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Diverticulosis and the Risk of Interval Colorectal Cancer

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Abstract

Background—Diverticulosis, a prevalent condition at screening colonoscopy, has been associated with colorectal cancers that develop after a clearing colonoscopy, or interval cancers.

Aims—To quantify the overal risk of diverticulosis in the development of interval cancers and examine this association in relevant subgroups.

Methods—Using a linked database containing SEER tumor registry data and Medicare claims, we identified patients aged ≥ 69 years with colorectal cancer who underwent colonoscopy within 6 months of diagnosis. Patients with an additional colonoscopy from 36-6 months prior to cancer diagnosis were characterized as having interval cancers. We compared characteristics of patients with interval cancers and detected cancers according to a diagnosis of diverticulosis not associated with a colonoscopy procedure from 1991 through the date of the most recent colonoscopy in both univariate and multivariate models.

Results—A previous diagnosis of diverticulosis was documented in 14,452 (26.9%) patients with detected cancers compared to 2,905 (69.3%) patients with interval cancers ($p<0.001$); these results were consistent in multivariable analysis. Moreover, the association was found as well in the proximal colon (OR 2.88, 95% CI 2.66, 3.12), distal colon (OR 3.56, 95% CI 3.09, 4.11) and rectum (OR 4.07, 95% CI 3.34, 4.95). The vast majority of diverticulosis diagnoses were without complications such as hemorrhage or diverticulitis.

Conclusions—Diverticulosis was strongly associated with interval colorectal cancers in all segments of the colon. Given its known predominance in the left colon, the findings argue against impaired visualization of lesions at colonoscopy as the only pathogenic factor.

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Keywords

Colonic diverticulosis; colonoscopy; colonic neoplasms; SEER program

Introduction

Although colonoscopy is generally considered to be the most accurate screening modality currently available, a subset of patients may develop colorectal cancer following a colonoscopy that was negative for carcinoma. These lesions, termed interval cancers, have been described in multiple studies from the United States (1–5), Canada (6–11) and Germany (12). Although the actual frequency of interval cancers depends on specific defintions that are used, a prevalence of 5–10% has generally been quoted (13).

Specific risk factors for interval cancers have been examined and have included location of cancer, with higher rates in the proximal colon, endoscopy quality metrics such as adenoma detection rate, and biological factors, such as CpG island methylator phenonotype (CIMP) status. In addition, in both Canadian and US based studies, a diagnosis of diverticulosis has also been found to be a risk factor for interval cancers (4,8,10). Although the underlying reason for this association is not evident, it has been speculated that the presence of diverticulosis could impede the endoscopist's ability to visualize intervening mucosa (10).

In order to better characterize the association of diverticulosis and interval cancer, we conducted a population-based analysis of an older cohort of patients with interval colorectal cancers. Our goals were to quantify the overal risk of diverticulosis in the development of interval cancers and examine this association in relevant subgroups of patients.

Methods

Data Sources

The present study is an extension of our previous work on risk factors for interval cancers (4), with additional analyses to further characterize and quantify the risk of diverticulosis. We used the linked SEER-Medicare database, which consists of Medicare eligible patients who are diagnosed with cancer and reside in one of the geographic areas contained in the SEER registries (14,15). Through the 1990's, the SEER Program encompassed about 14% of the US population (SEER 9), but with the addition of several new registries in 2000 (SEER 18), approximately 26% 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 three 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 includes all hospitalizations. Each Medicare claim contains diagnoses coded by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and procedures coded according to Common Procedural Terminology, 4th Edition (CPT-4) or ICD-9-CM. The Carrier and Outpatient claims also

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include physician specialty code and an encrypted version of the physician's unique personal identifier (UPIN), which was 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 one of the SEER areas but were cancer-free. The Medicare files available for this group were identical to those of the cancer cases and allowed for a more complete measure of physician practice. These files were used to categorize physicians according to two measures of endoscopist performance – the volume of colonoscopies in the database as well as the frequency of polypectomy procedures. The latter measure, which is a representation of the adenoma detection rate (16) 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 (17,18).

