Original Article

Prevalence and Predictors of Interval Colorectal Cancers in Medicare Beneficiaries

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BACKGROUND: After a colonoscopy that is negative for cancer, a subset of patients may be diagnosed with colorectal cancer, also termed interval cancer. The frequency and predictors have not been well studied in a population-based US cohort. **METHODS:** The authors used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database to identify 57,839 patients aged ≥69 years who were diagnosed with colorectal cancer between 1994 and 2005 and who underwent colonoscopy within 6 months of cancer diagnosis. Colonoscopy performed between 6 and 36 months before cancer diagnosis was a proxy for interval cancer. **RESULTS:** By using the case definition, 7.2% of patients developed interval cancers. Factors that were associated with interval cancers included proximal tumor location (distal colon: multivariable odds ratio [OR], 0.42; 95% confidence interval [CI], 0.390-0.46; rectum: OR, 0.47; 95% CI, 0.42-0.53), increased comorbidity (OR, 1.89; 95% CI, 1.68 2.14 for ≥3 comorbidities), a previous diagnosis of diverticulosis (OR, 6.00; 95% CI, 5.57-6.46), and prior polypectomy (OR, 1.74; 95% CI, 1.62-1.87). Risk factors at the endoscopist level included a lower polypectomy rate (OR, 0.70; 95% CI, 0.63-0.78 for the highest quartile), higher colonoscopy volume (OR, 1.27; 95% CI, 1.13-1.43), and specialty other than gastroenterology (colorectal surgery: OR, 1.45; 95% CI, 1.16-1.83; general surgery: OR, 1.42; 95% CI, 1.24-1.62; internal medicine: OR, 1.38; 95% CI, 1.17-1.63; family practice: OR, 1.16; 95% CI, 1.00-1.35). **CONCLUSIONS:** A significant proportion of patients developed interval colorectal cancer, particularly in the proximal colon. Contributing factors likely included both procedural and biologic factors, emphasizing the importance of meticulous examination of the mucosa. ***Cancer*** **2011;000:000–000.**

KEYWORDS: colorectal cancer, colonoscopy, Medicare, cancer screening, Surveillance, Epidemiology, and End Results Program.

INTRODUCTION

Colonoscopy currently is considered to be either 1 of several recommended screening options[1,2] or, in some professional guidelines,[3] the preferred option for colorectal cancer screening. Evidence for the efficacy of colonoscopy comes primarily from case-control and cohort studies. For example, the National Polyp Study,[4] a multicenter study of patients who underwent colonoscopy with removal of 1 or more adenomas, reported a lower observed-to-expected incidence of cancer in follow-up.[5,6]

Although few people would dispute the positive attributes of colonoscopy as a screening test, there have been several published studies that have questioned whether this procedure as currently practiced is truly ideal. First, using data derived from audits of newly diagnosed colorectal cancer cases[7] and postpolypectomy patients undergoing surveillance colonoscopy as part of chemoprevention studies,[8,9] there is a higher cancer incidence postcolonoscopy than originally reported in the National Polyp Study.[4] In addition, population-based studies have questioned the protective effect of colonoscopy on the development of right-sided cancers[10-13] and advanced adenomas.[14] Finally, 3 population-based studies, 2 from Canada[15,16] and 1 Medicare claims study,[17] have described the development of colorectal cancer after colonoscopy. When patients who had a colonoscopy between 6 months and 36 months before a colorectal cancer diagnosis were considered to have a new or missed cancer, then 3.4% to 7.9%[15-17] were classified as such. These presumed new or missed lesions also are termed "interval cancers." However, to date, there have been no comparable data from a population-based cohort of US patients that included tumor registry data.

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Therefore, we conducted the current study in a linked tumor registry-health claims database that contained cancer-specific, sociodemographic, and procedural data. Our objectives were to estimate the frequency of cancers that may have failed colonoscopic detection (interval cancers) and to determine the factors associated with interval cancers.

MATERIALS AND METHODS

Data Sources

The study used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which consists of Medicare-eligible patients who are diagnosed with cancer and reside in 1 of the geographic areas contained in the SEER registries.[18] Through the 1990s, the SEER Program encompassed approximately 14% of the US population; however, with the addition of several new registries in 2000, approximately 25% of the population is currently captured.

