Temporal Trends and Risk Factors for Postcolonoscopy Colorectal Cancer

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Background: Colonoscopy is effective for colorectal cancer (CRC) prevention, yet patients may develop CRC despite adhering to screening/surveillance intervals. There are limited data on predictive factors associated with these postcolonoscopy CRCs (PCCRCs). We aimed to measure PCCRC rates and identify risk factors for PCCRC.

Methods: We performed a case-control study, comparing patients with PCCRCs to spontaneous CRCs diagnosed during a 12.5-year period at an academic medical center. PCCRCs were defined as CRCs diagnosed in between guideline-recommended screening/surveillance intervals.

Results: During the 12.5-year period, of 1266 CRCs diagnosed, 122 (10%) were PCCRCs. 70% of PCCRCs were diagnosed within 5 years of a prior colonoscopy. There was an increasing trend for PCCRC rates in recent years [odds ratio (OR), 2.78; 95% confidence interval (CI), 1.51-5.09], with PCCRCs comprising 13.6% of cancers diagnosed in 2016 as compared with 5.7% of cancers diagnosed in 2005. Older age (OR per year, 1.02; 95% CI, 1.01-1.04), proximal colonic location (OR, 1.99; 95% CI, 1.20-3.33) and early stage (OR, 2.57; 95% CI, 1.34-4.95) were associated with PCCRCs. In total, 41% of PCCRCs were diagnosed by a different physician from the physician who did the prior colonoscopy, and 42% of physicians did not diagnose *any* of their PCCRC cases.

Conclusions: PCCRC rates are rising in recent years, likely reflecting the widespread adoption of colonoscopy as a primary screening tool, and are more common in older patients and those with proximal, early-stage tumors. The finding that a large proportion of PCCRCs are diagnosed by a different physician raises the concern that physicians are unaware of their own patients' PCCRCs.

Key Words: postcolonoscopy colorectal cancer, interval colorectal cancer, colorectal cancer prevention, colonoscopy quality, quality improvement

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The incidence of colorectal cancer (CRC) and CRC deaths in the United States is declining.[1] This has been ascribed to early detection and resection of precancerous lesions owing to increased use of CRC screening.[2–6] However, despite the demonstrated effectiveness of colonoscopy in reducing CRC incidence and mortality, 1.8% to 9.0% of CRCs are diagnosed within 6 to 36 months of a prior colonoscopy.[7] These postcolonoscopy CRCs (PCCRCs) reflect the limitations of screening efficacy, as guidelines recommend a 10-year screening interval following a negative colonoscopy.[8] The association between PCCRC risk and several clinical, demographic, physician, and colonoscopy-quality factors have been studied in the literature with variable results.[7,9–14] Studying this phenomenon is further compounded by the lack of well-defined systems to inform physicians about their PCCRC cases. Notification of a physician that he or she has a patient who developed a PCCRCs may be difficult given the sensitivity of the issue. For this reason, as well as the fragmented nature of medical care in many parts of the United States, physicians may be unaware of their own PCCRC rates; the adenoma detection rate is therefore utilized as a surrogate marker, given its association with the risk of PCCRC.[15,16]

In this study we aimed to identify demographic and clinical variables associated with PCCRC risk at an academic medical center, and to measure trends in PCCRC development over time.

METHODS

We analyzed the electronic medical records of 2101 patients who were diagnosed with colorectal adenocarcinoma at Columbia University Medical Center during the 12.5-year period spanning September 2004 to March 2017. Patients who had their adenocarcinoma diagnosis via colonoscopy at another medical institution, a history of familial adenomatous polyposis, hereditary nonpolyposis CRC, inflammatory bowel disease, or previous colorectal malignancy were excluded from the study. In addition, we excluded patients with polyps on a prior colonoscopy that were not resected due to anticoagulant use; and those with a prior CRC screening modality that was not a colonoscopy. Similar to the analysis by Kaminski et al,[15] a PCCRC was defined as a colorectal malignancy diagnosed within 6 to 120 months after a negative colonoscopy (no adenomas), 6 to 60 months after a colonoscopy with 1-2 nonadvanced adenomas or 6 to 36 months after a colonoscopy with 3 to 10 adenomas. Otherwise, the malignancy was classified as a spontaneous CRC (SCRC) (Fig. 1).

