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Research Article

Crohn's Disease and Small Bowel Adenocarcinoma:
A Population-Based Case–Control StudyAasma Shaukat¹, Daniel J. Virnig¹, David Howard³, Shanthi V. Sitaraman^{2,†}, Jonathan M. Liff⁴, and Frank A. Lederle⁵

Abstract

Background: Although Crohn's disease (CD) is thought to predispose to adenocarcinomas of the small bowel, the association has not been well studied in an older population.

Aims: The objective of our study was to evaluate the association of CD with small bowel cancer in a population-based case–control study.

Methods: All cases of small bowel cancer in persons 67 and older in the Surveillance, Epidemiology and End Results catchment area and in the Medicare claims data base were compared with cancer-free controls residing in the same geographic area. We used multivariable logistic regression models adjusted for demographic and other factors.

Results: We identified 923 cases of small bowel cancer and 142,273 controls. Although we found a strong association between CD and small bowel cancer (OR = 12.07; 95% CI: 6.07–20.80; $P < 0.001$), the prevalence of CD in patients with small bowel cancer was low (1.6%).

Conclusions: Although CD is a significant risk factor for small bowel cancers among individuals older than 67, the absolute risk is small.

Impact: Older individuals with CD can be reassured that although there is an association between CD and small bowel cancer, the absolute risk remains small. *Cancer Epidemiol Biomarkers Prev*; 20(6); 1120–3. ©2011 AACR.

Introduction

The incidence and prevalence rates of Crohn's disease (CD) have been reported to be increasing in the United States over the last 3 decades (1–3). Prevalence rates are variously estimated at 26 to 2,000 cases per 100,000 population (4). Patients with CD are extremely concerned about their risk of small bowel cancer, on the basis of the information on the World Wide Web (5). The association of CD and small bowel cancers has been studied primarily in European cohorts, and results

range from no increased risk (6) to a 60-fold increased risk of incident small bowel adenocarcinoma in patients with CD, compared with expected rates in the general population (7). These studies did not report an age breakdown of the study cohort. Only estimates from a U.S. cohort are from Olmstead county and reported a 40-fold increase in risk of small bowel adenocarcinoma in a cohort of 692 patients with CD (8). The same authors conducted a meta-analysis of 5 studies and reported the relative risk among patients with CD to be 27.1 (95% CI: 3.4–66.7) compared with the general population (9). However, the included studies either did not report an age breakdown of the population or had no patients with small bowel cancer older than age 60. Hence, the association of CD with small bowel cancers in an older population is unknown. The primary objective of our study was to study the association of CD with small bowel cancer compared with cancer-free controls in a population-based case–control study in older individuals.

Methods

Data source

We used data from Surveillance, Epidemiology and End Results (SEER)-Medicare linkage program of the National Cancer Institute (NCI; ref. 10). The linkage files of the SEER-Medicare database are a collaborative

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effort of the NCI and the Centers for Medicare and Medicare Services. The SEER program has collected comprehensive population-based cancer incidence and survival data from 5 states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and 6 metropolitan areas (Los Angeles, San Francisco, San Jose, Detroit, Seattle, and Atlanta) since 1992. For each resident of geographic catchment area of the registry diagnosed with cancer, the SEER program records demographic, tumor-specific, treatment, and follow-up information. The cancer incidence and survival data are linked to Medicare claims data collected for both Medicare parts A and B benefits. Medicare is the primary insurer for 97% of individuals older than age 65 in the United States. Linkage to Medicare data is reported to be successful in 93% of patients in SEER registries (10). The linkage files contain Medicare claims information from parts A and B data for all patients identified by SEER registries aged 65 and older with small bowel adenocarcinoma (cases) and a 5% sample of people without any known cancer who are enrolled in Medicare and residing in the same geographic regions as the cases (cancer-free controls). We used the following Medicare files: MEDPAR (inpatient), outpatient, and NCH (physician/supplier). We excluded patients with diagnoses of Celiac disease, familial adenomatous polyposis, Peutz-Jeghers syndrome and hereditary nonpolyposis colon cancer. For the cancer-free controls, we selected a date by using a randomly generated draw from a uniform distribution centered on the time of diagnosis of cases and used this as a reference date. We included only subjects enrolled in Medicare for at least 2 consecutive years prior to their cancer diagnosis (cases) or reference date (controls). This criterion resulted in a minimum age of 67 years of the study participants. The outpatient Medicare files are available 1991 onwards, and because we required individuals to be enrolled in Medicare for 2 years prior to diagnosis of cancer, we included cases that occurred between 1993 to 1999. In the Medicare record for each subject, we searched for diagnoses of the exposure, CD, by using ICD-9 codes (555.0–555.9) on Medicare outpatient, office, and inpatient claims during the 2 years prior to date of diagnosis. As an internal control, to check that the ICD-9 codes for CD were indeed for CD, and not for ulcerative colitis (UC), we also searched for diagnosis of UC (556.0) and included this as a covariate. On the basis of biological plausibility, we did not expect to find an association of small bowel cancers with UC.

Risk factors used as covariates in the analysis included age, sex, race, median income of zip code, dual enrollment in Medicaid, and year of diagnosis. The χ^2 and Student's *t* tests were used to compare proportions and means, respectively. Logistic regression analysis was used to determine variables associated with case-control status. All statistical tests were evaluated at the 0.05 alpha level.

