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Trends in inflammatory bowel disease and pancreatic cancer: an analysis of the National Inpatient Sample database

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Abstract

Background An association between inflammatory bowel disease (IBD) and pancreatic cancer has been suggested in the literature. We aimed to determine the trend in prevalence of pancreatic cancer amongst patients hospitalized for Crohn's disease (CD) or ulcerative colitis (UC) in the United States.

Methods An analysis of the National Inpatient Sample database was performed to identify adults diagnosed with pancreatic cancer and CD or UC, using validated ICD-9 and ICD-10 codes, from 2003-2017. Age, sex, and racial demographics were also collected. Surveillance, Epidemiology and End Results registry (SEER) data were analyzed for trends in the incidence and mortality of pancreatic cancer amongst the general population in the United States.

Results From 2003-2017, there was a significant increase in the hospitalizations related to pancreatic cancer, from 0.11% to 0.19% (P_{Trend}<0.001), representing a 72.73% increase, in CD patients, and from 0.08% to 0.38% (P_{Trend}<0.001), representing a 375.00% increase, in UC patients. According to the SEER 13 data on pancreatic cancer in the general population, the incidence of pancreatic cancer increased from 11.34 per 100,000 cases in 2003 to 12.74 per 100,000 cases in 2017, thus representing only a 12.35% increase over the study period.

Conclusions Our study indicates a trend for increasing prevalence of pancreatic cancer in patients hospitalized with CD and UC from 2003-2017 in the United States. This increasing trend observed in the IBD population parallels the increase in the incidence of pancreatic cancer reported among the general population, but at a much greater rate.

Keywords Ulcerative colitis, Crohn's disease, digestive system neoplasms, immunosuppressive agents

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Conflict of Interest: None

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Introduction

Patients with inflammatory bowel disease (IBD) have a greater susceptibility to malignancy. Several studies demonstrate a greater risk of intestinal cancer in patients with IBD compared to the general population [1,2]. It has been hypothesized that the carcinogenic effect of IBD applies not only within the walls of the intestinal tract, but also extends systemically. Extraintestinal cancers (EICs) have been observed in patients with IBD, including skin, hepatobiliary, and hematologic cancers. Although less well documented in the literature, other cancer types have been identified within this patient population, including pancreatic cancer [2].

The incidence of pancreatic cancer has been increasing yearly worldwide and is projected to continue to grow, thus increasing its burden on healthcare systems [3]. Given the increasing incidence and high mortality rate of pancreatic cancer, it is critical to identify patient groups, such as those with IBD, who may be at early risk for pancreatic cancer and thus could benefit from early detection programs [3]. The

etiology of pancreatic cancer, as with other extraintestinal malignancies, has been primarily attributed to the chronic systemic inflammation caused by the disease [4]. The immunosuppressive therapies used in the management of IBD have also been implicated in the development of pancreatic cancer [4]. An association between IBD and pancreatic cancer has been suggested in the literature, but is not well established given the limited number of studies [5]. Additional evidence is needed to support the association between IBD and pancreatic cancer, and to identify risk factors for the disease within this patient population.

The aim of this study was to determine the prevalence of pancreatic cancer amongst patients hospitalized for Crohn's disease (CD) or ulcerative colitis (UC) from 2003-2017 in the United States (US), using the National Inpatient Sample (NIS) database. The trends for pancreatic cancer in these patient populations were then further evaluated with respect to age, sex and race. In addition, Surveillance, Epidemiology and End Results (SEER) registry data were analyzed for trends in the incidence and mortality of pancreatic cancer amongst the general population in the US within that same period.

Materials and methods

The NIS database is the largest publicly available all-payer database in the US, containing deidentified data from 20% of hospitalizations within the US each year [6,7]. The database does not contain identifiable patient information, and thus the study was deemed exempt from review by the MedStar Washington Hospital Center Institutional Review Board. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc.), and complex SURVEY procedures were used to adjust for weighting, clustering, and stratification. Frequencies were reported as national estimates, and International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes were used to identify pathologies of interest.

