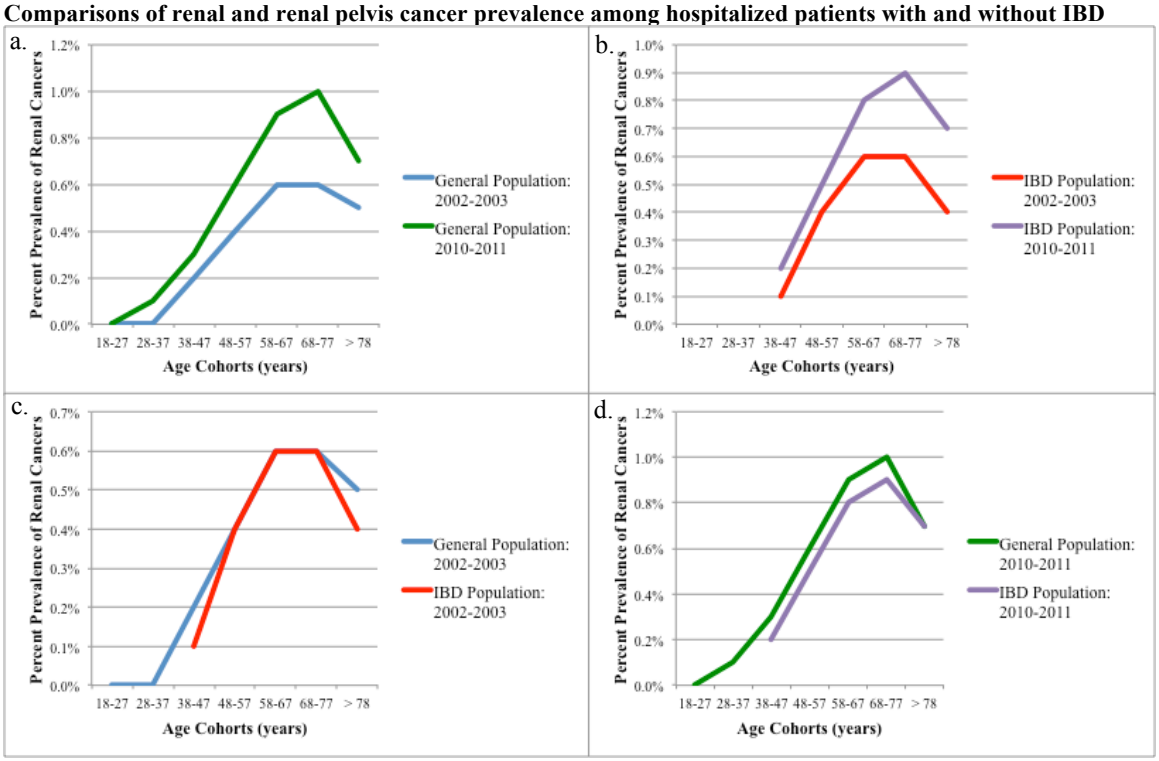
The prevalence of renal malignancies among patients with and without IBD in 2010-2011 was similar, with a non-statistically significant ~0.1% lower prevalence among IBD patients compared to the general population, in all age groups (Figure 12d).

Table 12. Prevalence of renal and renal pelvis cancers among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Renal Cancers			General Population with Renal Cancers			Percent Prevalence of Renal Cancers				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				1077 ± 147	1634 ± 157	0.007	0.0%		0.0%		
28-37				3725 ± 287	6562 ± 429	<0.001	0.0%		0.1%		
38-47	91 ± 25	216 ± 45	0.072	15652 ± 956	20811 ± 1156	<0.001	0.2%	0.1%	0.3%	0.2%	1.33
48-57	260 ± 44	547 ± 74	0.164	34970 ± 2020	58184 ± 2764	<0.001	0.4%	0.4%	0.6%	0.5%	0.83
58-67	287 ± 51	730 ± 81	0.188	50399 ± 2464	92112 ± 4020	<0.001	0.6%	0.6%	0.9%	0.8%	0.89
68-77	262 ± 42	676 ± 70	0.01	63937 ± 2676	97633 ± 3794	<0.001	0.6%	0.6%	1.0%	0.9%	0.90
> 78	165 ± 34	499 ± 57	0.009	55455 ± 2111	94449 ± 3493	<0.001	0.5%	0.4%	0.7%	0.7%	1.25

Absolute and percent prevalence renal and renal pelvis cancers among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of renal and renal pelvis cancers among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 12.
Comparisons of renal and renal pelvis cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of renal and renal pelvis cancers among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of renal and renal pelvis cancers was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Prevalence rate ratio was highest in the 38-47 age group, at 1.33, but was otherwise close to 1 in all other groups (Table 12).