Among the cancer-related variables that were collected, we included demographic characteristics, previous cancer diagnoses, date of cancer diagnosis, and data about the cancer, including stage, histology, and grade. Medicare claims are contained in 3 different files: the Carrier file, which includes provider claims; the Outpatient file, which includes claims from institutional outpatient providers; and the Medicare Provider Analysis and Review (MEDPAR) files, which include all hospitalizations. Each Medicare claim contains diagnoses coded by the International Classification of Diseases, ninth Revision, Clinical Modification (ICD-9-CM) and procedures coded according to Common Procedural Terminology, fourth Edition (CPT-4) or the ICD-9-CM. The Carrier and Outpatient claims also include physician specialty code and an encrypted version of the physician's unique personal identifier (UPIN), which is used to categorize practitioners according to specialty.

In addition to patients with a cancer diagnosis, we included the Medicare files from a 5% random sample of beneficiaries who resided in 1 of the SEER areas but were cancer-free. The Medicare files available for this control group were identical to those of the cancer cases. These files were used to categorize physicians according to 2 measures of endoscopist performance—the volume of colonoscopies in the database and the frequency of polypectomy procedures. The latter measure, which is a representation of the adenoma detection rate,[19] was obtained from the ratio of colonoscopy with polypectomy (codes defined below) divided by the total number of colonoscopies by that provider in the database and was adapted from previous studies.[20,21]

Patients and Measures

By using the SEER files from 1994 to 2005, we identified all individuals aged $\geq$69 years who had a diagnosis of colorectal adenocarcinoma from 1994 to 2005. The inclusion criteria were provided to ensure 3 years of Medicare eligibility (ie, beginning at age 65 years) and file availability before diagnosis. Patients were excluded if they were enrolled in a Medicare-sponsored managed-care plan or if they were not enrolled in Medicare Parts A and B from 3 years before diagnosis because of the likely presence of incomplete claims. Patients who had a previous diagnosis of cancer at any site according to SEER also were excluded as were patients with the only colonoscopy procedure coded as incomplete. Because of inconsistent reporting, patients with carcinoma in situ at entry were excluded; however, a previous diagnosis of carcinoma in situ was considered a covariate. We also excluded all patients who were diagnosed with ulcerative colitis or Crohn disease during the previous 3 years, because it is believed that cancer in this setting develops through a different biologic pathway. In the primary analysis, we excluded all patients without colonoscopy within 6 months before cancer diagnosis. Finally, to be able to measure the physician performance characteristics associated with colonoscopy, we excluded patients for whom the colonoscopy could not be linked to an encrypted UPIN.

The Carrier, Outpatient, and MEDPAR files from 3 years through the date of cancer diagnosis were examined for receipt of colonoscopy. Colonoscopies included diagnostic examinations (CPT-4 codes 44388, 44389, 45378, 45380, 45382, G0105, and G0121; ICD-9-CM codes 45.23, 45.41, 45.25, and 45.27) and polypectomy (CPT-4 codes 44392, 44393, 44394, 45383, 45384, and 45385; ICD-9-CM codes 45.42, 45.43, and 48.36) according to procedure codes, and the dates of all colonoscopies were recorded. Among the patients who underwent colonoscopy during both the 6 to 36-month and $<$6-month intervals, the last procedure during the 6 to 36-month interval was used to derive data about procedure specifics and endoscopist characteristics. Claims data from 1 year to 1 month before diagnosis were used to derive a previously validated comorbidity score.[22]

Colonoscopy procedures between 6 months and 3 years before diagnosis were considered to represent

interval lesions, as characterized in previous studies by our group[23] and others.[15-17] The rationale for this distinction assumes that, if a malignant lesion is detected at colonoscopy, then definitive therapy would be expected to performed within 6 months and that the typical progression from a benign, premalignant lesion to carcinoma occurs on the order of several years.[6,24]

To determine the robustness of our results, we conducted a series of secondary analyses. First, to account for delays in definitive treatment of a suspicious lesion, we extended the time period for detected lesions to 1 year before diagnosis, and interval cancers were shortened accordingly to 36 months to 1 year before diagnosis. Second, because patients who are diagnosed with cancer during hospitalization may differ in clinical presentation and subsequent evaluation, we only considered outpatient colonoscopies. Third, to account for patients who had an index colonoscopy and later presented emergently without undergoing a second preoperative colonoscopy, we also included patients with a colonoscopy only 6 to 36 months before diagnosis in the interval cancer group. The reference group included patients with a colonoscopy only within 6 months of cancer diagnosis.