Exposures

When comparing cases (PCCRC) to controls (SCRC) we investigated demographic, clinical, and colonoscopy-related factors. Patient variables include age, sex, race, ethnicity, and insurance status. Clinical variables include tumor location, tumor stage, microsatellite instability (MSI) status when available, year of diagnosis, and indication for colonoscopy. We also examined colonoscopy-related variables; this secondary analysis was restricted to those patients

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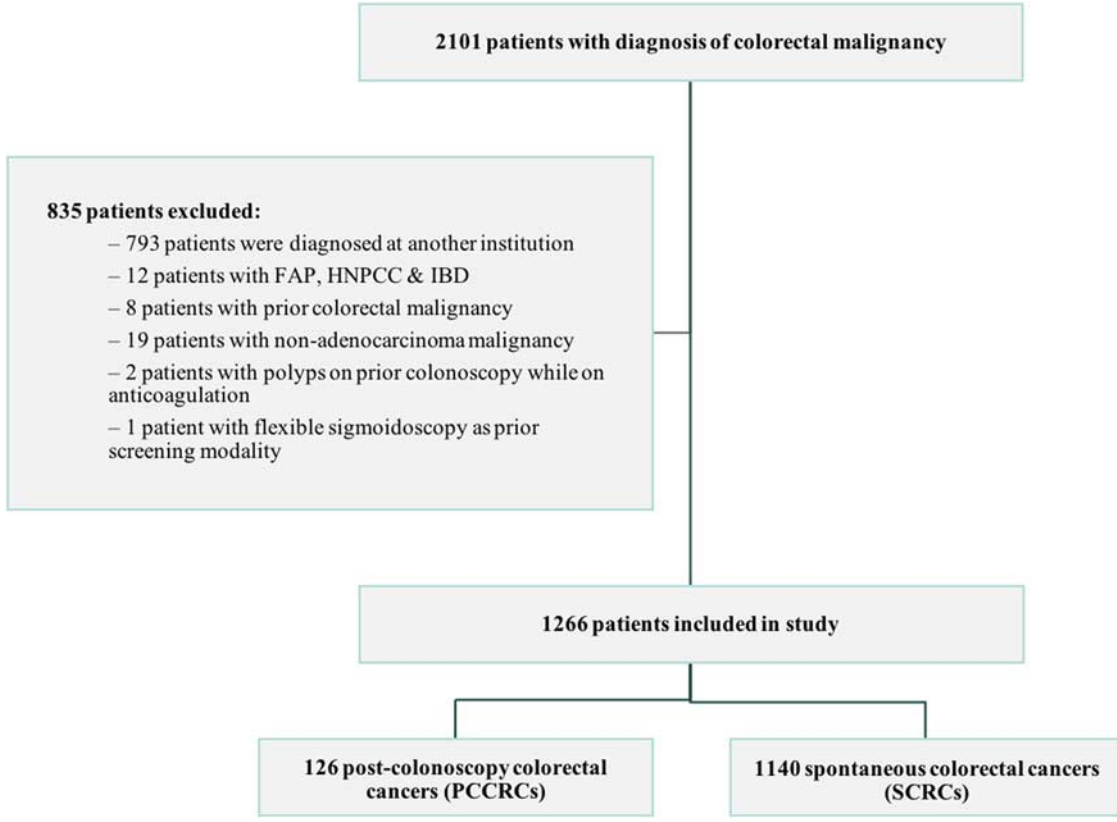

FIGURE 1. Inclusion and exclusion algorithm. FAP indicates familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colrectal cancer; IBD, inflammatory bowel disease; PCCRCs, postcolonoscopy colorectal cancers; SCRCs, spontaneous colorectal cancers.

who had a prior colonoscopy, consisting of all PCCRC cases, and those SCRC cases who had a remote colonoscopy; in that subset we considered the adequacy of bowel preparation, colonoscopy completion, physician specialty, interval between colonoscopies, presence of adenoma (confirmed via review of pathology reports) and the presence of diverticulosis.

We used χ^2 and Fisher exact tests for the univariate analysis and a logistic regression model for the multivariate analysis. We used SAS version 9.4 (Cary, NC) for all analyses. This study was approved by the Institutional Review Board of Columbia University Medical Center.

