Gastro Hep Advances 2022;1:277–286

ORIGINAL RESEARCH—CLINICAL

Patient and Endoscopic Characteristics of Postcolonoscopy Colon Cancer—A Case-control Study

Sonja P. Dawsey,[1] Pamela M. Vacek,[2] and Eric K. Ganguly[1]

[1]Division of Gastroenterology and Hepatology, University of Vermont Medical Center, Burlington, Vermont, and [2]Department of Medical Biostatistics, University of Vermont, Burlington, Vermont

BACKGROUND AND AIMS: Colonoscopy is imperfect for colorectal cancer (CRC) prevention. Postcolonoscopy CRC (PCCRC) is defined as CRC detected after a screening or surveillance colonoscopy. PCCRCs can be divided into noninterval CRC and interval CRC. We performed a case-control study to identify risk factors for PCCRCs and to compare risks between noninterval and interval PCCRCs. **METHODS:** We designed a retrospective case-control study. Using a Vermont tumor registry data set, we identified all PCCRCs diagnosed at our medical center from January 2012 to September 2017. Cases were matched 1:3 with controls of the same age, sex, and index colonoscopy date. **RESULTS:** Fifty-four PCCRCs were matched with 162 controls and divided into noninterval (N = 27) and interval (N = 27) subsets. Overall PCCRC risk and noninterval PCCRC risk were significantly associated with history of polyps (odds ratio [OR] PCCRC = 2.71, OR noninterval = 4.41), sessile serrated polyps (OR PCCRC = 3.94, OR noninterval = 5.79), and high-risk adenoma (HRA) (OR PCCRC = 6.58, OR noninterval = 16.46) and with the index colonoscopy having a large polyp (OR PCCRC = 4.45, OR noninterval = 10.46) or having an HRA (OR PCCRC = 3.68, OR noninterval = 8.04). PCCRC risk and interval PCCRC risk were significantly associated with follow-up recommendations that did not correlate with American Gastroenterological Association surveillance guidelines (OR PCCRC = 3.30, OR interval = 4.85). Approximately 30% of PCCRCs could be attributed to endoscopic quality. **CONCLUSION:** Overall PCCRC risk and noninterval PCCRC risk were significantly associated with traditional CRC risk factors including precancerous polyps and HRA on the index colonoscopy. Interval PCCRC was not associated with these risk factors. Many PCCRCs can be attributed to endoscopic quality, and nonadherence to CRC surveillance guidelines may be a novel risk factor.

Keywords: Interval Cancer; Postcolonoscopy Colorectal Cancer; Colorectal Cancer Risk; Colonoscopy

Introduction

Colorectal cancer (CRC), the second leading cause of cancer death in the United States,[1] can be prevented by detection and removal of precancerous lesions by colonoscopy.[2,3] Colonoscopy is considered the "gold standard" for the removal of early-stage neoplasia, and cancer prevention through screening and surveillance, however, is imperfect. Postcolonoscopy CRC (PCCRC) is defined as CRC detected after a screening or surveillance colonoscopy in which no cancer is found[4] and incidence estimates of PCCRC range from 2.9% to 9%.[5–10] In 2018, the World Endoscopy Organization (WEO) published a consensus statement on PCCRC, standardizing the definition as a CRC developing within 10 years of a colonoscopy. The WEO further divided PCRRCs into noninterval CRC and interval CRC. Noninterval CRC is defined as PCCRC identified at or after the recommended screening or surveillance period, up to 10 years after the baseline, or "index", colonoscopy. Interval CRC is defined as PCCRC diagnosed before the next recommended screening or surveillance examination.[11] Examples of these subsets of PCCRC are shown in Figure 1. Understanding the cause for PCCRC is important for its prevention. Common broad explanations for PCCRC include missed or incompletely resected lesions at the time of colonoscopy, incomplete colonoscopy examination, and alternate or more aggressive biology. Causes related to colonoscopy quality are potentially modifiable. Colonoscopy quality measures and endoscopic-related factors such as missed or incompletely removed lesions have been linked to PCCRC.[5,7,12–14] The adenoma detection rate (ADR), a quality metric reflecting the percentage of an endoscopist's screening colonoscopies in which an adenoma is detected, has been inversely correlated with both PCCRC and mortality from PCCRC.[15–17] The other, nonmodifiable risk factors for PCCRC that have been suggested include female sex,[18,19] older patients,[5,14,19–21] prior diverticular disease,[5,9,19,20,22] higher comorbidity score,[5,9,19,20] family history of CRC,[13,20] proximal location of polyps (defined as polyps in the cecum, ascending colon, hepatic flexure, or transverse colon),[5,9,13,14,18,20] and larger polyps (≥10 mm).[9] PCCRC has also been linked to tumor biology.[8,23–25]

Abbreviations used in this paper: **ADR, adenoma detection rate; CI, confidence interval; CRC, colorectal cancer; FDR, first-degree relative; HP, hyperplastic polyp; HRA, high-risk adenoma; MMR, mismatch repair; OR, odds ratio; PCCRC, postcolonoscopy CRC; SSP, sessile serrated poly; TA, tubular adenoma; UVMMC, University of Vermont Medical Center; WEO, World Endoscopy Organization.**