Analysis

The primary analysis focused on factors associated with the presence of interval colorectal cancers. Differences between these patients and those in the reference or detected groups (colonoscopy only within 6 months of diagnosis) were compared using chi-square tests. Variables of interest included demographic factors (age group, sex, race); comorbidity score; previous diagnoses of diverticulosis or colorectal carcinoma in situ; and cancer stage, grade, and location in the colon. Location was classified as proximal colon (cecum, ascending colon, hepatic flexure, transverse colon), distal colon (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction) and rectum. Procedure characteristics included type of colonoscopy (diagnostic or polypectomy), facility type (inpatient, outpatient, ambulatory surgical center), and year of procedure. Year of diagnosis was also divided into 3 time intervals based on Medicare colonoscopy reimbursement policies: no coverage for screening (before 1998), screening colonoscopy in high-risk beneficiaries (January 1998 to June 2001), and universal screening colonoscopy (July 2001 onward). Because several SEER registries were added in 2000, we stratified the time period analysis according to membership in the original registries (SEER 9). Physician characteristics included specialty and volume of colonoscopy procedures in the noncancer Outpatient and Carrier files from 1991 to 2005. By using all colonoscopies from the noncancer sample from 1991 to 2005, we also included the endoscopist's polypectomy rate and volume of colonoscopies. For most physicians with missing UPIN data, we were able to obtain specialty through the Medicare specialty code on the claim.

A hierarchical linear model was used to determine the odds of interval cancer with clustering of patients at the physician level. Independent variables included all predictors that we believed were clinically relevant. The data were obtained through a Data User Agreement from the National Cancer Institute, and the protocol was approved by the institutional review board at the Case Comprehensive Cancer Center.

RESULTS

In total, 299,260 patients initially were identified from the SEER-Medicare database. Patients were excluded for the following reasons: Medicare eligibility based on end-stage kidney disease or disability (n = 21,268), prior cancer diagnosis (n = 49,593), histology other than adenocarcinoma (n = 9170), carcinoma in situ at index diagnosis (n = 12,117), colorectal cancer diagnosis before 1994 (n = 34,619), age at diagnosis <69 years (n = 42,753), enrollment in Medicare health maintenance organization or nonenrollment in Medicare Parts A and B (n = 42,386), cancer diagnosis on autopsy or death certificate (n = 597), no colonoscopy performed during the study period (n = 19,201), only an incomplete colonoscopy performed (n = 978), no colonoscopy performed within 6 months of cancer diagnosis (n = 1119), missing UPIN identifier (n = 6706), and a previous diagnosis of inflammatory bowel disease (n = 914). For the primary analysis, our sample consisted of 57,839 patients, including 4192 who had a colonoscopy in the 6 to 36-month period before diagnosis and 53,647 who had a colonoscopy only within 6 months of diagnosis. The patients who had a colonoscopy in the 6 to 36-month period, which was considered to represent patients with interval cancer, accounted for 7.2%.

The demographic characteristics of the patients in the cohort are listed in Table 1. The mean age of the cohort was 78.9 years, 56.1% were women, and 84.6% were Caucasian. Compared with others, those patients with interval cancers were somewhat older, less likely to be Asian, and more likely to be African American. Patients with interval cancers had higher comorbidity scores and

Table 1. Patient, Geographic, Procedure, and Facility Characteristics Comparing Patients With Interval Cancers (Colonoscopy From 6 to 36 Months) Versus Patients With Detected Cancers (Colonoscopy Within 6 Months)