RESULTS

There were 1,266 patients with colorectal adenocarcinoma who met the inclusion criterion for the analysis (Fig. 1). In total, 122 patients (9.6%) had PCCRC while 1144 (90.4%) had SCRC. The demographic characteristics of patients with PCCRC and SCRC are listed in Table 1. There was no statistically significant difference between the distribution of sex and ethnicity between the PCCRC and SCRC groups. The PCCRC group had an older mean age compared with the SCRC group (72.91 vs. 68.34 y; $P = 0.0006$). In total, 10.6% (n = 121) of SCRC cases were diagnosed in patients younger than 50 years. The proportion of cancers that were PCCRC was lower among black patients compared with white patients (4.86% vs. 11.53%; $P = 0.0187$). This association persisted after adjusting for covariates [odds ratio (OR), 0.45; 95% confidence interval (CI), 0.22-0.95]. Regardless of PCCRC status, black patients were statistically less likely to have ever undergone a prior colonoscopy (OR, 0.52; 95% CI, 0.29-0.92). Similarly, the proportion of PCCRCs was also lower among patients enrolled in Medicaid compared with non-Medicaid patients ($P = 0.025$). However, after adjusting for covariates, this association was no longer statistically significant.

Clinical Characteristics

The clinical characteristics of PCCRC cases and SCRC cases are detailed in Table 2. On multivariable analysis, PCCRC cases were more likely to be early-stage cancers at diagnosis (OR, 2.57; 95% CI, 1.34-4.95). When restricted to PCCRC cases, there was no association between stage at presentation and year of diagnosis ($P = 0.4401$). PCCRC cases were more likely to be located in the proximal colon than in the distal colon (OR, 1.99; 95% CI, 1.20-3.33). The number of PCCRC diagnoses was higher in recent years when compared with base year interval of 2004 to 2007 (OR, 2.78; 95% CI, 1.51-5.09). There was no statistically significant difference in the percentage of cancers with MSI in PCCRC versus SCRC cases; however, MSI testing was not performance in 86% of patients included in the study. Although the presence of diverticulosis was associated with PCCRC status, this was no longer statistically significant on multivariate analysis.

Prior Colonoscopy-related Measures

A median of 5258 colonoscopies were performed yearly at the center (range, 4911 to 5904). Among the subset of patients with CRC who had any prior colonoscopy, the characteristics of prior colonoscopies for PCCRC cases and

TABLE 1. Patient Demographic Characteristics for Postcolonoscopy Colorectal Cancer Cases Versus Spontaneous Colorectal Cancer Cases

	Univariate Analysis			Multivariate Analysis	
Variables	**PCCRC Cases (N = 122) [n (%)]**	**SCRC Cases (N = 1144) [n (%)]**	***P***	**Adjusted Odds Ratio (95% CI) (PCCRC:SCRC)***	***P***
Age (reference: 50, 59) (y)	72.9098	68.3409	**0.0006**	1.021 (1.004-1.037)	0.0131
< 50	1 (0.82)	121 (99.18)	**< 0.0001**	0.163 (0.021-1.291)	0.0857
50-59	11 (5.67)	183 (94.33)		1	
60-69	38 (12.67)	262 (87.33)		2.162 (1.053-4.436)	0.0356
70-79	37 (11.01)	299 (88.99)		1.725 (0.840-3.545)	0.1378
> 80	35 (11.15)	279 (88.85)		1.732 (0.829-3.616)	0.1438
Gender (reference: male)					
Male	58 (9.72)	539 (90.28)	0.9287	1	
Female	64 (9.57)	605 (90.43)		0.986 (0.663-1.468)	0.9463
Race (reference: white)					
White	71 (11.53)	545 (88.47)	**0.0187**	1	
Black	9 (4.86)	176 (95.14)		0.454 (0.217-0.948)	0.0356
Other/unknown	42 (9.03)	423 (90.97)		0.743 (0.420-1.315)	0.3078
Ethnicity (reference: non-Hispanic)					
Non-Hispanic	66 (10.30)	575 (89.70)	0.5766	1	
Hispanic	22 (8.06)	251 (91.94)		0.912 (0.526-1.582)	0.7437
Unknown	34 (9.66)	318 (90.34)		1.150 (0.617-2.142)	0.6593
Insurance (reference: non-Medicaid)					
Non-Medicaid	121 (10.05)	1083 (89.95)	**0.0248**	1	
Medicaid	1 (1.61)	61 (98.39)		0.236 (0.032-1.765)	0.1597

Bold value indicates statistically significant.