Patients and Measures

Using the 1994–2005 SEER files, we identified all individuals aged 69 and older with a diagnosis of colorectal adenocarcinoma from 1994–2005. The inclusion criteria were provided to ensure three years of Medicare eligibility (i.e, beginning at age 65) and file availability prior to diagnosis. Patients were excluded if they were enrolled in a Medicare sponsored managed care plan or not enrolled in Medicare Parts A and B from three years prior to diagnosis because of the likely presence of incomplete claims. Patients with a previous diagnosis of cancer at any site according to SEER were also excluded, as were patients with the only colonoscopy procedure coded as incomplete. We also excluded all patients diagnosed with ulcerative colitis or Crohn's disease during the previous three years, as cancer in this setting is thought to develop through a different biological pathway. All patients without colonoscopy within six months prior to cancer diagnosis were excluded. Finally, in order to be able to measure physician performance characteristics associated with the colonoscopy, we excluded patients for whom the colonoscopy could not be linked to an encrypted UPIN.

Our primary independent variable was a diagnosis of diverticulosis, which was obtained by examining all Medicare claims from 1991 through the date of the most recent colonoscopy. Codes included diverticulosis without hemorrhage (ICD-9-CM 562.10), diverticulitis without hemorrhage (562.11), diverticulosis with hemorrhage (562.12) and diverticulitis with hemorrhage (562.13). In order to minimize ascertainment bias among patients with more frequent colonoscopies, we only included a diagnosis of diverticulosis associated with an office visit or hospitalization. We further categorized the diagnosis codes into three non-mutually exclusive groups – diverticulitis (562.11, 562.13), diverticular hemorrhage (562.12, 562.13) and uncomplicated diverticulosis (562.10). Cancer location was characterized as proximal (splenic flexure to cecum), distal (rectosigmoid, sigmoid and descending colon) and rectum.

The Carrier, Outpatient and MEDPAR files from three years through the date of cancer diagnosis were examined for receipt of colonoscopy. Colonoscopies included both diagnostic examinations (CPT-4 44388, 44389, 45378, 45380, 45382, G0105, G0121;

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ICD-9-CM 45.23, 45.41, 45.25, 45.27) and polypectomy procedures (CPT-4 44392, 44393, 44394, 45383, 45384, 45385; ICD-9-CM 45.42, 45.43, 48.36) according to procedure codes, and the dates of all colonoscopies were recorded. Among patients with colonoscopy during both the 36-6 month and < 6 month intervals, the last procedure during the 36-6 month interval was used to derive data about procedure specifics and endoscopist characteristics. Claims data from one year to one month prior to diagnosis were used to derive a previously validated, weighted comorbidity score which was a claims database adaptation of the Charlson index (19).

As characterized in previous studies by our group (4) and others (10,11), cancers associated with colonoscopy procedures between six months and three years before diagnosis were considered to represent interval lesions. The rationale for this distinction assumes that if a malignant lesion is detected at colonoscopy, 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 (20,21).

Analysis

We first compared the prevalence of a previous diagnosis of diverticulosis among patients with interval cancers and detected cancers (colonoscopy only within 6 months of diagnosis) using chi-square testing. Next, among patients with interval colorectal cancers, we compared characteristics of patients with and without a previous diagnosis of diverticulosis using chi-square analysis. Variables of interest included demographic factors (age group, gender, race), comorbidity score, and cancer stage, grade and location in the colon. Physician characteristics included specialty and volume of colonoscopy procedures in the noncancer Outpatient and NCH files from 1991–2005. Using all colonoscopies from the noncancer sample from 1991–2005, we also included the endoscopist's polypectomy rate. For most physicians with missing UPIN data, we were able to obtain specialty through the Medicare specialty code on the claim.

Finally, a generalized estimating equation (GEE) model was used to determine the independent association of diverticulosis with interval cancer, stratified by tumor location. In this analysis, we clustered patients at the physician level.