Characteristic	No. of Patients (%)			*P*
	Overall Population, n = 57,839	Interval Cancers, n = 4192	Detected Cancers, n = 53,647	
Patient measures				
Age group, y				
69-74	16,533 (28.6)	1107 (26.4)	15,426 (28.8)	.003
75-79	15,744 (27.2)	1214 (29)	14,530 (27.1)	
80-84	13,829 (23.9)	1037 (24.7)	12,792 (23.8)	
≥85	11,733 (20.3)	834 (19.9)	10,899 (20.3)	
Sex				
Men	25,406 (43.9)	1821 (43.4)	23,585 (44)	.51
Women	32,433 (56.1)	2371 (56.6)	30,062 (56)	
Race				
Caucasian	48,920 (84.6)	3584 (85.5)	45,336 (84.5)	<.001
African American	3957 (6.8)	322 (7.7)	3635 (6.8)	
Hispanic	2226 (3.9)	150 (3.6)	2076 (3.9)	
Asian or Pacific Islander	2483 (4.3)	117 (2.8)	2366 (4.4)	
Other/unknown	253 (0.4)	19 (0.4)	234 (0.4)	
Comorbidity score				
0	35,438 (61.3)	2203 (52.5)	33,235 (61.9)	<.001
1	13,623 (23.6)	1087 (25.9)	12,536 (23.4)	
2	5166 (8.9)	484 (11.6)	4682 (8.7)	
≥3	3612 (6.2)	418 (10)	3194 (6)	
Diverticulosis				
No	40,482 (70)	1287 (30.7)	39,195 (73.1)	<.001
Yes	17,357 (30)	2905 (69.3)	14,452 (26.9)	
Carcinoma in situ				
No	56,301 (97.3)	4018 (95.9)	52,283 (97.5)	<.001
Yes	1538 (2.7)	174 (4.1)	1364 (2.5)	
Cancer characteristics				
Cancer stage				
I	14,701 (25.4)	1323 (31.6)	13,378 (24.9)	<.001
II	16,915 (29.3)	1121 (26.7)	15,794 (29.5)	
III	13,119 (22.7)	929 (22.2)	12,190 (22.7)	
IV	6950 (12)	362 (8.6)	6588 (12.3)	
Unknown	6154 (10.6)	457 (10.9)	5697 (10.6)	
Grade				
Well or moderately differentiated	42,002 (72.6)	2989 (71.3)	39,013 (72.7)	.08
Poorly differentiated	10,412 (18)	808 (19.3)	9604 (17.9)	
Undifferentiated or unknown	5425 (9.4)	395 (9.4)	5030 (9.4)	
Cancer location				
Proximal colon	28,721 (49.7)	2851 (68)	25,870 (48.2)	<.001
Cecum	12,286 (21.2)	1270 (30.3)	11,016 (20.5)	
Ascending colon	9543 (16.2)	911 (21.7)	8504 (15.9)	
Hepatic flexure	3004 (5.1)	280 (6.7)	2677 (5)	
Transverse colon	4134 (7)	390 (9.3)	3673 (6.8)	
Distal colon	18,740 (32.4)	819 (19.5)	17,921 (33.4)	
Splenic flexure	1494 (2.6)	92 (2.2)	1402 (2.6)	
Descending colon	2145 (3.7)	117 (2.8)	2028 (3.8)	
Sigmoid colon	10,809 (18.7)	456 (10.9)	10,353 (19.3)	
Rectosigmoid	4292 (7.4)	154 (3.7)	4138 (7.7)	
Rectum	9332 (16.1)	434 (10.4)	8898 (16.6)	
Unspecified	1046 (1.8)	88 (2.1)	958 (1.8)	
Medicare reimbursement policy change				
Before January 1998	12,358 (21.4)	775 (18.5)	11,583 (21.6)	<.001
January 1998-July 2001	16,699 (28.9)	1107 (26.4)	15,592 (29.1)	
After July 2001	28,782 (49.8)	2310 (55.1)	26,472 (49.3)	

(Continued)

Table 1. (Continued)