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2772-5723
https://doi.org/10.1016/j.gastha.2022.01.001

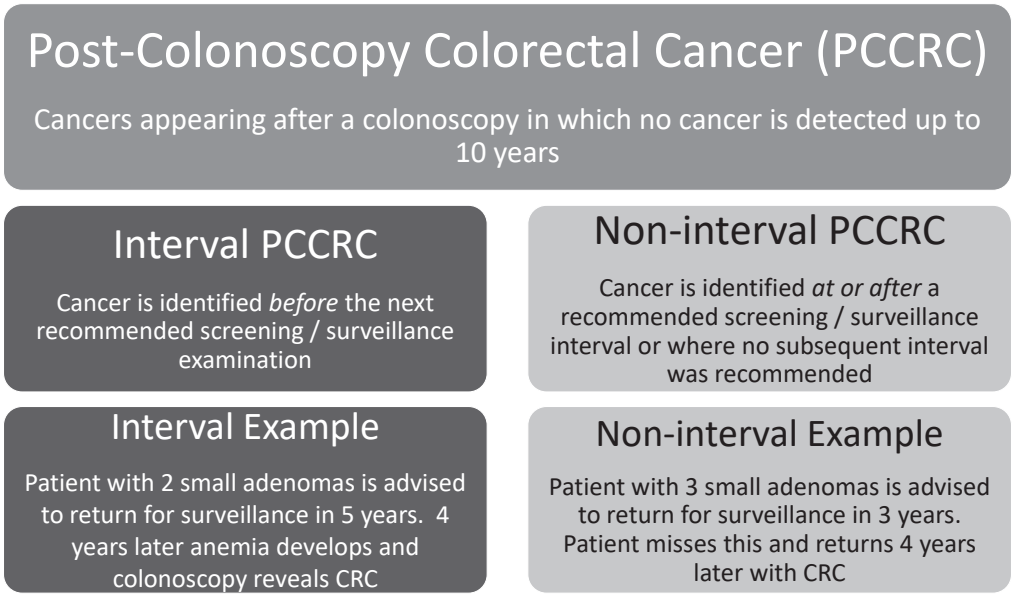

Figure 1. Definitions of PCCRC and its subdivisions of interval PCCRC and noninterval PCCRC with examples of each.

The degree of influence that these factors have on the development of different PCCRC types remains to be determined. To address this, we performed a study to confirm previously known or identify new risk factors for PCCRCs and to identify differences between noninterval and interval PCCRCs using the WEO classifications—to our knowledge, this has not been previously performed. The WEO also proposed an algorithm to standardize the possible explanations for PCCRC (Figure 2),[11] and we categorized our cases into plausible PCCRC explanations as per this algorithm.

Methods

Study Setting and Design

We designed a retrospective case-control study. Using a Vermont tumor registry data set, we identified all CRCs diagnosed at the University of Vermont Medical Center (UVMMC) from January 2012 to September 2017, and data were extracted from the UVMMC electronic medical record. This study was approved by the UVMMC institutional review board.

Case and Control Identification

Patients with PCCRCs were included if they were ≥18 years of age who had a prior colonoscopy within 10 years in which no cancer was identified. The most recent prior colonoscopy was considered the "index" colonoscopy. Exclusion criteria for PCCRCs included patients with prior CRC, history of inflammatory bowel disease, index colonoscopy performed elsewhere, known inadequate or incomplete polyp resection, or history of hereditary CRC syndromes. Controls were identified from a cohort of colonoscopies performed at the UVMMC from 2003 to 2017. The controls never had CRC, had colonoscopies performed for screening purposes, and were still followed at the UVMMC at the time they were identified (3/2019). For each case, 3 controls of the same age and sex with colonoscopy dates closest to the index colonoscopy of the case were selected.

Variables

Historical factors collected included known first-degree relative (FDR) with CRC, history of cancer other than CRC (non-CRC), history of tobacco or alcohol use, and history of polyps on a prior colonoscopy whether it be during the index colonoscopy or otherwise. For patients with a history of prior polyps, additional variables were included about these polyps such as if they were hyperplastic polyps (HPs) only, sessile serrated polyps (SSPs), or high-risk adenomas (HRAs) defined as ≥10 mm, villous histology, or high-grade dysplasia.

Index colonoscopy variables included whether a gastroenterologist performed the colonoscopy, bowel preparation, whether a polyp was found, number of polyps found (0, 1, 2, 3+), location of polyp(s) (distal, proximal, or both distal and proximal), largest polyp size category (<5 mm, 5–10 mm, ≥10 mm, or not reported), polyp histology (HP or other histology), whether the polyp was an HRA, and detailed polyp histology (tubular adenoma [TA], HP, SSP, TA + SSP, TA + HP, or other histology). We also examined the concordance of the endoscopist-recommended surveillance timeline with those of the published American Gastroenterological Association (AGA) guidelines' (2012) interval recommendations after colonoscopy.[26]

WEO Definitions and Subgroups: Noninterval and Interval PCCRC

We subdivided PCCRCs as per the WEO's consensus statement definitions into noninterval or interval PCCRCs.[11] Definitions and examples can be seen in Figure 1.