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

A total of 299,260 patients were initially 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=9,170), carcinoma-in-situ at index diagnosis (n=12,117), colorectal cancer diagnosis prior to 1994 (n=34,619), age at diagnosis < 69 (n=42,753), enrollment in Medicare HMO or non-enrollment 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

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(n=19,201), only an incomplete colonoscopy performed (n=978), no colonoscopy performed within six months of cancer diagnosis (n=1,119), missing UPIN identifier (n=6,706), and a previous diagnosis of inflammatory bowel disease (n=914). Our sample consisted of 57,839 patients, including 4,192 with a colonoscopy in the 6 to 36 month period prior to diagnosis and 53,647 with only a colonoscopy within 6 months of diagnosis. The patients with a colonoscopy in the 6-36 month period, which was considered to represent patients with interval cancer, accounted for 7.2%.

In the time period prior to cancer diagnosis, a diagnosis of diverticulosis was documented in 12,678 (23.6%) patients with detected cancers compared to 2,145 (51.2%) patients with interval cancers ($p<0.001$). Non-mutually exclusive subtypes of diverticular disease in the patients with interval cancers included diverticulitis (11.5%), diverticular hemorrhage (4.3%) and uncomplicated diverticulosis (54.2%). In the detected cancer group, the corresponding frequencies were diverticulitis (6.5%), diverticular hemorrhage (1.1%) and uncomplicated diverticular disease (19.7%). The median time from first diagnosis of diverticulosis to cancer diagnosis was 3.29 years (25^{th}–75^{th} percentile 1.90–5.58 years) in the interval cancer group and 2.08 years (25^{th}–75^{th} percentile 0.02–5.05 years) in the detected cancer group.

Among patients with interval cancer, we examined factors associated with a previous diagnosis of diverticulosis (Table 1). Patients with diverticulosis were older, more likely to be male and Caucasian and more frequently had comorbidity scores of 3 or higher. There were no significant differences in the stage of cancer. Diverticulosis associated interval cancers were somewhat more likely to be in the proximal colon and less likely to be in the distal colon or rectum. Diverticulosis associated interval cancers were also soemwhat more likely among endoscopists with the highest and lowest polypectomy rate but were not associated with endoscopist procedure.

In a similar analysis of patients with detected cancers, patients with a previous diagnosis of diverticulosis were also more likely to be older, male and Caucasian with comorbidity scores of 1 or higher (Table 2). Diverticulosis associated cancers tended to be earlier stage and were much more likely to occur in the proximal colon. There was no association of endoscopist measures.

In a multivariate GEE model, we determined the independent association of diverticulosis with interval cancer, stratified by location of tumor (Table 3). In this analysis, a previous diagnosis of diverticulosis was associated with interval cancers in the proximal colon (OR 2.88, 95% CI 2.66–3.12), distal colon (OR 3.56, 95% CI 3.09–4.11) and rectum (OR 4.07, 95% CI 3.34–4.95). Other factors associated with interval cancers included age ≥ 85, male gender, and increased comorbidity. Physician factors associated with interval cancers included specialty other than gastroenterology, lower polypectomy rates and higher colonoscopy volume.

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Discussion

Colorectal cancers that are diagnosed after a “clearing” colonoscopy, or interval cancers, remain an important problem, accounting for up to 10% of cancers that are diagnosed in the US. Because a previous diagnosis of diverticulosis has been described as a risk factor for interval cancers, we sought to better characterize the association. In this large, population-based study of older patients with interval colorectal cancers, we found that diverticulosis was strongly associated with interval cancers.

Other studies have also documented an association of diverticulosis with interval colon cancers. Using a population-based cohort from Ontario, Canada, Bressler and colleagues found that diverticulosis was documented in 38% of interval cancers, compared to only 7% of detected cancers, and these differences were maintained in multivariate analysis (10). A second Canadian study from Manitoba also found an association of diverticulosis with interval cancers, though the strength of the association was not as strong as in the Ontario study and the differences were not observed in a multivariable model (8). In an older series, the association between diverticular disease was a strong risk factor for missed cancer in the sigmoid colon on barium enema with the highest miss rate found in patients with more than 15 diverticula (22). The latter study suggests that the presence of diverticulosis or its complications such as diverticulitis may interfere with the ability to recognize precancerous and malignant lesions at colonoscopy. In addition, the endoscopic appearance of neoplastic tissue is sometimes mistaken for an area of severe inflammation.