*Logistic regression model included the following variables: age, gender, race, ethnicity, insurance, tumor stage, tumor location, diverticulosis, microsatellite instability status, and year of diagnosis.

CI indicates confidence interval; PCCRC, postcolonoscopy colorectal cancer; SCRC, spontaneous colorectal cancer.

TABLE 2. Clinical Characteristics for Postcolonoscopy Colorectal Cancer Cases Versus Spontaneous Colorectal Cancer Cases

	Univariate Analysis			Multivariate Analysis	
Variables	**PCCRC Cases (N = 122) [n (%)]**	**SCRC Cases (N = 1144) [n (%)]**	***P***	**Adjusted Odds Ratio (95% CI) (PCCRC: SCRC)***	***P***
Tumor stage (reference: stage 4)					
Stage 0 and stage 1	52 (14.02)	319 (85.98)	**0.0008**	2.573 (1.338-4.949)	**0.0046**
Stage 2	30 (12.00)	220 (88.00)		2.130 (1.057-4.291)	**0.0343**
Stage 3	17 (6.32)	252 (93.68)		1.144 (0.530-2.466)	0.7320
Stage 4	13 (5.46)	225 (94.54)		1	
Unknown	10 (7.25)	128 (92.75)		1.408 (0.581-3.414)	0.4484
Tumor location (reference: distal colon)					
Proximal colon	79 (13.96)	487 (86.04)	**< 0.0001**	1.999 (1.200-3.328)	**0.0078**
Distal colon	23 (7.08)	302 (92.92)		1	
Rectum and rectosigmoid junction	20 (5.81)	324 (94.19)		0.786 (0.416-1.484)	0.4572
Unknown	0 (0.00)	31 (100.00)			
Diverticulosis (reference: absence)					
Absence	96 (8.76)	1000 (91.24)	**0.0072**	1	
Presence	26 (15.29)	144 (84.71)		1.197 (0.724-1.979)	0.4832
MSI status (reference: APC pathway)					
APC pathway	14 (10.37)	121 (89.63)	0.8714	1	
MSI pathway	4 (10.53)	34 (89.47)		0.748 (0.218-2.563)	0.6441
Unknown	104 (9.52)	989 (90.48)		1.052 (0.554-1.998)	0.8758
Year of diagnosis (reference: 2007, 2004)					
2004-2007	20 (5.70)	331 (94.30)	**0.0195**	1	
2008-2011	39 (10.18)	344 (89.82)		2.345 (1.211-4.543)	**0.0115**
2012-2014	38 (12.67)	262 (87.33)		2.776 (1.514-5.092)	**0.0010**
2015-2017	25 (10.78)	207 (89.22)		1.997 (1.115-3.575)	**0.0200**

Bold value indicates statistically significant.

*Logistic regression model included the following variables: age, gender, race, ethnicity, insurance, tumor stage, tumor location, diverticulosis, MSI status, and year of diagnosis.

APC indicates adenomatous polyposis coli gene; CI, confidence interval; MSI, microsatellite instability; PCCRC, postcolonoscopy colorectal cancer; SCRC, spontaneous colorectal cancer.

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TABLE 3. Characteristics of Prior Colonoscopies in Postcolonoscopy Colorectal Cancer Cases Versus Spontaneous Colorectal Cancer Cases