Statistical Analysis

Conditional logistic regression comparing each PCCRC case with its matched controls was used to assess associations of patient history variables and findings on the index colonoscopy with PCCRC risk while controlling for patient sex, age, and time of index colonoscopy. Differences in the characteristics of noninterval and interval PCCRCs were assessed by chi-square tests.

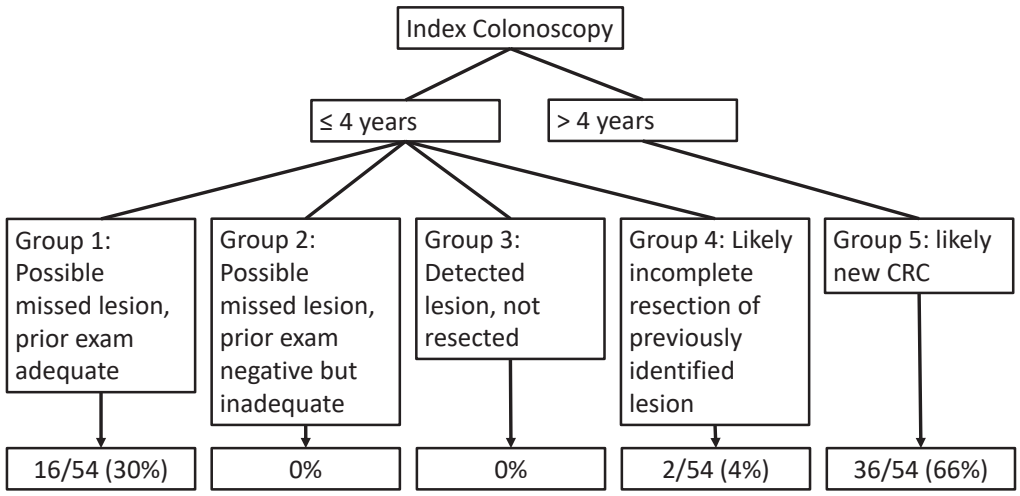

Figure 2. Plausible PCCRC etiologies as per the World Endoscopy Organization's algorithm.

Results

Patient Characteristics and Associations With PCCRC

Patient characteristics and colonoscopy findings of PCCRCs (N = 54) and controls (N = 162) are shown in Tables 1–3. The average age at PCCRC diagnosis was 69 years old (range 46–89 years), and the 54% were male. Table 4 shows association with the overall risk of PCCRC, noninterval PCCRC risk, and interval PCCRC risk. Two broad features distinguished the overall PCCRC risk: (a) a history of polyps before index colonoscopy and (b) polyp characteristics at the time of index colonoscopy. The risk of PCCRC was significantly associated with a history of polyps (odds ratio [OR] = 2.71, confidence interval [CI] = 1.30–5.66), a history of non-HPs (OR = 2.97, CI = 1.37–6.46), a history of SSPs (OR = 3.94, CI = 1.40–11.07), and a history of HRA (OR = 6.58, CI = 2.76–15.74). Having 2 polyps (OR = 2.67, CI = 1.13–6.33), a polyp ≥10 mm (OR = 4.45, CI = 1.47–13.45), and an HRA (OR = 3.68, CI = 1.50–8.99) on the index colonoscopy was also associated with the risk of PCCCR (Table 4). By contrast, known FDR with CRC, personal history of non-CRC, bowel preparation, distal location of polyp, physician performing the procedure, and tobacco and alcohol use were not significantly related to overall PCCRC risk, noninterval PCCRC risk, or interval PCCRC risk. Although these overall findings raise the possibility that PCCRC emergence is influenced by polyp biology, it is possible that the profiles of noninterval and interval PCCRCs would be distinct. We therefore sought to examine the characteristics of PCCRCs as per the subtype.

Associations With Noninterval PCCRC

A history of polyps (OR = 9.23, CI = 2.07–41.12), a history of non-HPs (OR = 17.60, CI = 2.96–104.69), a history of SSPs (OR = 5.79, CI = 1.09–30.83), and a history of an HRA (OR = 16.46, CI = 3.72–72.85) were all associated with a significantly increased risk of noninterval PCCRC (Table 4). Having 1 or more polyps found on the index colonoscopy was significantly associated with noninterval PCCRC risk (OR = 4.59, CI = 1.60–13.15), and the risk increased with the number of polyps (1: OR = 3.93, CI = 1.26–12.26; 2: OR = 5.45, CI = 1.27–23.46; 3 or more: OR = 8.46, CI = 1.65–43.30). Increased risk was also significantly associated with having a proximately located polyp (OR = 6.87, CI = 1.72–27.55), a polyp ≥10 mm (OR = 10.46, CI = 2.10–52.12), a non-HP (OR = 8.84, CI = 2.33–33.58), a TA (OR = 7.86, CI = 2.23–27.75), and an HRA (OR = 8.04, CI = 2.19–29.48) on the index colonoscopy. In summary, risk for noninterval PCCRC was increased in patients with a history of polyps and an index colonoscopy with polyps including proximal, large, or HRAs, which are known risk factors for developing CRC.