Characteristic	No. of Patients (%) Overall Population, n = 57,839	Interval Cancers, n = 4192	Detected Cancers, n = 53,647	*P*
Procedure and facility characteristics				
Type of colonoscopy				
Polypectomy	24,690 (42.7)	2283 (54.5)	22,407 (41.8)	<.001
Diagnostic	33,149 (57.3)	1909 (45.5)	31,240 (58.2)	
Facility type				
Inpatient	18,727 (32.4)	1227 (29.3)	17,500 (32.6)	<.001
Outpatient	29,359 (50.7)	2200 (52.5)	27,159 (50.6)	
Ambulatory surgical center	8141 (14.1)	647 (15.4)	7494 (14)	
Other	1612 (2.8)	118 (2.8)	1494 (2.8)	
Physician specialty				
Gastroenterology	34,221 (59.2)	2234 (53.3)	31,987 (59.6)	<.001
Colorectal surgery	2174 (3.8)	170 (4.1)	2004 (3.7)	
General surgery	6253 (10.8)	514 (12.3)	5739 (10.7)	
Internal medicine	3304 (5.7)	279 (6.7)	3025 (5.6)	
Family practice	4908 (8.5)	352 (8.4)	4556 (8.5)	
Other	3990 (6.9)	342 (8.2)	3648 (6.8)	
Unknown	2989 (5.2)	301 (7.2)	2688 (5)	
Colonoscopy volume from noncancer sample				
1-48	14,806 (25.2)	1055 (23.5)	13,751 (25.3)	<.001
49-85	14,649 (24.9)	1098 (24.5)	13,551 (25)	
86-140	14,540 (24.8)	1085 (24.2)	13,455 (24.8)	
≥141	14,758 (25.1)	1247 (27.8)	13,511 (24.9)	
Polypectomy rate from noncancer sample, %				
0-0.24	14,453 (25)	1151 (27.5)	13,302 (24.8)	<.001
0.24-0.33	14,499 (25.1)	1,066 (25.4)	13,433 (25)	
0.33-0.43	14,415 (24.9)	1,014 (24.2)	13,401 (25)	
≥0.43	14,472 (25.05)	961 (22.9)	13,511 (25.2)	

were more likely to have previous diagnoses of diverticulosis or colorectal carcinoma in situ. There was also a higher frequency of interval cancers in the most recent Medicare reimbursement period (after July 2001).

Compared with patients in the detected group, patients with interval cancers were more likely to have earlier stage tumors. There were significant site differences, with proximal colon tumors much more common in the interval cancer group (Fig. 1). Overall, the proportion of interval cancers was 9.9% in the proximal colon, 4.4% in the distal colon, and 4.6% in the rectum. It is noteworthy that, although the prevalence of diverticulosis was similar among interval cancers in each location, the prevalence compared with detected cancers was disproportionately high in the distal colon or rectum (distal, 66.5% vs 20.3%; rectum, 70% vs 20.3%; proximal, 70% vs 51.5%).

We also examined procedural factors associated with interval cancers. Previous colonoscopies associated with polypectomy were more likely to be associated with interval cancers than diagnostic colonoscopy. Specialty

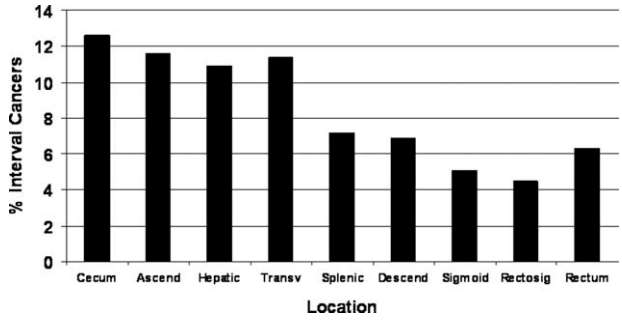

Figure 1. The sites of distribution of interval colorectal cancers are illustrated.

type at initial colonoscopy was associated with interval cancer risk: Gastroenterologists had a lower risk than primary care physicians, general surgeons, or colorectal surgeons. There was an association of facility type, with procedures performed in hospital outpatient or ambulatory surgical centers more likely to be associated with interval cancers than inpatient procedures. The physician

Table 2. Patient, Geographic, Facility, and Procedure Predictors of Interval Colorectal Cancers