Results

We identified 923 cases of small bowel cancer and 142,273 cancer-free controls. Among small bowel cancer cases, the proportion in the duodenum, jejunum, ileum, and not otherwise specified were 41%, 10%, 26%, and 23%, respectively. Small bowel cancer was associated with male gender (48% vs. 39%), black race (12.6% vs. 7.2%), and with median income (based on zip code) of more than \$50,000 (54% vs. 42%; Table 1).

In multivariable logistic regression, the strongest association of small bowel cancer was with CD (OR = 12.07; 95% CI: 6.07–20.84; *P* < 0.001). However, CD was present in 15 patients with small bowel cancer (1.6%) compared with 175 controls (0.12%). Significant associations were also found for age older than 85 compared with ages 65 to 74 (OR = 1.71; 95% CI: 1.42–2.16), male gender (OR = 1.5; 95% CI: 1.29–1.70), and Black race (OR = 1.90; 95% CI: 1.53–2.36). Small bowel cancers were not associated with UC, median income of zip code, or dual Medicaid enrollment (Table 2).

Discussion

This study is an effort to systematically evaluate the association of CD and demographic factors as well as small bowel cancers in a population-based case-control study of older persons in the United States. We found CD

Table 1. Demographic characteristics of small bowel cancer cases and cancer-free controls

	Small bowel cancer cases (<i>n</i> = 923)	Cancer-free controls (<i>n</i> = 142,273)	<i>P</i>
Mean age, y	77	76	
Age, y			
65–74	39	45	<0.001
75–85	46	39	
85+	15	16	
Sex			
Male	48	39	<0.001
Female	52	61	
Race			<0.001
White	80.4	82.1	
Black	12.6	7.2	
Hispanic	1.2	2.5	
Asian	2.6	4.4	
Other	3.2	3.8	
Medicaid/enrollment	12.3	12.7	
Median income >\$50K ^a	54	42	<0.001

NOTE: All the values are in percent, except mean age and *P* value.

^aMedian income for zip code of residence.

Table 2. Logistic regression analysis examining the association between each risk factor and small bowel cancer compared with cancer-free controls

	Adjusted OR (95% CI)	P
CD	12.07 (6.07–20.80)	<0.001
UC	1.19 (0.40–3.85)	0.69
Sex		
Male	1.50 (1.29–1.70)	<0.001
Age group, y		
65–74	1.00	
75–84	1.48 (1.28–1.73)	<0.001
85+	1.71 (1.42–2.16)	<0.001
Race/ethnicity		
White	1.00	
Black	1.90 (1.53–2.36)	<0.001
Hispanic	0.44 (0.22–0.86)	0.017
Medicaid		
Yes	1.03 (0.84–1.28)	0.72
Median income above \$50K		
Yes	0.91 (0.77–1.07)	0.26

to be the most important risk factor for small bowel adenocarcinomas, with a 12-fold difference between cancer cases and controls. There are no population-based case-control studies, particularly in this older age group to compare our results with, but cohort studies have shown a 3-fold to 40-fold increase in incidence of small bowel cancer in patients with CD compared with incidence in a population without CD (9). Nevertheless, the prevalence of CD in patients with small bowel cancer was low (1.6%). Primary small bowel adenocarcinoma are rare neoplasms, with incidence rates of approximately 4 per million population (11, 12). Clinicians taking care of patients with CD, should be aware of the increased relative risk of small bowel cancer among their elderly patients with CD, but also realize that the absolute risk of small bowel adenocarcinoma is low. Screening older individuals with CD for small bowel adenocarcinoma is unlikely to be worthwhile.

Male gender and older age were associated with diagnosis of small bowel cancer in our study, consistent with reports in the literature (11, 13). In a retrospective series of small bowel adenocarcinoma cases, Verma and colleagues found the average age of diagnosis to be in the sixth decade and twice as likely to be male. Chow

and colleagues also found the incidence of small bowel cancer cancers to be higher among men and older individuals. We found black race to be associated with small bowel cancer, also consistent with observations by others (12).

The strength of our study is the large sample size. We identified all small bowel cancers in the SEER-Medicare files. The study is population based and likely the best representative of the national population older than 65 years of age. The 11 SEER registries represent 13.8% of the U.S. population, and 12.2% of the U.S. population older than 65 years of age. This study also has several limitations. We are unable to investigate cancers in small segment of population (<3%) that does not use Medicare. We could not determine small bowel surgery rates prior to enrollment in Medicare. Duration of disease, extent of involvement, treatment, and compliance could not be assessed as well.

We found a significant association of small bowel cancer and CD, though the absolute risk was small. Future research efforts are needed to explore differences in incidence rates, duration and extent of disease, medication use, compliance with medications and surveillance, and other disease modifying factors such as smoking that may modulate the risk.

Disclosure of Potential Conflicts of Interest

A. Shaukat had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved final draft of the manuscript.

Authors contributions

A. Shaukat participated in study design, acquired data, critical appraisal, interpretation, and writing the manuscript. D.J. Virnig participated in critical appraisal and writing the manuscript. D. Howard participated in data analysis and interpretation. S.V. Sitaraman participated in study design, interpretation, and writing the manuscript. J.M. Liff participated in study design, acquiring the data, interpretation, and writing the manuscript, and F.A. Lederle participated in data analysis, interpretation, and writing the manuscript.

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