Despite the higher prevalence in Western counties of more extensive diverticular disease in the left colon (23), we found that the risk of diverticulosis for interval cancers was similar at all sites in the colon. Moreover, most cases of diverticular associated interval cancers were among patients with uncomplicated disease as opposed to diverticulitis or diverticular hemorrhage. These factors suggest that impaired visualization of cancers and/or their precursor adenomas is likely not the only mechanism for the association. Alternative mechanisms include biological factors, or potentially the presence of shared risk factors. Another potential mechanism is diverticulosis impeding the endoscopist’s ability to reach the cecum, though we excluded incomplete examinations from our analysis. As patients in both the interval and detected cancer groups underwent colonoscopy that led to the cancer diagnosis, the association is likely not merely due to underreporting of diverticulosis among patients with a finding of cancer. Although we also found that patients with diverticulosis associated interval cancers were more likely to be older men, but differences were probably not great enough to justify changes in current screening practices.

Epidemiological studies have also suggested a link between diverticulosis and colorectal cancer, with some studies documenting a more frequent rectosigmoid distribution of carcinoma and advanced adenomas in patients with diverticulosis, compared to controls (24). This association has been strongest for patients with previous diverticulitis and/or extensive disease, and there has been a suggestion that diverticulosis at a young age at onset represents a risk factor for carcinoma (25). Although the presence of this association has been refuted in other studies (26–29), biological mechanisms including chronic inflammation, extracellular matrix alterations, and the presence of abberant crypt foci have

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all been speculated (30). Others have argued that this association is an artifact of missclassification and more intensive surveillance (31). Also, the presence of diverticulosis may have been associated with an inferior bowel preparation quality and may have impeded visualization of colonic neoplasia.

We recognize several limitations of the current study. First, the study was conducted in a cohort of older Medicare beneficiaries receiving care in fee-for-service arrangements. Thus, the generalizability of findings to other patient groups, including younger individuals and those under managed care is unknown. Second, procedure related details such as number, size and distribution of diverticulosis, and quality of bowel preparation were not available. Although we did exclude patients who had their only colonoscopy coded as incomplete, a completed procedure with a poor prep attributed in part to diverticulosis could have been included. Third, as the diagnosis codes for diverticulosis do not indicate the affected segement(s) of the bowel, we could not determine whether the presence of diverticulosis directly impeded visualization of adenomas and/or carcinoma. Fourth, although diagnosis codes included the presence of diverticulitis and diverticular hemorrhage, the presence and severity of these complications could not be validated in this database. Fifth, specifics about the colonoscopy, including use of polypectomy and physician specialty were obtained from administrative data. Although data are collected for billing purposes and not research, the completeness of Medicare claims for measuring colonoscopy use is thought to be relatively high (32). A study that compared Medicare claims to colonoscopy reports found a high sensitivity and specificity for a diagnosis of polyps as well as interventions that were performed (33). Sixth, given the large sample size, certain statistically significant differences may not have been clinically relevant. Finally, although we limited the inclusion criteria for diverticulosis to non-colonoscopy claims, based on the defintion of interval cancers, more colonosocpies were performed prior to cancer diagnosis than among patients with detected cancers. Thus, there is still potential for ascertainment bias with diagnoses in other claims reflecting the colonoscopy findings.

In summary, in this population-based analysis, a previous diagnosis of diverticulosis was associated with an increased risk of interval cancers in all segments of the colon. However, because of the high prevalence of diverticular disease in an age appropriate screening population, at this point, more frequent screening intervals are probably not justified to reduce this risk.