Associations With Interval PCCRC

In contrast, the risk of interval PCCRC was not significantly related to any of the previously described polyp history or index colonoscopy factors (Table 4). These findings raise the possibility that something other than polyp biology influences interval PCCRC development.

Noninterval Compared With Interval PCCRC Cases

Comparison of noninterval and interval PCCRC cases is shown in Table 5. In comparison with interval PCCRCs, noninterval PCCRCs more commonly had a history of polyps (93% noninterval vs 63% interval, $P = .009$), a history of non-HPs (85% noninterval vs 41% interval, $P = .003$), a history of an HRA (59% noninterval vs 22% interval, $P = .006$), a polyp on index colonoscopy (78% noninterval vs 52% interval, $P = .046$), a proximal polyp on index colonoscopy (48% noninterval vs 14% interval, $P = .039$), a non-HP on index colonoscopy (90% noninterval vs 57% interval, $P = .021$), an HRA at index colonoscopy (41% noninterval vs 11% interval, $P = .013$). These findings are consistent with the concept that polyp biology adversely affects the impact of delayed colonoscopy with respect to the emergence of PCCRC. This does not exclude the possibility of the

Table 1. Patient Characteristics

Patient characteristics	Cases (N = 54) N (%)	Controls (N = 162) N (%)	Total (N = 216) N (%)	OR (95% CI)
Age				
45–59	21 (38.9)	63 (38.9)	84 (38.9)	
60–69	14 (25.9)	42 (25.9)	56 (25.9)	
≥70	19 (35.2)	57 (35.2)	76 (35.2)	
Sex				
Male	29 (53.7)	87 (53.7)	116 (53.7)	
Female	25 (46.3)	75 (46.3)	100 (46.3)	
Known FDR with CRC				
No	41 (75.9)	125 (77.6)	166 (77.2)	
Yes	13 (24.1)	36 (22.4)	49 (22.8)	1.12 (0.53–2.34)
History of other cancer (non-CRC)				
No	35 (64.8)	110 (67.9)	145 (67.1)	
Yes	19 (35.2)	52 (32.1)	71 (32.9)	1.17 (0.58–2.36)
GI physician doing colonoscopy				
No	7 (13.0)	14 (8.6)	21 (9.7)	
Yes	47 (87.0)	148 (91.4)	195 (90.3)	0.63 (0.24–1.67)
Endoscopist's recommendations agree with AGA guidelines				
No	24 (44.4)	28 (18.7)	52 (25.5)	**3.30 (1.63–6.67)**
Yes	30 (55.6)	122 (81.3)	152 (75.5)	
History of tobacco use				
Never	26 (48.1)	88 (54.3)	114 (52.8)	
Current	4 (7.4)	13 (8.0)	17 (7.9)	1.05 (0.30–3.70)
Former	24 (44.4)	61 (37.7)	85 (39.4)	1.33 (0.70–2.55)
History of alcohol use				
Never	19 (35.2)	48 (29.6)	67 (31.0)	
Current	33 (61.1)	105 (64.8)	138 (63.9)	0.78 (0.39–1.54)
Former	2 (3.7)	9 (5.6)	11 (5.1)	0.55 (0.11–2.83)
Alcoholic drinks/wk				
None/rarely	22 (43.1)	72 (46.5)	94 (45.6)	
≤1	10 (19.6)	24 (15.5)	34 (16.5)	1.29 (0.55–3.06)
2–6	8 (15.7)	26 (16.8)	34 (16.5)	0.98 (0.35–2.74)
7–14	10 (19.6)	26 (16.8)	36 (17.5)	1.10 (0.47–2.60)
>14	1 (2.0)	7 (4.5)	8 (3.9)	0.46 (0.05–3.98)
Ever history of polyps				
No	13 (24.1)	73 (45.1)	86 (39.8)	
Yes	41 (75.9)	89 (54.9)	130 (60.2)	**2.71 (1.30–5.66)**
Ever history of hyperplastic polyps				
No polyps	12 (22.2)	68 (42.0)	80 (37.0)	
Hyperplastic polyps only	8 (14.8)	26 (16.1)	34 (14.8)	1.79 (0.65–4.91)
Other histology	34 (70.0)	68 (42.0)	102 (47.2)	**2.97 (1.37–6.46)**
Ever history of SSP				
No	44 (81.5)	152 (98.3)	196 (90.7)	
Yes	10 (18.5)	10 (6.2)	20 (9.3)	**3.94 (1.40–11.07)**
Ever history of HRA				
No	32 (59.3)	143 (88.3)	175 (81.0)	
Yes	22 (40.7)	19 (11.7)	31 (19.0)	**6.58 (2.76–15.74)**

Bold entries indicate statistically significant results.

involvement of endoscopist-related factors, such as adherence to surveillance guidelines, which is described in the following.