Discussion:

Between 2002-2003 and 2010-2011 the prevalence of cancers of the kidney and renal pelvis has not changed among IBD patients, except in the older age groups (68-77 and 78 and up). During this time period, the prevalence of renal malignancies among the hospitalized general population increased by the same magnitude when comparing age-matched cohorts. Furthermore, the prevalence rate ratio of 0.9 in the 68-77 year old cohort, where the greatest increase in prevalence among IBD patients was reported, suggests that the rate of change of prevalence among IBD patients between 2002-2003 and 2010-2011 was actually slightly slower than the rate of change among the general population. Therefore, although several studies have cited increased rates of renal cell carcinoma among IBD patients, this data suggests the prevalence is comparable to that of the general population.

As the trends of prevalence of renal cancers across all age groups were similar between 2002-2003 and 2010-2011, it is also less likely that the changes in management of IBD have affected the chronology by which IBD patients develop renal cancers. However this study is not equipped to directly assess the association between biologic therapies and development of renal malignancies, and finer analysis will be required to definitively establish the strength of this association.

Cancer of Thyroid:

Results:

In comparing the prevalence of thyroid cancers between hospitalized IBD patients in 2002-2003 and 2010-2011, the only difference detected was in the 38-47 year age group (Figure 13b). In this age bracket, 0.1% of patients had thyroid cancer in 2002-2003 compared to 0.4% in 2010-2011 ($p<0.001$). In all other age groups, the prevalence of thyroid cancer was comparable, with rates generally 0.1% higher in the 2010-2011 versus 2002-2003. These differences were not statistically significant (Table 13).

In the hospitalized general population of 2002-2003, there was also a narrow range of prevalence of thyroid cancers in each age bracket, between 0.2%-0.3%. In 2010-2011, the prevalence was approximately 0.1% higher across all age groups, which was statistically different in all but the 18-27 year old cohort. The overall trend across age groups of the general population were the same between 2002-2003 and 2010-2011, with the peak prevalence in the 38-47 year old group, and steady decline in prevalence in older cohorts (Figure 13a).

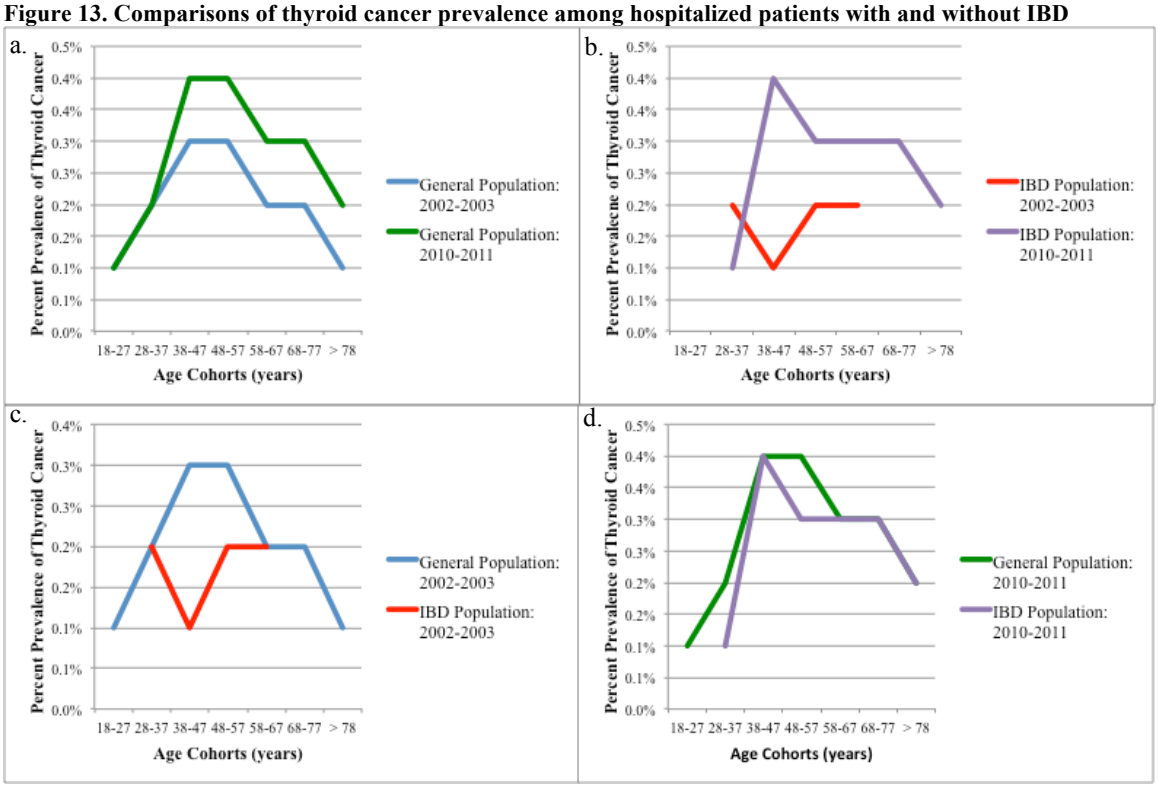
In 2002-2003, the same prevalence of thyroid cancer was reported in most age groups of the IBD and general populations. The 38-47 age group was an exception, with 0.1% of IBD patients carrying a diagnosis of thyroid cancer compared to 0.3% in the general population (Figure 13c). In this cohort in 2010-2011, the rate of thyroid cancer was the same as that of the general population, at 0.4% (Figure 13d). The ratio of prevalence ratios for the 38-47 year age group was 3, whereas it was non-significant in all other categories, with ratios approximately 1 (Table 13).