	Univariate Analysis			Multivariate Analysis	
Variables	**PCCRC Cases (N = 122) [n (%)]**	**SCRC Cases (N = 41) [n (%)]**	***P***	**Adjusted Odds Ratio (95% CI) (PCCRC:SCRC)***	***P***
Interval (y)					
Early interval (≤ 5)	86 (70.49)	3 (7.32)	**< 0.0001**		
Late interval (> 5)	36 (29.51)	37 (92.68)			
Indication (reference: screening)					
Screening	44 (36.07)	12 (29.27)	0.2272	1	
Surveillance	29 (23.77)	7 (17.07)		2.033 (0.532-7.773)	0.2997
Diagnostic	42 (34.43)	20 (48.78)			
Therapeutic	5 (4.10)	0 (0.00)		0.740 (0.266-2.058)	0.5642
Unknown	2 (1.64)	2 (4.88)			
Bowel preparation (reference: adequate)					
Adequate	67 (54.92)	9 (21.95)	**< 0.0001**	1	
Inadequate	18 (14.75)	3 (7.32)		0.435 (0.089-2.133)	0.3047
Unknown	37 (30.33)	29 (70.73)		0.114 (0.040-0.326)	**< 0.0001**
Colonoscopy completion (reference: cecal intubation)					
Cecal intubation	115 (94.26)	40 (97.56)	0.7605	1	
No cecal intubation	6 (4.92)	1 (2.44)		3.412 (0.277-42.03)	0.3381
Unknown	1 (0.82)	0 (0.00)			
Diverticulosis (reference: absence)					
Absence	57 (46.72)	20 (48.78)	0.8193	1	
Presence	65 (53.28)	21 (51.22)		0.818 (0.329-2.035)	0.6654
Physician specialty (reference: gastroenterologist)					
Gastroenterologist	112 (91.80)	36 (87.80)	0.6115	1	
Colorectal surgeon	3 (2.46)	1 (2.44)		0.331 (0.020-5.382)	0.4372
General surgeon	7 (5.74)	4 (36.36)		0.275 (0.045-1.658)	0.1589
Adenoma (reference: absence)					
Presence	49 (40.16)	27 (65.85)	**0.0092**	0.224 (0.087-0.574)	**0.0019**
Absence	73 (59.84)	14 (34.15)		1	
Variables	PCCRC Cases (N = 49)	SCRC Cases (N = 27)	*P*	Odds ratio (95% CI) (PCCRC:SCRC)	*P*
Aspects of prior colonoscopies with adenomas in post colonoscopy colorectal cancer cases versus spontaneous colorectal cancer cases					
Cancer site (reference: different site)					
Same site as adenoma	20 (40.82)	10 (37.04)	0.7470	1.172 (0.446-3.083)	0.7471
Different site from adenoma	29 (59.18)	17 (62.96)		1	

Bold value indicates statistically significant.

*Logistic regression model included the following variables: age, gender, race, ethnicity, indication, bowel preparation, colonoscopy completion, diverticulosis, physician specialty and adenoma.

CI indicates confidence interval; PCCRC, postcolonoscopy colorectal cancer; SCRC, spontaneous colorectal cancer.

SCRC cases are described in Table 3. The majority of PCCRC cases (70%) occurred within 5 years of a prior colonoscopy (Fig. 2). Patients with PCCRCs were less likely to have had an adenoma on prior colonoscopy in comparison with patients with SCRCs who had a remote prior colonoscopy (OR, 0.22; 95% CI, 0.087-0.574). In PCCRC cases with adenomas on prior colonoscopy (N = 49), the majority of the cancers (59.18%) were located at a site different from that of the adenoma. Among PCCRC and SCRC cases, the distributions for screening and surveillance indications for prior colonoscopies were similar. The distribution of colonoscopy completion rates, physician specialty, and diverticulosis rates were similar among PCCRC cases and SCRC cases.

Of all of the PCCRC cases, 31.2% had prior colonoscopies performed by 3 physicians who were performing colonoscopies throughout the entire study period (Table 4). Among all 8 physicians who were active throughout the study period, the proportions of PCCRC cases and SCRC cases were similar ($P = 0.3899$). In total, 59% of PCCRC cases in the study were diagnosed by the same physician who performed the prior colonoscopy. There was a large variability in the proportion of self-diagnosed PCCRC cases among physicians. Notably, 13 of 31 physicians (42%) did not diagnose any of their subsequent PCCRC cases.