Adherence to Guidelines

Table 6 shows the AGA guideline recommendation that should have been given for both noninterval and interval PCCRCs. Twenty-four of 54 (44%) patients with PCCRCs and 30 of 162 (18.5%) controls had recommendations from endoscopists that deviated from AGA guideline recommendations. Table 7 shows the types of discordant recommendations given. In noninterval PCCRCs, 73% of the incorrect recommendations were too long, for example, the endoscopist recommended follow-up in 5 years, but AGA guidelines (2012) recommend 3 years. For interval PCCRCs and controls, 54% and 60%, respectively, of the discordant recommendations were too

Table 2. Index Colonoscopy Characteristics

Index colonoscopy characteristics	Cases (N = 54) N (%)	Controls (N = 162) N (%)	Total (N = 216) N (%)	OR (95% CI)
Prep				
Excellent	4 (7.4)	12 (7.4)	16 (7.4)	
Good	43 (79.6)	136 (84.0)	179 (82.9)	0.91 (0.26–3.18)
Fair	4 (7.4)	10 (6.2)	14 (6.5)	1.16 (0.22–6.18)
Adequate/poor	3 (5.6)	4 (2.5)	7 (3.3)	2.10 (0.34–13.17)
Polyp found				
No	19 (35.2)	79 (48.8)	98 (45.4)	
Yes	35 (64.8)	83 (51.9)	118 (54.6)	1.80 (0.94–3.45)
Number of polyps				
0	19 (35.2)	79 (4.8)	98 (45.4)	
1	14 (25.9)	47 (29.0)	61 (28.2)	1.24 (0.56–2.75)
2	13 (24.1)	21 (13.0)	34 (15.7)	**2.67 (1.13–6.33)**
3 or more	8 (14.8)	15 (9.3)	23 (10.6)	2.52 (0.87–7.30)
Location of polyp(s)				
No polyp	19 (35.2)	74 (48.8)	93 (45.4)	
Proximal	12 (22.2)	32 (19.8)	44 (20.4)	1.58 (0.67–3.74)
Distal	10 (18.5)	31 (19.1)	41 (19.0)	1.35 (0.55–3.34)
Both proximal and distal	13 (24.1)	20 (12.3)	33 (15.3)	**2.89 (1.15–7.22)**
Largest polyp size category				
No polyp	19 (35.2)	79 (48.8)	98 (45.5)	
<5 mm	12 (22.2)	32 (19.8)	44 (20.4)	1.57 (0.67–3.66)
5–10 mm	6 (11.1)	21 (13.0)	27 (12.5)	1.22 (0.40–3.77)
≥10 mm	8 (14.8)	7 (4.3)	15 (6.9)	**4.45 (1.47–13.45)**
Not reported	9 (16.7)	23 (14.2)	32 (14.8)	1.68 (0.70–4.06)
Polyp histology				
No polyp	19 (35.2)	79 (48.8)	98 (45.4)	
Hyperplastic polyp	8 (14.8)	23 (14.2)	31 (14.3)	1.44 (0.57–3.65)
Other histology	27 (50.0)	60 (37.0)	86 (40.3)	1.96 (0.97–3.97)
HRA				
No	40 (74.1)	146 (90.1)	186 (86.1)	
Yes	14 (25.9)	16 (9.9)	30 (13.9)	**3.68 (1.50–8.99)**

Bold entries indicate statistically significant results.

short, for example, the endoscopist recommended a repeat examination in 5 years, but the AGA guidelines (2012) recommend 10 years. Incorrect guideline recommendations were associated with overall PCCRC risk (OR = 3.30, CI = 1.63–6.67) and interval PCCRC risk (OR = 4.85, CI = 1.67–14.08), but not noninterval PCCRC risk (Table 4). These findings suggest that endoscopist nonadherence to surveillance guidelines may be a risk factor for interval PCCRC development.

WEO Criteria and Our Cohort

We categorized our PCCRCs as per the WEO's criteria into groups 1–5 as shown in Figure 2. Groups 1–4 were

Table 3. Index Colonoscopy Polyp Characteristics

Index colonoscopy polyp characteristics	Cases (N = 54) N (%)	Controls (N = 162) N (%)	Total (N = 216) N (%)	OR (95% CI)
Polyp found				
No	19 (35.2)	79 (48.8)	98 (45.4)	
Yes	35 (64.8)	83 (51.9)	118 (54.6)	1.80 (0.94–3.45)
Detailed polyp histology				
No polyp	19 (35.2)	79 (48.8)	98 (45.4)	
TA	15 (27.8)	40 (24.7)	55 (25.5)	1.61 (0.73–3.57)
Hyperplastic only	8 (14.8)	23 (14.2)	31 (14.4)	1.45 (0.57–3.70)
SSP	3 (5.6)	3 (1.9)	6 (2.8)	4.29 (0.80–23.12)
TA + SSP	1 (1.9)	3 (1.9)	4 (1.9)	1.71 (0.16–18.04)
TA + HP/other	8 (14.8)	14 (8.7)	22 (10.2)	3.60 (0.17–11.06)