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Table 1

Patient characteristics associated with diverticulosis among interval cancers (n =4,192)

Characteristics	Diverticulosis (n=2145)		No Diverticulosis (n=2047)		p-value
	N	%	N	%	
Demographics					
Age group					< 0.001
69 – 74	457	21.3	650	31.8	
75 – 79	622	29.0	592	28.9	
80 – 84	568	26.5	469	22.9	
≥ 85	498	23.2	336	16.4	
Sex					< 0.001
Male	841	39.2	980	47.9	
Female	1304	60.8	1067	52.1	
Race					< 0.001
White	1881	87.7	1703	83.2	
Black	145	6.8	177	8.7	
Hispanic	73	3.4	77	3.8	
Asian or Pacific Islander	36	1.7	81	4.0	
Other/Unknown	*		*		
Charlson Comorbidity					0.02
0	1059	49.4	1144	55.9	
1	565	26.3	522	25.5	
2	270	12.6	214	10.5	
≥ 3	251	11.7	167	8.2	
Clinical presentation					
Cancer stage					0.8
I	686	32.0	637	31.1	
II	584	27.2	537	26.2	
III	468	21.8	461	22.5	
IV	180	8.4	182	8.9	

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Characteristics	Diverticulosis (n=2145)		No Diverticulosis (n=2047)		p-value
	N	%	N	%	
Unknown	227	10.6	230	11.2	
Tumor Grade					0.05
Well or moderately differentiated	1533	71.5	1456	71.1	
Poorly differentiated	431	20.1	377	18.4	
Cancer location					0.03
Proximal colon	1501	70.0	1350	66.0	
Distal colon	396	18.5	423	20.7	
Rectum	202	9.4	232	11.3	
Unspecified	46	2.1	42	2.1	
Physician specialty					0.002
Gastroenterology	1172	54.6	1062	51.9	
Colorectal surgery	71	3.3	99	4.8	
General surgery	279	13.0	235	11.5	
Internal medicine	142	6.6	137	6.7	
Family practice	192	9.0	160	7.8	
Other	158	7.4	184	9.0	
Unknown	131	6.1	170	8.3	
Colonoscopy volume from noncancer sample					0.31
1 – 48	483	22.5	511	25.0	
49 – 85	539	25.1	496	24.2	
86 – 140	524	24.4	477	23.3	
≥ 141	599	27.9	563	27.5	
Polypectomy rate from noncancer sample (%)					0.02
0 – 0.24	608	28.3	543	26.5	
0.24 – 0.33	505	23.5	561	27.4	
0.33 – 0.43	517	24.1	497	24.3	
≥ 0.43	515	24.0	446	21.8	

*Cell sizes suppressed due to NCI policy

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Table 2

Patient characteristics associated with diverticulosis among detected cancers (n = 53,647)

Characteristics	Diverculosis (n=12678)		No Diverculosis (n=40969)		p-value
	N	%	N	%	
Demographics					
Age group					< 0.001
69 – 74	2764	21.8	12662	30.9	
75 – 79	3256	25.7	11274	27.5	
80 – 84	3304	26.1	9488	23.2	
≥ 85	3354	26.5	7545	18.4	
Sex					< 0.001
Male	7847	61.9	22215	54.2	
Female	4831	38.1	18754	45.8	
Race					< 0.001
White	11117	87.7	34219	83.5	
Black	746	5.9	2889	7.1	
Hispanic	483	3.8	1593	3.9	
Asian or Pacific Islander	290	2.3	2076	5.1	
Other/Unknown	42	0.3	19	0.5	
Charlson Comorbidity					< 0.001
0	7374	58.2	25861	63.1	
1	3165	25.0	9371	22.9	
2	1249	9.9	3433	8.4	
≥3	890	7.0	2304	5.6	
Clinical presentation					
Cancer stage					< 0.001
I	3311	26.1	10067	24.6	
II	3835	30.3	11959	29.2	
III	2818	22.2	9372	22.9	
IV	1350	10.7	5238	12.8	