DISCUSSION

With the widespread adoption of colonoscopy as a screening tool for CRC, an increase in the occurrence of PCCRCs may be anticipated. This may explain our finding of an increase in the percentage of CRCs that were PCCRCs in recent years (Fig. 3). In total, 5.74% of CRCs in 2005 were PCCRCs, whereas 13.93% were PCCRCs in 2016. A Canadian population-based study found that there was no decline in PCCRC rates between 1996 and 2010.[17] In the United States, where colonoscopy is frequently used as a primary screening modality, it may be anticipated that there would be an increase in proportion of PCCRCs, even as the overall incidence of CRC declines. Understanding the characteristics of PCCRCs will be helpful in identifying risk factors for

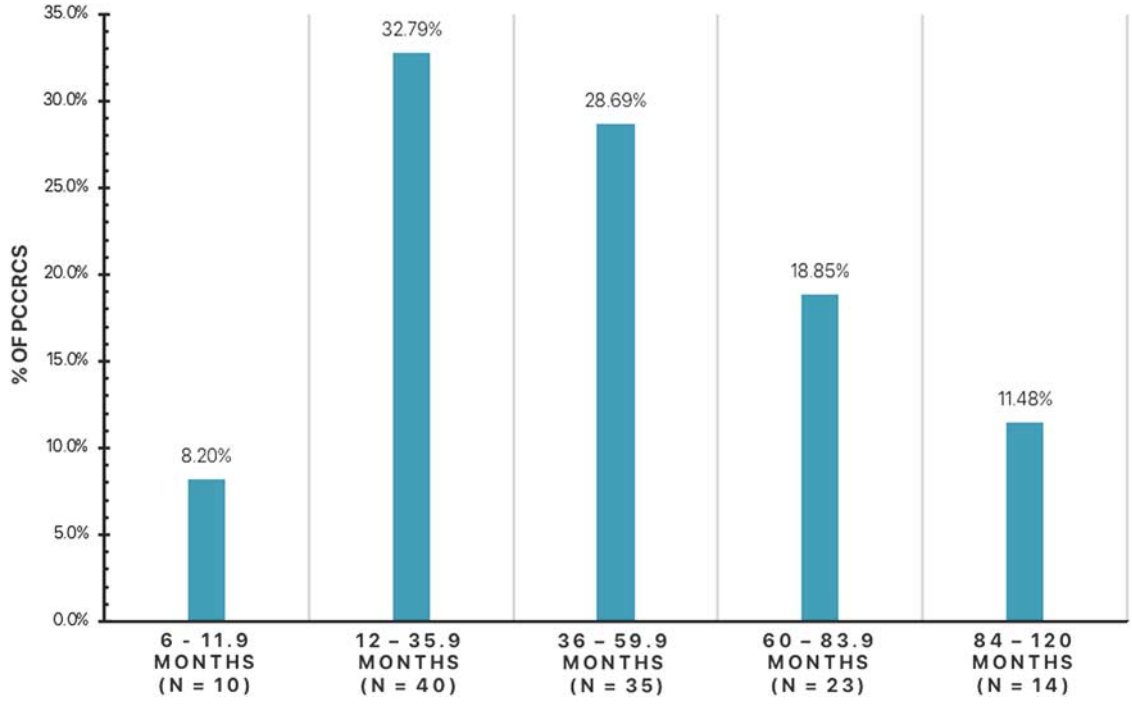

FIGURE 2. Colonoscopy interval before PCCRC diagnosis (months). PCCRC indicates postcolonoscopy colorectal cancer.

PCCRCs, devising quality improvement strategies, and ultimately, curbing the rising incidence of PCCRCs.

We found that older patients had higher odds of having a PCCRC. This result is corroborated by several studies in the literature that have found an association between advanced age and risk of PCCRC.[7,13,15,18–21] Proposed explanations for the positive association between age and PCCRC risk include an increased likelihood of morbidities such as diverticulosis which could impair colonoscopy visualization.[7] However, in this study, neither diverticulosis on prior colonoscopy nor diverticulosis on the colonoscopy that diagnosed the cancer were predictors of PCCRC risk.

Most screening guidelines recommend that CRC screening begin at age 50.[8,22] We found nearly 10% of CRC cases included in this study occurred in patients younger than 50 (age range, 22 to 49). All but one of the CRC cases diagnosed in this subpopulation were spontaneous (the PCCRC case was in a patient who was undergoing colonoscopy before 50 years of age due to a family history of CRC). Approximately 53% of these patients presented with advanced disease (ie, stage 3 or 4). The increase in CRC incidence among patients younger than 50 has also been recently reported in the literature.[23–25] Our findings suggest that even if PCCRCs were effectively prevented, 10% of CRCs would still develop in the presence of current screening guidelines.