Table 4. Associations With Risk of Postcolonoscopy CRC, Noninterval PCCRC, and Interval PCCRC

Variable	PCCRC (N = 54) OR (95% CI)	Noninterval PCCRC (N = 27) OR (95% CI)	Interval PCCRC (N = 27) OR (95% CI)
General variable			
Known FDR with CRC	1.12 (0.53–2.34)	1.65 (0.62–4.35)	0.63 (0.18–2.18)
History of non-CRC cancer	1.17 (0.58–2.36)	0.73 (0.29–1.80)	2.39 (0.79–7.24)
GI physician doing colonoscopy	0.63 (0.24–1.67)	0.47 (0.12–1.78)	0.87 (0.21–3.63)
Recommendation **not** consistent with AGA guidelines	**3.30 (1.63–6.67)**	0.42 (0.16–1.10)	**4.85 (1.67–14.08)**
Prior polyp history			
Ever history of polyps	**2.71 (1.30–5.66)**	**9.23 (2.07–41.12)**	1.12 (0.44–2.84)
Ever history of hyperplastic only	1.79 (0.65–4.91)	3.00 (0.42–21.67)	1.32 (0.37–4.64)
Ever history of other histology	**2.97 (1.37–6.46)**	**17.6 (2.96–104.69)**	1.05 (0.39–2.84)
Ever history of SSP	**3.94 (1.40–11.07)**	**5.79 (1.09–30.83)**	3.00 (0.78–11.51)
Ever history of HRA	**6.58 (2.76–15.74)**	**16.46 (3.72–72.85)**	2.55 (0.74–8.83)
Index colonoscopy variable			
Yes polyp found	1.80 (0.94–3.45)	**4.59 (1.60–13.15)**	0.82 (0.35–1.95)
1 polyp	1.24 (0.56–2.75)	**3.93 (1.26–12.26)**	0.31 (0.09–1.12)
2 polyps	**2.67 (1.13–6.33)**	**5.45 (1.27–23.46)**	2.04 (0.69–6.04)
3 + polyps	2.52 (0.87–7.30)	**8.46 (1.65–43.30)**	0.70 (0.14–3.52)
Proximal location only	1.58 (0.67–3.74)	**6.87 (1.72–27.55)**	0.31 (0.06–1.55)
Both proximal and distal locations	**2.89 (1.15–7.22)**	**10.01 (2.13–46.92)**	1.15 (0.33–4.00)
Polyp size: <5 mm	1.57 (0.67–3.66)	**4.39 (1.25–15.41)**	0.58 (0.16–2.09)
Polyp size: 5–10 mm	1.22 (0.40–3.77)	3.86 (0.66–22.69)	0.55 (0.12–2.46)
Polyp size: ≥10 mm	**4.45 (1.47–13.45)**	**10.46 (2.10–52.12)**	2.60 (0.50–13.62)
Hyperplastic histology only	1.44 (0.57–3.65)	1.45 (0.27–7.68)	1.26 (0.39–3.99)
Other histology (nonhyperplastic)	1.96 (0.97–3.97)	**8.84 (2.33–33.58)**	0.65 (0.24–1.78)
TA (only or with others)	1.99 (0.97–4.08)	**7.86 (2.23–27.75)**	0.66 (0.24–1.85)
SSP (only or with others)	3.12 (0.72–13.61)	9.88 (0.76–127.50)	1.38 (0.20–9.35)
HRA	**3.68 (1.50–8.99)**	**8.04 (2.19–29.48)**	1.16 (0.26–5.09)

Bold entries indicate statistically significant results.

defined as cases in which the index colonoscopy was ≤4 years before diagnosis. Group 5 was defined as cases in which the index colonoscopy was >4 years before diagnosis.[11] Sixteen of 54 (30%) of our PCCRCs were in group 1, described as a possible missed lesion, prior examination adequate. There were none in group 2, described as a possible missed lesion, prior examination negative but inadequate. There were also none in group 3, described as a detected lesion, not resected (however, known incompletely resected lesions were excluded in this study). Two of 54 (4%) were in group 4, described as likely incomplete resection of a previously identified lesion. Thirty-six of 54 (66%) were in group 5, described as a likely new CRC. Groups 1 and 5 were differentiated by the time of CRC detection (≤4 years for group 1 and >4 years for group 5) as described previously by the WEO.

Discussion

PCCRC, defined as CRC detected after a screening or surveillance colonoscopy in which no cancer is found,[4] has an estimated incidence of 2.9%–9%.[5–10] PCCRC has been associated broadly with missed or incompletely resected lesions at the time of colonoscopy, incomplete colonoscopy examination, or alternate/more aggressive biology. In this retrospective case-controlled study, traditional risk factors for CRC such as a history of polyps (history of any polyp, non-HP histology, SSP, HRA) and an index colonoscopy with HRAs were significantly associated with PCCRC risk. Our findings are consistent with previous studies that have implicated traditional CRC risk factors with PCCRC.[9,10,20] In a recent, large community-based study conducted in California, PCCRC was associated with colonic polyps ≥10 mm, incomplete examination, and history of any adenoma.[9] Incomplete resection of polyps in general, and large polyps (≥10 mm) in particular, which are more likely to be incompletely resected, has been implicated in PCCRC. Our data add to this growing evidence.[5,7,12,13,15,16,19] Known FDR with CRC, personal history of non-CRC, distal location of a polyp, and tobacco and alcohol use were not significantly associated with PCCRC risk. Although these risk factors are associated with developing CRC, they do not appear to be associated with PCCRC, possibly due to power of study.