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Characteristics	Diverculosis (n=12678)		No Diverculosis (n=40969)		p-value
	N	%	N	%	
Unknown	1364	10.8	4333	10.6	
Tumor Grade					0.15
Well or moderately differentiated	9148	72.2	29865	72.9	
Poorly differentiated	2342	18.5	7262	17.7	
Cancer location					< 0.001
Proximal colon	7210	56.9	18660	45.6	
Distal colon	3686	29.1	14235	34.8	
Rectum	1560	12.3	7338	17.9	
Unspecified	222	1.8	736	1.8	
Physician specialty					< 0.001
Gastroenterology	7648	60.3	24339	59.4	
Colorectal surgery	469	3.7	1535	3.8	
General surgery	1433	11.3	4306	10.5	
Internal medicine	758	6.0	2267	5.5	
Family practice	1099	8.7	3457	8.4	
Other	715	5.6	2933	7.2	
Unknown	556	4.4	2132	5.2	
Colonoscopy volume from noncancer sample					0.06
1 – 48	3279	25.9	10318	25.2	
49 – 85	3235	25.5	10159	24.8	
86 – 140	3073	24.2	10214	24.9	
≥ 141	3091	24.4	10278	25.1	
Polypectomy rate from noncancer sample (%)					0.16
0 – 0.24	3083	24.3	10219	24.9	
0.24 – 0.33	3249	25.6	10184	24.9	
0.33 – 0.43	3199	25.2	10202	24.9	
≥ 0.43	3147	24.8	10364	25.3	

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Table 3

Factors Associated with Interval Cancers in Multivariable Analysis

Characteristics	Adjusted OR (95% CI)	p-value
Diverculosis versus non-Diverculosis		
Right colon	2.88 (2.66, 3.12)	<0.001
Left colon	3.56 (3.09, 4.11)	<0.001
Rectum	4.07 (3.34, 4.95)	<0.001
Unspecified	3.65 (2.35, 5.65)	<0.001
Demographics		
Age group		
69 – 74 (ref)	1	
75 – 79	1.03 (0.95, 1.13)	0.46
80 – 84	0.93 (0.85, 1.02)	0.14
≥ 85	0.80 (0.72, 0.88)	<0.001
Sex		
Female (ref)	1	
Male	1.12 (1.05, 1.20)	<0.001
Race		
White (ref)	1	
Black	1.13 (1.00, 1.28)	0.05
Hispanic	0.96 (0.80, 1.13)	0.60
Asian or Pacific Islander	0.85 (0.70, 1.03)	0.10
Charlson Comorbidity		
0 (ref)	1	
1	1.22 (1.13, 1.33)	<0.001
2	1.43 (1.29, 1.59)	<0.001
≥ 3	1.81 (1.61, 2.03)	<0.001
Clinical presentation		
Cancer stage		
I (ref)	1	
II	0.64 (0.59, 0.70)	<0.001
III	0.71 (0.65, 0.78)	<0.001
IV	0.54 (0.48, 0.61)	<0.001
Unknown	0.86 (0.76, 0.97)	0.01
Tumor Grade		
Well or moderately differentiated (ref)	1	
Poorly differentiated	1.06 (0.97, 1.15)	0.18
Physician specialty		
Gastroenterology (ref)	1	
Colorectal surgery	1.47 (1.18, 1.83)	<0.001

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Characteristics	Adjusted OR (95% CI)	p-value
General surgery	1.44 (1.26, 1.65)	<0.001
Internal medicine	1.40 (1.20, 1.64)	<0.001
Family practice	1.18 (1.01, 1.37)	0.03
Other	1.41 (1.16, 1.71)	<0.001
Unknown	2.07 (1.80, 2.38)	<0.001
Colonoscopy volume from noncancer sample		
1 – 48 (ref)	1	
49 – 85	1.11 (1.00, 1.23)	0.04
86 – 140	1.18 (1.05, 1.31)	0.004
≥ 141	1.30 (1.16, 1.46)	<0.001
Polypectomy rate from noncancer sample (%)		
0 – 0.24 (ref)	1	
0.24 – 0.33	0.89 (0.81, 0.99)	0.03
0.33 – 0.43	0.86 (0.79, 0.97)	0.01
≥ 0.43	0.82 (0.74, 0.90)	<0.001