We analyzed NIS data from adult (age ≥18 years) hospitalizations during the years 2003-2017 with primary or secondary diagnoses of pancreatic cancer (ICD-9 code 157.x or ICD-10 code C25.x) and a co-diagnosis of UC (ICD-9 code 556.x or ICD-10 code K51.x) or CD (ICD-9 code 555.x or ICD-10 code K50.x). National frequencies of pancreatic cancer were reported by year for UC and CD, and by age group, sex, and race/ethnicity. Cochran-Armitage and Jonckheere-Terpstra tests were used analyze annual rates of pancreatic cancer diagnosis in the CD and UC groups, as well as by demographic subgroups. Statistical significance was defined as a P-value <0.05.

Data from SEER registries 9 and 13 were used to assess trends in pancreatic cancer from 2003-2017 [8,9]. The pancreatic cancer death rate per 100,000 persons per year over the study period was obtained from the SEER 9 database [8]. The rate of new cases of pancreatic cancer per 100,000 persons per year was obtained from the SEER 13 database [9].

Results

Characteristics of the study population

Our review of the NIS database yielded a total of 2,235,413 CD hospitalizations from 2003-2017. Among these hospitalizations, 3,590 (0.16%) were found to be related to pancreatic cancer (Table 1). There were 1830 (50.98%) female and 1760 (49.02%) male CD hospitalizations related to pancreatic cancer. Among these hospitalizations, there were 40 (1.11%) patients aged 18-35, 346 (9.63%) patients aged 36-50, 1393 (38.79%) patients aged 51-65, and 1811 (50.47%) patients over the age of 65. When these hospitalizations were stratified by race, there were 3057 (86.84%) Whites, 331 (9.41%) Blacks, 86 (2.44%) Hispanics, 31 (0.88%) Asians, and 15 (0.43%) Native Americans (Table 1).

The database review yielded a total of 1,324,746 UC hospitalizations from 2003-2017. Among these hospitalizations, 2878 (0.22%) were found to be related to pancreatic cancer (Table 1). There were 1387 (48.20%) female and 1491 (51.80%) male UC hospitalizations related to pancreatic cancer. Among these hospitalizations, there were 20 (0.70%) patients aged 18-35, 265 (9.21%) patients aged 36-50, 846 (29.40%) patients aged 51-65, and 1746 (60.69%) patients over the age of 65. When these hospitalizations were stratified by race, there were 2337 (83.96%) Whites, 244 (8.77%) Blacks, 138 (4.96%) Hispanics, 59 (2.13%) Asians, and 5 (0.18%) Native Americans (Table 1).

Trends in pancreatic cancer-related hospitalizations

During the study period from 2003-2017, there was a significant increase in CD hospitalizations related to pancreatic cancer from 0.11% to 0.19% (P_{Trend}<0.001), which represents a 72.73% increase in prevalence (Fig. 1). The proportional prevalence of pancreatic cancer in CD increased from 1 to 1.72 over the study period (Fig. 2). There was a trend for increasing prevalence of pancreatic cancer in both males and females with CD from 2003-2017 (Fig. 3). The prevalence of pancreatic cancer in females with CD increased from 2.17% to 10.66% (391.24% increase) while in males it increased from 3.38% to 9.09% (168.93% increase). In addition, the proportion of female to male pancreatic cancer hospitalizations in the CD cohort grew over the course of the study period from 40.09% to 54.93% (P_{Trend}=0.001). We did not observe an increasing trend in the proportional prevalence of pancreatic cancer in the group aged over 65 compared to younger age groups with CD (P=0.3975).