Table 13. Prevalence of thyroid cancer among hospitalized patients in 2002-2003 and 2010-2011

Age Cohorts (years)	Patients with IBD and Thyroid Cancer			General Population with Renal Cancers			Percent Prevalence of Renal Cancers				Prevalence Rate Ratio
	2002-2003	2010-2011	p-value	2002-2003	2010-2011	p-value	General Population: 2002-2003	IBD Population: 2002-2003	General Population: 2010-2011	IBD Population: 2010-2011	
18-27				5869 ± 423	6172 ± 432	0.397	0.1%		0.1%		
28-37	96 ± 23	128 ± 31	0.817	14098 ± 848	15823 ± 1042	0.011	0.2%	0.2%	0.2%	0.1%	0.5
38-47	86 ± 20	317 ± 54	< 0.001	20214 ± 1094	23596 ± 1559	<0.001	0.3%	0.1%	0.4%	0.4%	3
48-57	123 ± 32	273 ± 43	0.253	20787 ± 1145	34405 ± 2049	<0.001	0.3%	0.2%	0.4%	0.3%	1.125
58-67	80 ± 21	269 ± 44	0.077	18056 ± 914	34218 ± 1836	<0.001	0.2%	0.2%	0.3%	0.3%	1
68-77		248 ± 40		17179 ± 863	29521 ± 1427	<0.001	0.2%		0.3%	0.3%	
> 78		163 ± 39		12163 ± 565	24677 ± 1035	<0.001	0.1%		0.2%	0.2%	

Absolute and percent prevalence thyroid cancer among hospitalized patients with and without IBD, stratified by age. A prevalence rate ratio was calculated to assess of rate of change of the prevalence of thyroid cancer among IBD patients, relative to rate of change among patients without IBD. A prevalence rate ratio value = 1 reflects identical rates of change, while >1 indicates faster change and <1 indicates slower change among IBD patients. Missing values represent non-reportable data due to limited population size.

Figure 13. Comparisons of thyroid cancer prevalence among hospitalized patients with and without IBD



Graphical representations of the prevalence of thyroid cancer among hospitalized patients with IBD ("IBD population") and without ("general population"), in 2002-2003 and 2010-2011, as stratified by age. Prevalence of thyroid cancer was compared between general populations of 2002-2003 and 2010-2011 (a), IBD patients in 2002-2003 and 2010-2011 (b), the general population and the IBD population in 2002-2003 (c), and the general population and the IBD population in 2010-2011 (d).