TABLE 4. Proportion of Postcolonoscopy Colorectal Cancer Cases For Long-term Providers*

Provider	PCCRC Cases	SCRC Cases	Total CRC Cases	PCCRC Proportion	*P*
A	11	3	14	0.79	0.3899
B	15	6	21	0.71	
C	12	4	16	0.75	
D	7	2	9	0.78	
E	2	2	4	0.50	
F	6	4	10	0.60	
G	7	2	9	0.78	
H	1	4	5	0.20	
I	1	1	2	0.50	

*A long-term provider is defined as a provider who performed colonoscopies throughout the entire study period, that is, from September 2004 and March 2017.

CRC indicates colorectal cancer; PCCRC, postcolonoscopy colorectal cancer; SCRC, spontaneous colorectal cancer.

A large population-based cohort study of Medicare beneficiaries found that the risk of PCCRCs was significantly elevated in black patients when compared with white patients.[12] In addition, it was previously reported that black patients were more likely to have their prior colonoscopies performed by physicians with lower polyp detection rates, which contributed to increased PCCRC risk.[12] Surprisingly, in this study, we found that black patients had a lower risk of developing PCCRCs than white patients (OR, 0.45; 95% CI, 0.22-0.95). However, black patients in this study were significantly less likely to ever have a prior screening colonoscopy compared with white patients (OR, 0.52; 95% CI, 0.29-0.92). A possible explanation is a disparity in access to colonoscopy screening for black populations. Studies have shown that black patients are more likely to receive health care in underresourced settings.[12,26,27] Similarly, Medicaid patients were less likely than non-Medicaid patients to develop a PCCRC; however, this association did not persist after controlling for covariates.

We found that PCCRCs were more likely than SCRCs to be early stage at diagnosis ($P = 0.0008$). PCCRCs were also more likely to be located in the proximal colon compared with the distal colon (OR, 1.99; 95% CI, 1.20-3.33). This finding has been well documented in the literature.[7,11,14,19] Various explanations have been proposed for why PCCRCs are more

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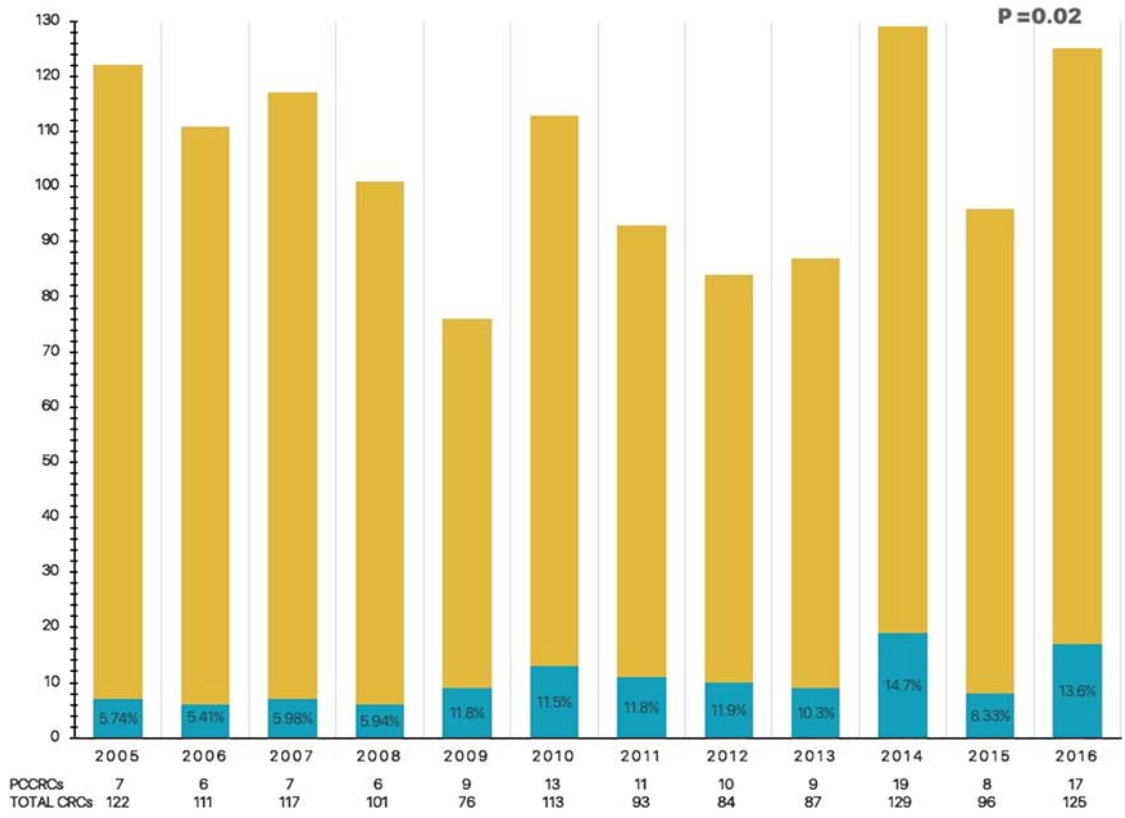