To our knowledge, this is the first study to investigate PCCRCs based on the WEO definitions of noninterval and interval PCCRCs. Risk factors for interval PCCRCs and noninterval PCCRCs differed substantially. Noninterval PCCRCs were significantly associated with "traditional" CRC risk factors (polyp history, higher risk polyps at the index colonoscopy), whereas interval PCCRCs were not associated with these risk factors. The strength of the association of noninterval PCCRC with these traditional risk factors was

Table 5. Comparison of Noninterval and Interval PCCRCs

Variable	Noninterval cases (N = 27) N (%)	Interval cases (N = 27) N (%)	*P*-value
Age			
45–59	8 (29.6)	13 (48.1)	.148
60–69	10 (37.0)	4 (14.8)	
≥70	9 (33.3)	10 (37.0)	
Sex			
Male	14 (51.9)	15 (55.6)	.785
Female	13 (48.1)	12 (44.4)	
Known FDR of CRC			
No	18 (66.7)	23 (85.2)	.112
Yes	9 (33.3)	4 (14.8)	
History of non-CRC cancer			
No	18 (66.7)	17 (63.0)	.776
Yes	9 (33.3)	10 (37.0)	
History of tobacco use			
Never	14 (51.9)	12 (44.4)	
Current	2 (7.4)	2 (7.4)	.852
Former	11 (40.7)	13 (48.1)	
History of alcohol use			
Never	11 (40.7)	8 (29.6)	.286
Current	16 (59.3)	17 (63.0)	
Former	0 (0.0)	2 (7.4)	
Alcoholic drinks/wk			
None/rarely	12 (46.2)	10 (40.0)	.798
≤1	5 (19.2)	5 (20.0)	
2–6	3 (11.5)	5 (20.0)	
7–14	5 (19.2)	5 (20.0)	
>14	1 (3.8)	0 (0.0)	
Ever history of polyps			
No	2 (7.4)	10 (37.0)	**.009**
Yes	25 (92.6)	17 (63.0)	
Ever history of hyperplastic polyps			
No polyps	10 (37.0)	2 (7.4)	**.003**
Hyperplastic polyps only	6 (22.2)	2 (7.4)	
Other histology	11 (40.7)	23 (85.2)	
Ever history of HRA			
No	21 (77.8)	11 (40.7)	**.006**
Yes	6 (22.2)	16 (59.3)	
Polyp found on index colonoscopy			
No	13 (48.1)	6 (22.2)	.046
Yes	14 (51.9)	21 (77.8)	
Number of polyps on index colonoscopy			
0	6 (22.2)	13 (48.1)	.129
1	10 (37.0)	4 (14.8)	
2	6 (22.2)	7 (25.9)	
3 or more	5 (18.5)	3 (11.1)	
Location of polyp(s)			
Proximal	10 (47.6)	2 (14.3)	**.039**
Distal	3 (14.3)	7 (50.0)	
Both proximal and distal	8 (38.1)	5 (35.7)	
Largest polyp size category			
<5 mm	8 (38.1)	4 (28.6)	.704
5–10 mm	3 (14.3)	3 (21.4)	
≥10 mm	5 (23.8)	3 (21.4)	
Not reported	5 (23.8)	4 (28.6)	
Histology on index colonoscopy			
Hyperplastic only	2 (9.5)	6 (42.9)	**.021**
Other histology	19 (90.5)	8 (57.1)	

Table 5. Continued

Variable	Noninterval cases (N = 27) N (%)	Interval cases (N = 27) N (%)	*P*-value
Detailed polyp histology on index colonoscopy			
TA	12 (57.1)	3 (21.4)	.086
HP only	2 (9.5)	6 (42.9)	
SSP	2 (9.5)	1 (7.1)	
TA + SSP	0 (0.0)	1 (7.1)	
TA + HP/other	5 (23.8)	3 (21.4)	
HRA on index colonoscopy			
No	16 (59.3)	24 (88.9)	**.013**
Yes	11 (40.7)	3 (11.1)	

enough to show significance for the PCCRC cohort as a whole, despite no association with the interval subgroup. Noninterval and interval PCCRC might behave differently given their time frames of colonoscopy, and not surprisingly, having more polyps leads to worse outcomes when surveillance is too late. The contrast between interval and noninterval PCCRC supports several important conclusions. First, our findings support this WEO subclassification of PCCRC. Noninterval PCCRC, with traditional CRC risks factors, would seem best addressed by current CRC screening programs, as well as careful surveillance strategies for patients with findings on colonoscopy based on 2012 guidelines used during that time, and ongoing efforts to improve colonoscopy quality. Second, our findings suggest that factors beyond traditional CRC risks and colonoscopy quality are involved in interval PCCRC. It would seem logical that if colonoscopy quality issues (missed lesions, incompletely resected lesions) explained most interval PCCRCs, this subgroup should have higher risk lesions at the index colonoscopy. Given that interval PCCRCs did not differ from controls in this regard, it could be speculated that novel or aggressive biology is contributing; however, more study is needed.