Discussion:

There was a significant increase in the prevalence of thyroid cancer among the 38-47 year old IBD population in 2010-2011 compared to 2002-2003. Although there were statistically significant increases in the prevalence of thyroid cancer in most age groups of the 2010-2011 general population compared to prior, the absolute change in percent prevalence was only 0.1% in the 38-47 age group, whereas the change in percent prevalence in the age-matched IBD cohort was 0.3%. Prevalence ratio analysis for this age group also indicates that thyroid cancer prevalence increased 3 times as quickly among IBD patients relative to the rate of change among the general population. This indicates there are unique factors, either intrinsic to the pathology of IBD or the way we manage IBD, that have driven the increase in prevalence. Of these two possibilities, it is much more likely that a change in our management of IBD has driven the increase in prevalence in the timespan examined.

While the manner by which anti-TNFα therapies are related to thyroid malignancies is unclear, our data certainly suggests there may be an association that bears further investigation, with attention to histological subtypes of thyroid cancers, distinctions that were not made within this database. In the interim, it will be important to screen IBD patients carefully for thyroid malignancies, especially younger patients and those treated with immunomodulator and biologic therapies.

Overall Discussion

In summary, this data indicates that there have been substantial changes in the prevalence of several types of cancers among hospitalized patients with IBD. There continues to be an increased risk of colon, anal, and rectal cancers. Overall, there have been no reductions in rates of these malignancies among hospitalized IBD patients in the past 9 years.

The data also indicate that prevalence of bladder cancer, pancreatic cancer, melanoma, Hodgkin lymphoma, and leukemias among hospitalized patients with IBD has not significantly increased. These cancers may not be as significant in the independent pathology of IBD. In these cancers, the lack of significant changes between the earlier and later endpoint also indirectly indicates any changes in managing IBD have not substantially modified the risk of developing these malignancies.

This study has also identified several cancers that may be more strongly associated with IBD than is currently believed, and thus merit further investigation. These include thyroid cancer - particularly among younger patients, non-epithelial squamous cell cancers, non-Hodgkin lymphoma, and cervical cancer. IBD patients demonstrated a significantly increased rate of these malignancies relative to the rate in 2002-2003, with a disproportionate rise relative to changes within the general population. Taken together, this suggests there are independent factors related to the way IBD is managed that is responsible for their increased prevalence.

As mentioned above, the underlying cause of increased prevalence of specific cancers among IBD patients cannot be identified in our study. In fact, an increase in

prevalence among hospitalized patients does not necessarily equate to an increased prevalence in the population as a whole. It does, however, serve as an indirect indicator of specific malignancies which are concerning in the IBD population.

There are two major considerations, as discussed above with respect to each malignancy, in explaining the changing prevalence of cancers among inpatients. The first involves the universal improvements in the standards for diagnosing and treating each malignancy, which have undoubtedly improved over the time frame studied. With increased frequency of diagnosis and improved outpatient management of malignancies, patients have better overall prognoses. This manifests as a cumulative increase in prevalence over time.

The second consideration revolves around changes specific to patients with IBD in the study period. This could include changes in patient demographics, particularly individual, modifiable risk factors, or the shifts in the paradigm for managing IBD with biologic therapies.

Although the prevalence rate ratio was used, when possible, to tease apart what portion of the changes in prevalence for a particular age group was due to either "universal" or IBD specific factors, the dataset does not provide enough granularity to definitely associate the cause with our observed effect. Therefore, this study does not and cannot definitively explain the why cancer prevalence has changed. The data simply indicates that the management of IBD has modified certain types of malignancies affecting patients with IBD, which is a step towards fully defining the potential long-term sequelae of long-standing IBD.

Limitations:

There are several limitations of our study.

Most significantly, our study only examines the cross section of IBD patients who are hospitalized. Although all-cause hospitalizations are included in this analysis, the demographics of patients with IBD studied here are almost certainly different that the characteristics of the general IBD population, as a whole. Therefore, the prevalence of cancers in the hospitalized IBD patient population may not represent the prevalence in the IBD population as a whole. At best, it is an indirect indicator of the types of malignancies that are concerning in this group.

A second limitation is that this is an administrative database based on billing records. While it is assumed that only active diagnoses are captured, it is possible that resolved diagnoses are also recorded, which would falsely elevate the prevalence analysis.

Lastly, this dataset lacks clinical granularity. Most significantly, the HCUP-NIS does not capture medication data. Therefore, the salient question regarding how, exactly, the use of anti-TNFα agents has modified the risks of specific malignancies among IBD patients is unanswerable. To further examine this question would require a more comprehensive dataset.

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