Characteristic	Adjusted OR (95% CI)	*P*
Age group, y		
69-74	1.00 (Ref)	—
75-79	1.02 (0.93-1.11)	.73
80-84	0.93 (0.85-1.03)	.16
≥85	0.84 (0.76-0.94)	<.001
Sex		
Women	1.00 (Ref)	—
Men	1.07 (0.99-1.16)	.07
Race		
Caucasian	1.00 (Ref)	—
African American	1.24 (1.09-1.41)	.001
Hispanic	0.97 (0.81-1.16)	.73
Asian or Pacific Islander	0.93 (0.76-1.13)	.45
Other/unknown	1.03 (0.63-1.70)	.90
Comorbidity score		
0	1.00 (Ref)	—
1	1.21 (1.11-1.31)	<.001
2	1.43 (1.28-1.60)	<.001
≥3	1.89 (1.68-2.14)	<.001
Diverticulosis		
No	1.00 (Ref)	—
Yes	6.00 (5.57-6.46)	<.001
Carcinoma in situ		
No	1.00 (Ref)	—
Yes	1.61 (1.35-1.93)	<.001
Cancer stage		
I	1.00 (Ref)	—
II	0.76 (0.70-0.84)	<.001
III	0.85 (0.77-0.93)	<.001
IV	0.70 (0.62-0.80)	<.001
Unknown	0.97 (0.86-1.10)	.67
Cancer location		
Proximal colon	1.00 (Ref)	—
Distal colon	0.42 (0.39-0.46)	<.001
Rectum	0.47 (0.42-0.53)	<.001
Unspecified	0.93 (0.73-1.17)	.53
Interaction of SEER 9 and Medicare reimbursement policy change		
SEER 9		
Before January 1998	1.00 (Ref)	—
From January 1998 to July 2001	0.87 (0.77-0.99)	.03
After July 2001	1.22 (1.08-1.36)	<.001
Non-SEER 9		
Before January 1998	1.00 (Ref)	—
From January 1998 to July 2001	0.92 (0.76-1.13)	.43
After July 2001	1.05 (0.86-1.27)	.64
Type of colonoscopy		
Diagnostic	1.00 (Ref)	—
Polypectomy	1.74 (1.62-1.87)	<.001
Facility type		
Inpatient	1.00 (Ref)	—
Outpatient	1.43 (1.32-1.56)	<.001
Ambulatory surgical center	1.58 (1.34-1.86)	<.001
Other	1.64 (1.33-2.01)	<.001
Physician specialty		
Gastroenterology	1.00 (Ref)	—
Colorectal surgery	1.16 (1.00-1.35)	.05
General surgery	1.38 (1.17-1.63)	<.001
Family practice	1.45 (1.16-1.83)	.001
Internal medicine	1.42 (1.24-1.62)	<.001
Other	1.22 (0.94-1.59)	.14
Unknown	1.66 (1.43-1.94)	<.001
Polypectomy rate by physician from noncancer sample. %		
0-0.24	1.00 (Ref)	—
0.24-0.33	0.84 (0.76-0.93)	.001
0.33-0.43	0.80 (0.72-0.89)	<.001
≥0.43	0.70 (0.63-0.78)	<.001
Colonoscopy volume by physician from noncancer sample		
1-48	1.00 (Ref)	—
49-85	1.10 (0.99-1.22)	.07
86-140	1.17 (1.04-1.31)	.01
≥141	1.27 (1.13-1.43)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference categoroy; SEER 9, Surveillance, Epidemiology, and End Results 9 registries.

polypectomy rate, which was derived from the noncancer sample, was associated inversely with interval cancer risk, whereas procedure volume was correlated positively with risk.

In a multivariable model, we determined sociodemographic, clinical, and procedure-related factors associated with interval cancers (Table 2). Among sociodemographic characteristics, interval cancers were less frequent in patients aged ≥85 years and more frequent in African Americans. Clinical factors associated with interval cancers included increasing comorbidity and previous diagnoses of diverticulosis or carcinoma in situ. In addition, interval cancers more often were stage I tumors. Like in the univariate analysis, there was a strong association of proximal cancer site and interval cancers in the multivariate model. Interval cancers were more common in the most recent Medicare reimbursement period, but only among SEER registries that were included in the entire study period (SEER 9).

Consistent with univariate analyses, interval cancers were more common in patients who underwent previous polypectomy and who had colonoscopies performed in locations other than an inpatient setting. There also was a greater likelihood of interval cancers among endoscopists

with lower polypectomy rates or highest procedure volume. Finally, compared with gastroenterologists, there was a greater likelihood of interval cancers among other specialties.