FIGURE 3. Colorectal cancer cases by year. PCCRC indicates postcolonoscopy colorectal cancer.

likely to be located in the proximal colon. Some studies show that CRCs in the proximal colon are more likely to demonstrate MSI.[9,10] However, data on the association between MSI and the risk of PCCRC are conflicting.[9,28,29] In this study, 79% of cancers with MSI were located in the proximal colon, and we found no association between MSI and PCCRC risk. Of note, 86% of patients in our study did not have MSI testing performed, making our results difficult to interpret. Another explanation for proximally located PCCRCs is the finding that proximally located neoplasms are smaller, flatter and therefore, easier to miss.[13,30]

We found that 70% of PCCRCs were diagnosed within 5 years of a prior colonoscopy. These data imply that the practice of shortening a recommendation of 10 years to 5 years after a normal screening colonoscopy in an average-risk individual would not be effective at preventing most PCCRCs. Proposed mechanisms underlying the development of PCCRCs include missed lesions, inadequate adenoma resection, failed biopsy, and new rapidly growing neoplasms.[7,13] In this study, we found that patients with PCCRCs were significantly less likely than patients with SCRCs to have an adenoma identified on a prior colonoscopy (OR, 0.22; 95% CI, 0.09-0.57). In addition, among PCCRCs, ~60% of the adenomas detected on the prior colonoscopy were located in a site different from the location of the eventual cancer. This finding favors a missed lesion as the most common etiology of PCCRCs. In a pooled multicohort study, missed lesions were found to be responsible for 52% of PCCRCs.[13] The notion that most PCCRCs are missed lesions is supported by 2 large studies that found that adenoma detection rate has been found to be an independent predictor of PCCRC risk.[15,16] Although 31% of all PCCRCs were limited to 3 long-term physicians who were active throughout the study period, the ratio of PCCRCs to SCRCs was similar among all 8 long-term physicians ($P = 0.3899$). This suggests that clustering is related not to physician effects, but rather, the fact that these physicians had performed more colonoscopies.

Strengths of this study include its long follow-up time and the availability of records for confirmation of adenomas, diverticulosis, and other clinical details. This study also has a number of limitations. Patients may have received prior colonoscopies from other health facilities, resulting in misclassification of PCCRC status. Data for this study were obtained from the electronic medical record, which was incomplete for certain variables such as bowel preparation, serrated adenomas, adenoma resection methods, and particularly for MSI; molecular characteristics of CRCs have been shown to be associated with PCCRCs.[4,9,10,21,31–34] The paucity of prior remote colonoscopies for SCRCs limited our analysis of technical factors associated with PCCRC risk.

In conclusion, we found that PCCRC rates are rising in recent years, likely reflecting the widespread adoption of colonoscopy as a primary screening tool, and are more common in older patients and those with proximal, early-stage tumors. Our results corroborate the findings that PCCRCs are more likely to be early stage and located in the proximal colon. The finding that a large proportion of PCCRCs are diagnosed by a different physician raises the concern that physicians are unaware of their own patients' PCCRCs. Developing a systematized nonjudgmental PCCRC notification system would be helpful in measuring PCCRC rates and improving

colonoscopy quality. Optimizing colonoscopy quality is an important tool for reducing PCCRC burden, especially as our study demonstrates an increasing proportion of PCCRCs in recent years.

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