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Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease

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Abstract

Introduction: Primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) frequently co-occur. PSC is associated with increased risk for colorectal cancer (CRC). However, whether PSC is associated with increased risk of extraintestinal cancers or affects mortality in an IBD cohort has not been examined previously.
Methods: In a multi-institutional IBD cohort of IBD, we established a diagnosis of PSC using a novel algorithm incorporating narrative and codified data with high positive and negative predictive value. Our primary outcome was occurrence of extraintestinal and digestive tract cancers. Mortality was determined through monthly linkage to the social security master death index.
Results: In our cohort of 5506 patients with CD and 5522 patients with UC, a diagnosis of PSC was established in 224 patients (2%). Patients with IBD–PSC were younger and more likely to be male

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compared to IBD patients without PSC; three-quarters had UC. IBD–PSC patients had significantly increased overall risk of cancers compared to patients without PSC (OR 4.36, 95% CI 2.99–6.37). Analysis of specific cancer types revealed that a statistically significant excess risk for digestive tract cancer (OR 10.40, 95% CI 6.86–15.76), pancreatic cancer (OR 11.22, 95% CI 4.11–30.62), colorectal cancer (OR 5.00, 95% CI 2.80–8.95), and cholangiocarcinoma (OR 55.31, 95% CI 22.20–137.80) but not for other solid organ or hematologic malignancies.
Conclusions: PSC is associated with increased risk of colorectal and pancreatobiliary cancer but not with excess risk of other solid organ cancers.

1. Introduction

As inflammatory bowel diseases (IBD) often have their onset during young adulthood and are associated with preserved life-expectancy, there is considerable interest in the long-term outcomes including risk of malignancy.[1–4] In a large Danish cohort, both Crohn's disease (CD) and ulcerative colitis (UC) were associated with a modest increase in risk of cancer involving the gastrointestinal tract as well as extraintestinal cancers.[5] However, while there was a temporal decrease in the incidence of gastrointestinal cancers, the incidence of extraintestinal cancers remained stable or proportionally increased over time. Other cohorts have variably demonstrated this increased extra-intestinal cancer risk, and emphasize the need for continued study.[6,7]

Between 2 and 5% of patients with IBD have associated primary sclerosing cholangitis (PSC), an autoimmune inflammatory disease of the biliary system that is associated with progressive fibrosis, cirrhosis, and end-stage liver disease.[8,9] In contrast, nearly 80% of patients with PSC have underlying IBD. Several studies have examined the natural history of patients with IBD–PSC and have described a distinct disease phenotype with more frequent occurrence of ulcerative pancolitis and a milder course of underlying IBD.[8–12] It is well recognized that patients with PSC–IBD have a greater risk of colorectal cancer and cholangiocarcinoma.[9,13] However, there has been only limited examination of whether co-existing PSC is associated with an increase in risk of extra-intestinal cancer.

One challenge in addressing this question has been the need for a large cohort of patients with IBD–PSC and prolonged follow-up. It has been difficult to define PSC accurately in large datasets without prospectively recruited patients as many of the features supporting a diagnosis of PSC are non-specific (for example, elevated liver function tests). In addition, the utility of administrative billing codes that serve as a useful first-pass to define eligible cases are limited as the diagnosis code for PSC is used more commonly for cholangitis from other etiologies such as gallstone disease, and consequently has low specificity and positive predictive value.[14] With increasing adoption of electronic medical records (EMR), there is an important unmet need for accurate definition of PSC in such data sources that may allow for efficient accrual of cohorts and definition of eligible cases. We have previously demonstrated that natural language processing (NLP) allows for the identification of free text phrases from within such EMR cohorts, improving the predictive value of case definition algorithms without compromising sensitivity.[15,16]

We performed this study with the aims of (i) developing a case-definition algorithm for identifying patients with PSC with high accuracy in a validated EMR IBD cohort; (ii) examining the impact of co-existing PSC on the risk of gastrointestinal and extraintestinal cancers in patients with IBD; and (iii) defining the impact of PSC on mortality in patients with IBD and identifying risk factors for such outcomes.

2. Methods

2.1. Data source

The data source for our study was a validated EMR IBD cohort. The development of our cohort has been described in detail in our previous publications.[15,17–19] In brief, from a cohort comprising the entire population receiving care at one of two major tertiary referral hospitals (Massachusetts General Hospital and Brigham and Women's Hospital) or affiliated hospitals and practices in the Greater Boston area, we identified all potential IBD patients with at least one International classification of diseases, 9th edition, clinical modification code for Crohn's disease (555.x) or ulcerative colitis (556.x). Using codified and narrative data including free text mentions of terms identified using natural language processing with the clinical Text Analysis and Knowledge Extraction System (cTAKES),[20] we developed a classification algorithm that identified patients with true diagnosis of CD or UC with a high specificity and positive predictive value. This resulted in a final cohort of 5522 UC and 5506 CD patients. The validity of our algorithm was confirmed in an independent random sample from our cohort.[15]

2.2. Determination of primary sclerosing cholangitis

Due to the lack of a specific ICD-9-CM code for PSC and poor specificity of the ICD-9-CM code for cholangitis (576.1) in identifying patients with PSC,[14] we adopted a two-step approach to define patients with confirmed PSC (Fig. 1). First, we identified all patients with possible PSC through a preliminary screen which consisted of: 1) at least one ICD-9-CM code for any of the following — cholangitis (576.1), cholangiocarcinoma (155.1), liver transplantation (V42.7, 50.5), ICD-9-CM or current procedural terminology (CPT) codes for endoscopic retrograde cholangiopancreatography (ERCP) or liver biopsy, receiving at least one prescription for ursodeoxycholic acid (ursodiol), or 2) at least one narrative mentions of 'primary sclerosing cholangitis' 'PSC' 'sclerosing

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