From 2003-2017, there was a significant increase in UC hospitalizations related to pancreatic cancer from 0.08% to 0.38% (P_{Trend}<0.001), which represents a 375.00% increase in prevalence (Fig. 1). The proportional prevalence of pancreatic cancer in UC increased from 1 to 4.75 over the study period (Fig. 2). There was a trend in increasing prevalence of pancreatic cancer in both males and females with UC from 2003-2017 (Fig. 4). The prevalence of pancreatic cancer in

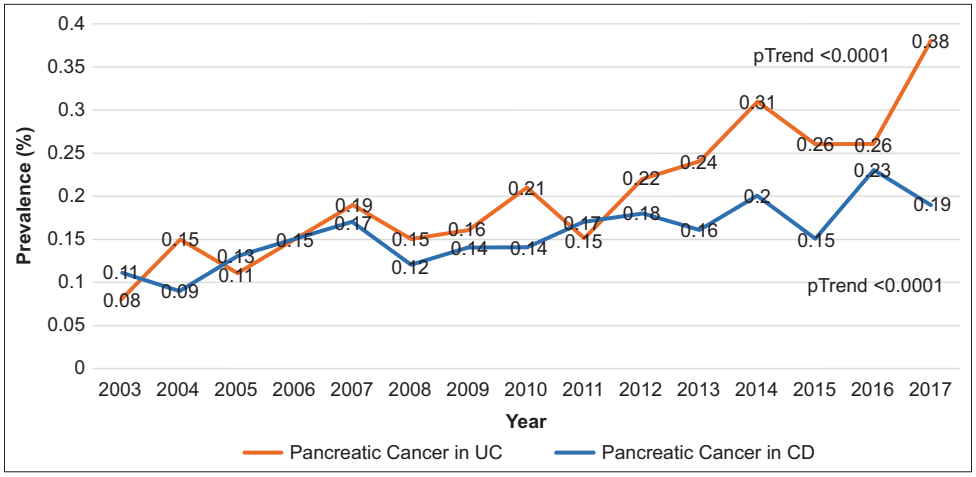

Figure 1 Trends in annual prevalence of pancreatic cancer in patients with Crohn's disease (CD) and ulcerative colitis (UC) based on National Inpatient Sample data

Table 1 Demographics of inflammatory bowel disease hospitalizations related to pancreatic cancer from 2003-2017 according to National Inpatient Sample data

Parameters	Crohn's disease n (%)	Ulcerative colitis n (%)
Pancreatic cancer-related hospitalizations	3590 (0.16)	2878 (0.22)
Sex		
Female	1830 (50.98)	1387 (48.20)
Male	1760 (49.02)	1491 (51.80)
Age		
18-35	40 (1.11)	20 (0.70)
36-50	346 (9.63)	265 (9.21)
51-65	1393 (38.79)	846 (29.4)
>65	1811 (50.47)	1746 (60.69)
Race		
White	3057 (86.84)	2337 (83.96)
Black	331 (9.41)	244 (8.77)
Hispanic	86 (2.44)	138 (4.96)
Asian	31 (0.88)	59 (2.13)
Native American	15 (0.43)	5 (0.18%)

females with UC increased from 1.41% to 16.22% (1050.35% increase) while in males it increased from 1.73% to 14.76% (753.18% increase). The proportion of female to male pancreatic cancer hospitalizations in the UC cohort grew over the course of the study period from 43.11% to 50.56% but the difference did not reach statistical significance (P_{Trend}=0.3). The proportional prevalence of pancreatic cancer in the age over 65 group compared to younger age groups with UC increased significantly from 56.48% to 64.05% over the study period (P<0.001).

According to the SEER 13 data on pancreatic cancer in the US general population, the incidence of pancreatic cancer increased from 11.34 per 100,000 cases in 2003 to 12.74 per 100,000 cases in 2017, thus representing only a 12.35% increase over the study period. The proportional incidence of pancreatic cancer in the general population increased from 1 to 1.12 over the study period (Fig. 2). Based on data from SEER 9, the death rate increased from 10.55 per 100,000 cases in 2003 to 11.11 per 100,000 cases in 2017, which represents a 5.3% increase over the study period.