To evaluate the robustness of results, we considered 3 other samples. First, to account for delays in definitive cancer diagnosis, the time period for interval cancers was changed from 36 months to 12 months before diagnosis, and colonoscopies that were performed within 12 months were considered to have detected the cancer. By using this definition, 6.2% of cancers were considered interval lesions, and predictors and their magnitude of risk were similar to those in the primary analysis. Second, because screening colonoscopy typically is an outpatient procedure, we excluded colonoscopies performed in the inpatient setting. Among 39,112 patients, 2965 (7.6%) were considered to have interval cancers. Again, the major risk factors for interval cancers were consistent with other analyses. In the current analysis, compared with hospital outpatient procedures, colonoscopies performed in ambulatory surgery centers were associated with higher odds of interval cancers (multivariate odds ratio [MOR], 1.26; 95% confidence interval [CI], 1.08-1.47). Finally, if patients who underwent colonoscopy only during the 6 to 36-month period and not within 6 months of diagnosis were included in the interval group, then the proportion of interval cancers decreased to 1.8%. Predictors of interval lesions were similar to other case definitions, although, for previous polypectomy (MOR, 1.16; 95% CI, 1.00-1.35) and diverticulosis (MOR, 1.97; 95% CI, 1.73-2.26), the magnitude of risk was decreased.

DISCUSSION

Although colonoscopy generally is considered the most accurate screening modality currently available, a subset of patients may develop colorectal cancer after a colonoscopy that was negative for carcinoma. These lesions, termed interval cancers, largely have been described in studies from Canada[10-13,15,16] and Germany[14] and have a greater prevalence in the proximal colon. Skeptics of findings from these previous studies have questioned the generalizability to US practice. However, in the current study, which, to our knowledge, is the first US population-based analysis to include validation of cancer diagnoses through registry data, we documented an interval cancer frequency of 7.2 %. Although risk factors for interval cancers generally are consistent with studies from other countries, the results highlight limitations of colonoscopy as currently practiced in the United States.

The underlying reason for the consistent findings of a higher frequency of interval cancers in the right colon is unclear and is likely multifactorial. An unknown proportion of interval cancers could be attributed to microsatellite instability (MSI), which, even in patients without Lynch syndrome,[25] may be more prevalent.[26] MSI cancers are associated with more rapid lesion growth and are known to be more common in the right colon. In addition, MSI cancers more commonly are associated with precursor sessile serrated adenomas, lesions that may be more difficult to detect at colonoscopy.[27-29] Their presence has been postulated as a mechanism for the failure of colonoscopy to protect against proximal cancers.[30] Another potential factor is inability of the endoscopist to reach the cecum. A previous study from Ontario, where billing requirements are to document each segment examined, reported an incomplete colonoscopy frequency as high as 13%.[31] Because reimbursement in the United States potentially is the same for advancing to any segment beyond the splenic flexure, comparable data are not available. Although there is a modifier code for an incomplete examination, it is used infrequentl,y[32] and these patients were excluded from the current study.

In addition to proximal tumor location, we identified other predictors of interval cancers. Diverticulosis, which also has been identified as a risk factor in other studies,[15-17] presumably impedes the endoscopist's ability to observe intervening mucosa and/or reach the cecum and, if documented in diagnosis codes, may be associated with more severe disease. In addition, older literature has documented the association between sigmoid diverticulosis and missed cancers on barium enema.[33] Our finding of a greater risk for diverticulosis with interval cancers in the distal colon suggests that impaired visualization may be the predominant effect.

Prior polypectomy, as defined in our analysis, referred to the last procedure performed during the 6 to 36-month interval or <6-month interval preceding cancer diagnosis. For patients who had an initial colonoscopy shortly before diagnosis, it may have been diagnostic of the cancer. This finding was supported by the lower odds ratio in the secondary analysis, which included only interval cancers diagnosed within 6 to 36 months of diagnosis. For patients who had an earlier colonoscopy, an incompletely removed polyp may have progressed to cancer. Alternatively, undergoing polypectomy elsewhere in the colon may have served as a predictor of subsequent cancer

risk. The underlying mechanism for other predictors of interval cancer, such as comorbidity, is less intuitive. Comorbidity is associated with more frequent contact with the health care system and, thus, may provide more opportunity for the detection of subclinical cancer. Alternatively, it also could be an indicator of more difficulty with bowel preparation. We also observed lower odds with procedures performed in the inpatient setting; the reason for this is not clear, but it may represent differences in clinical presentation. It is noteworthy that, when inpatient cases were excluded, the results remained constant.