Discussion

Patients with IBD show a higher risk for malignancy, including both intestinal and EICs [2,5]. A previous systemic review and meta-analysis demonstrated the overall greater risk of EICs to be 43% in CD patients and 15% in UC patients [2]. Pancreatic cancer is one of the various EICs observed in patients with IBD; however, there are few studies that have looked for an association between IBD and pancreatic cancer [5]. A nationwide study in Korea evaluated the risk of cancer in patients with IBD and revealed an elevated risk of pancreatic cancers in females with CD [1]. A study in Scandinavia further investigated this excess risk in comparison to the general population by conducting a large binational registry-based cohort study. Their analysis showed a higher risk of pancreatic cancer and pancreatic cancer death in patients with IBD compared to matched reference individuals [5]. A recent case–control study using SEER data demonstrated an increased association between IBD and pancreatic cancer, although this result did not reach statistical significance [10]. Given the findings of these studies, our goal was to determine the prevalence of pancreatic cancer among patients with IBD in the US and evaluate the trend of pancreatic cancer in this patient population over a 15-year period.

In our study, we found that 0.16% of the 2,235,413 CD hospitalizations and 0.22% of the 1,324,746 UC hospitalizations were related to pancreatic cancer. Over the course of the study period from 2003-2017, there was an overall increase in hospitalizations related to pancreatic cancer in patients with IBD (Fig. 1). The number of hospitalizations associated with pancreatic cancer increased significantly by 72.73% in the CD cohort, but an even greater

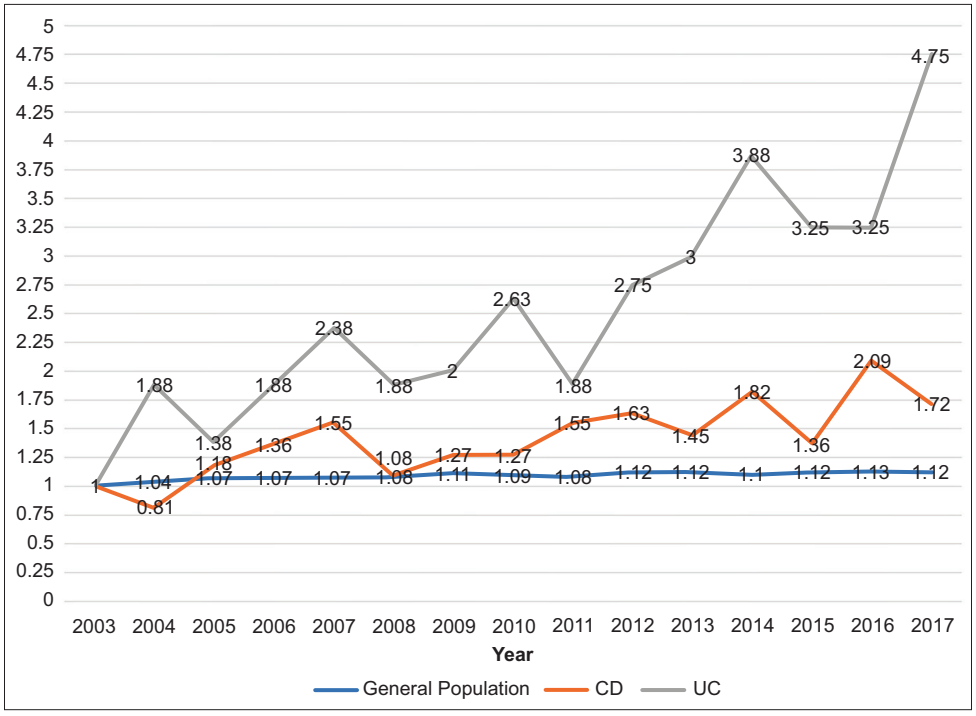

Figure 2 Trends in proportional prevalence of pancreatic cancer in Crohn's disease (CD) and ulcerative colitis (UC) based on National Inpatient Sample data, compared to the trend in proportional incidence rate of pancreatic cancer for the general population based on Surveillance, Epidemiology and End Results 13 data

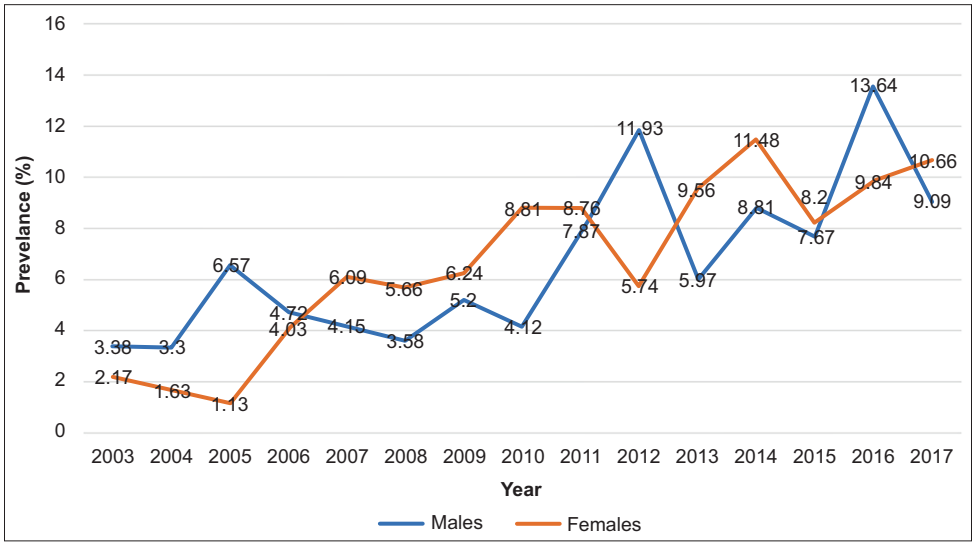

Figure 3 Trends in sex-related prevalence of pancreatic cancer in patients with Crohn's disease based on National Inpatient Sample data

increase of 375.00% was seen in the UC cohort. This observed increase provides further evidence in support of the increased risk of pancreatic cancer in the IBD population described in other population-based studies [1,2,5]. One binational cohort study reported a 20-year incidence that was higher in the UC cohort (0.35%) than in the CD cohort (0.29%), consistent with our findings [5]. In our study, we showed that the prevalence of pancreatic cancer is rising among patients with CD and UC; this rise parallels the 12.35% increase in the incidence of pancreatic cancer in the general US population, but at a much greater rate in those with IBD (Fig. 2). This significant increase in pancreatic cancer incidence in IBD may have contributed to the 5.3% increase in the death rate of pancreatic cancer seen in the general population over the study period, as IBD patients are sicker at baseline; however, this will require further investigation.

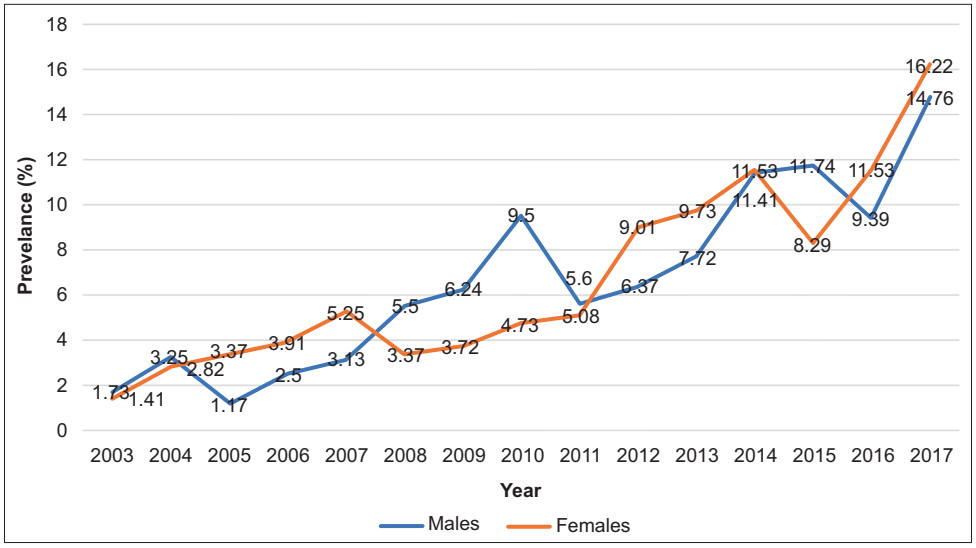

Figure 4 Trends in sex-related prevalence of pancreatic cancer in patients with ulcerative colitis based on National Inpatient Sample data