Our study documented the association of endoscopist specialty and colonoscopy metrics with the risk of interval cancer. A recent study of interval cancers from Ontario[34] documented associations with a lower overall polypectomy and colonoscopy completion rates as well as a nongastroenterology or surgery specialty. Another recent Ontario-based study[35] also reported a greater likelihood of interval cancer after a negative colonoscopy if the examination was performed at a hospital by a nongastroenterologist. Our study also documented an association between interval cancers and the endoscopist's polypectomy rate, which has been suggested as an indirect measure of the adenoma detection rate.[20,21] Given the differences from Canada in billing documentation, we were unable to accurately measure the colonoscopy completion rate.

A recent study from Manitoba also found a higher likelihood of colorectal cancer after a negative colonoscopy if the procedure was performed by a nongastroenterologist.[12] The similar findings are noteworthy despite differences in demographics of endoscopists in the US versus Canada, where a much lower proportion are gastroenterologists.[10-13,15,31] Also of note is that 2 recently published Medicare-based studies have found the prevalence of other potential quality measures such as polyp detection and removal rates[36] and need for repeat colonoscopy[37] to be inferior among nongastroenterologists.

One potential method to increase lesion detection at colonoscopy is the use of newer imaging modalities.[38] Unfortunately, the most commonly used technology, narrow band imaging, has not demonstrated the ability to increase adenoma detection.[39] However, other less commonly used techniques, such as indigo carmine spraying, may increase the detection of nonpolypoid neoplasia, which is more common in the right colon and may be more likely to harbor carcinoma.[40]

We recognize several limitations of the current study. First, the study was conducted in a cohort of older Medicare beneficiaries who received care in fee-for-service arrangements. Thus, the generalizability of our findings to other patient groups is unknown. Second, procedure-related details, such as size and morphology of polyps detected, quality of bowel preparation, and ability to complete the examination to the cecum, were not available. Third, we could not ascertain whether the follow-up colonoscopy that diagnosed the cancer was a scheduled or unscheduled examination. In the former case, the endoscopist may have recognized the risk for subsequent cancer based on procedural factors or limited visualization and arranged for repeat colonoscopy. Fourth, specifics about colonoscopy, including use of polypectomy and physician specialty, were obtained from administrative data. Although data are collected for billing purposes and not research, it is believed that the completeness of Medicare claims for measuring colonoscopy use is relatively high.[41] A recent study that compared Medicare claims with colonoscopy reports indicated high sensitivity and specificity for a diagnosis of polyps as well as interventions that were performed.[32] Fifth, our measures of endoscopist performance characteristics, such as frequency of polypectomy, were derived from Medicare beneficiaries alone and do not reflect colonoscopy in other patients. However, for other procedures, such as cancer resection, there is a strong correlation between provider-specific volume in Medicare patients and non-Medicare patients.[42] Sixth, given the large sample size, certain statistically significant differences may not have been clinically relevant. Seventh, the study was limited to patients who underwent colonoscopy before cancer diagnosis. In related work, we examined the nearly 20% of patients who did not undergo colonoscopy within 6 months of diagnosis.[43] These patients were more likely to be elderly with multiple comorbidities, to be nursing home residents, and to present emergently and with late-stage disease; thus, their exclusion may have biased the sample toward healthier patients. Finally, a subset of patients may have received part of their care, including colonoscopies, at a Veterans Administration facility, and data on these procedures would not be available.

In conclusion, we have used US population-based data to demonstrate a frequency of interval cancers after colonoscopy of 7.2%. The frequencies were particularly high in the proximal colon, which may be attributed to procedural and biologic factors. The findings emphasize the importance of meticulous inspection at the time of colonoscopy to detect precursor lesions. Moreover, if the impact of colonoscopy on cancer prevention is to be maximized, then quality metrics proposed by professional societies should be targeted.[19]

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The authors made no disclosures.

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