The current literature suggests that there are demographic differences among those who develop pancreatic cancer in IBD. One study found an increased risk of pancreatic cancer in Korean females with CD compared to the general population. However, the risk of pancreatic cancer in males with CD, as well as in females and males with UC, was comparable to that observed in the general population [1]. In a binational population-based cohort, the stratified analysis according to sex revealed a significant increase in the risk of pancreatic cancer in males and females with CD and in males with UC. The standardized incidence rate in females with CD was 9.19 events per 100,000 person years, compared to 6.74 in the reference group, and 9.47 events per 100,000 person years in males with CD, compared to 7.46 in the reference group. In males with UC, the standardized incidence rate was 10.66 events per 100,000 person years, compared to 7.61 in the reference group. The risk of pancreatic cancer was not significantly greater in females with UC, with a standardized incidence rate of 6.65 per 100,000 person years, compared to 6.56 in the reference group [5]. In our study, the total number of hospitalizations related to pancreatic cancer was similar between females and males in the CD and UC groups (Fig. 3, 4). Over the study period, we observed an increase in the prevalence of pancreatic cancer-related hospitalizations in both female and male patients in the CD and UC cohorts, but at a greater rate of increase in females. Furthermore, the proportion of females to males in pancreatic cancer hospitalizations increased in both cohorts, though only reaching statistical significance in the CD group. Our findings diverge from the sex differences observed in the general population, where the incidence of pancreatic cancer is higher in males than females; thus, further study will be necessary to understand the underlying causes [3].

Pancreatic cancer is often thought of as a disease primarily affecting the elderly, as it is rarely diagnosed prior to age 30. It is most frequently seen in the general population in the age group 65-74 years, with a median age of 70 [3]. An age-stratified analysis predicted that by 2050 the age group over 65 will have the highest incidence of pancreatic cancer [3]. Our findings were similar to those seen in the general population, with the predominant age in the CD and UC cohorts being over 65 years old. There was a significant increase in the proportional prevalence of pancreatic cancer-related hospitalizations in the age group over 65 in the UC cohort; however, it is notable that such an increase was not observed in the CD cohort. Overall, these results suggest that IBD patients over the age of 65 will make the largest contribution to the pancreatic cancer disease burden, a finding similar to those in the general population.

There is variation in the rates of pancreatic cancer across ethnicities among the general population worldwide, with a reported increased risk in African American and indigenous peoples [3]. On the other hand, IBD is most frequently observed among non-Hispanic Whites in the US. One study analyzed data from the National Health Interview Survey and found a point prevalence of IBD 3-fold higher in Whites than in other racial groups [11]. In our study, pancreatic cancer-related hospitalizations were found to be predominantly in Whites, which represented more than 5 times the hospitalizations observed in the other racial groups combined over the study period in both the CD and UC cohorts (Table 1). Our findings may be attributed to the higher prevalence of IBD seen in Whites among the US population.

Our study demonstrated an increasing prevalence of pancreatic cancer among patients with IBD in the US over a 15-year period. This is in need of further investigation of the underlying causes responsible for the significant increase in pancreatic cancer observed within the IBD population. Some potential causes may be related to the implementation of diagnostic modalities, such as endoscopic ultrasound and magnetic resonance imaging, that can detect pancreatic lesions more effectively than computerized tomography [12]. Another consideration is the increased life expectancy among female and male patients with IBD, which has been attributed to the

greater availability of specialist care and improved medical care, including the use of newer biologic therapies [13]. As the chronic inflammatory nature of the disease itself remains unchanged, the increasing use of immunotherapies and biologics resulting in immunosuppression in the treatment of IBD is a likely contributing factor, even with the better disease control achieved with the use of these therapies [4,10]. In a recent case–control study using SEER data, the statistically significant association between IBD and EICs demonstrated in the initial analysis became non-significant after adjustment for medications [10]. One metanalysis reported an overall increase in the relative risk of cancer, from 1.3 to 1.7, with the use of thiopurines in IBD, although the specific cancer types that demonstrated an increased cancer risk secondary to immunosuppression in IBD were hematologic, urinary tract and skin cancers [14]. Another study found no increase in the risk of intestinal or hematologic cancers with the use of 5-aminosalicylate acid, thiopurine or biologic agents, but the authors noted that the short follow-up period may have been responsible for the lack of an association [1]. Furthermore, there are limited studies that have specifically taken account of exposure to immunosuppressive medications in patients with IBD who have been diagnosed with pancreatic cancer. In a previous review of EICs in IBD patients, one study demonstrated an association between the use of thiopurines and the development of pancreatic cancer in patients with UC, while another study included in their review reported no correlation between the use of thiopurines and non-colorectal gastrointestinal cancers [2]. In our study, the greater increase in prevalence of pancreatic cancer in the UC cohort compared to the CD cohort suggests that there may also be other etiologies responsible for this trend, given that UC patients are less often exposed to immunomodulatory and biologic agents. Additional studies will be required to elucidate any association between pancreatic cancer and the immunomodulatory and biologic agents used in the treatment of IBD.

A major strength of our study is the large amount of patient sample data, obtained from the NIS database, a well-validated US patient database [6,7]. As the database is updated annually, we were able to determine the trends of pancreatic cancer among patients with IBD over a 15-year period. In addition, it provided us with information regarding patient demographics, which allowed us to perform further analyses with respect to sex, age and race [6,7]. However, the nature of the inpatient database limited our study to hospitalizations, rather than individual patient encounters; therefore, hospitalizations may represent either a new hospitalization or multiple readmissions of an individual patient [15]. Furthermore, since there are many patients with IBD who are not hospitalized during their lifetime, our study population may be confined to patients with more severe and/or chronically active disease. The time course of each diagnosis could not be derived from the data; therefore, the diagnosis of pancreatic cancer may or may not have preceded the diagnosis of CD or UC. It was unknown whether the IBD patients were receiving treatment for their disease, or the specific details of the therapeutic agents used [6,7]. In addition, the data obtained from the NIS registry did not allow for the assessment of other risk factors for pancreatic cancer in the study population, such as family history, alcohol or tobacco use.

In conclusion, our study demonstrated an increasing prevalence of pancreatic cancer in patients hospitalized with CD and UC from 2003-2017 in the US. This increasing trend observed in the IBD population parallels the increasing incidence of pancreatic cancer reported among the general population, but at a much greater rate. Additionally, the increase in prevalence of pancreatic cancer observed in the UC cohort was notably higher than that observed in the CD cohort. In patients with IBD, this increase in pancreatic cancer was seen in both females and males, with an increasing female proportional prevalence; this is different from the general population, where the incidence of pancreatic cancer is higher among males than females. The highest proportion of pancreatic cancer was in elderly and White patients with CD and UC. These results agree with the predominance of pancreatic cancer among the elderly in the general population, but diverge from the variation in ethnicity reported globally. The exact cause of the observed increase in prevalence of pancreatic cancer among patients with IBD is unknown, but more frequent use of immunosuppressive and biologic therapies for treatment of IBD over the recent years is suspected as one of the potential causes. However, further studies are necessary to investigate each of these therapies as a significant contributing factor, as well as to find other underlying pathogenic causes.

Summary Box

What is already known:

- Patients with inflammatory bowel disease (IBD) have a higher susceptibility to malignancy
- Pancreatic cancer has a high mortality rate and its incidence has been increasing annually worldwide
- An association between IBD and pancreatic cancer has been suggested in the literature, but is not well established given the limited number of studies

What the new findings are:

- There is an increasing prevalence of pancreatic cancer in patients hospitalized with Crohn's disease (CD) and ulcerative colitis (UC) that parallels the increasing incidence of pancreatic cancer reported among the general United States population, but at a much greater rate
- The increase in the prevalence of pancreatic cancer observed in UC patients is greater than that observed in CD patients
- The prevalence of pancreatic cancer is rising in both females and males with IBD, but with an increasing female proportion
- The highest proportion of pancreatic cancer is among elderly and White CD or UC patients

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