The role of biology in PCCRC has been previously investigated. It has been well documented that mutations in DNA mismatch repair (MMR) genes and microsatellite instability are more common in PCCRCs than in other CRCs as well as other molecular features.[23,24,27,28] Recent large population-based studies in Utah (microsatellite instability) and Denmark (MMR deficiencies) add to this literature.[8,25] The serrated pathway has shown inconclusive associations with PCCRC.[24,27,28] Our study showed mixed results concerning an association of SSP and PCCRC. There was an increased risk of PCCRC if a patient had a history of SSPs, but no significantly increased risk if an SSP was found on the index colonoscopy. Future study includes genetic analysis of PCCRC subgroups. Although not statistically significant, interval PCCRCs in our study tended to be younger than noninterval PCCRCs. Although the incidence of CRC overall is declining, early-onset CRC (CRC that develops at <50 years) is increasing, and it has been suggested that early-onset CRC may be biologically different than late-onset CRC. Early-onset CRCs are often more advanced at diagnosis, are left-sided, and are more frequently found in minorities. They may also have different molecular characteristics and often lack an association with family history of CRC.[29–31] Given that interval PCCRCs in our study were younger than noninterval PCCRCs and polyp biology does not seem to be associated, larger studies looking at the relationship of age with interval CRC are needed, and studies comparing early-onset interval CRC with early-onset noninterval and sporadic CRCs seem warranted.

Table 6. AGA Guideline Recommendations (2012) for Cases

Guideline recommendation	Noninterval cases (N = 27)	Interval cases (N = 27)
10 y	0	14 (52%)
5 y	16 (59%)	9 (33%)
3 y	10 (37%)	4 (15%)
<3 y	1 (4%)	0

Although biology is important, around 30% of our PCCRCs can be attributed to endoscopic quality based on the proposed WEO algorithm to determine etiology of PCCRC. Our findings are similar to that of a UK group who also used this algorithm.[10] This suggests that endoscopic factors, which have frequently been associated with PCCRC,[5,7,13,15,16,19] also substantially impact PCCRC at our center. This subset of PCCRCs is likely "avoidable" with improved endoscopic technique. Multiple previous studies have shown an inverse relationship between the endoscopist ADR and PCCRC.[6,12,15] A recent study by Lam et al[17] showed that being in the highest ADR quintile had a 4-fold lower interval PCCRC risk and that quality improvement in this metric decreased interval PCCRC.

This study also examined whether the endoscopist followed the AGA's surveillance recommendation guidelines (2012). Recommendations for both PCCRCs overall and interval PCCRCs diverged from these guidelines substantially. Endoscopist "decision-making", as suggested in other studies,[10] likely has an impact on PCCRC. This may reflect the endoscopists' uncertainty during an examination or unfamiliarity with these guidelines.[26] The impact of guideline adherence appears to be considerable and has not been

Table 7. Description of Incorrect Recommendations for Controls and Cases

Incorrect recommendation	Incorrect controls (N = 30)	Incorrect noninterval cases (N = 11)	Incorrect interval cases (N = 13)
Too long (told 5 y, rec is 3 y)	7 (23%)	8 (73%)	2 (15%)
Too short (told 5 y, rec is 10 y)	18 (60%)	2 (18%)	7 (54%)
No recommendation given	5 (17%)	1 (9%)	4 (31%)

previously identified as a risk factor for PCCRC. This should be investigated in future studies. This will be increasingly important with the recent publication of new surveillance guidelines.[32] Quality improvement would likely be impactful in this area.

This study's strengths included evaluating PCCRCs in subdivided groups (noninterval and interval PCCRCs) as per guideline recommendations, which, to our knowledge, has not been previously performed. Another strength was performing all endoscopies in a single medical center, which allowed for consistent data gathering across cases and controls and the ability to have a thorough chart review. We also had a well-defined and large control group that is matched to cases of the same age and sex. Limitations of this study included its retrospective design, the relatively small number of PCCRCs, and the lack of ADR data for the endoscopists. It is also possible that undetected Lynch syndrome in patients may have accounted for some of the interval PCCRCs. Any contribution of these cases, however, is likely to be insignificant, given the high rate of testing for MMR in our CRC cohort (87%).

In conclusion, significant risk factors for developing PCCRCs overall and for noninterval PCCRCs included usual CRC risk factors such as a history of polyps (history of any polyp, non-HP histology, SSP, HRA) and an index colonoscopy with larger polyps or HRA. Risk factors for interval PCCRC differ considerably from noninterval PCCRC, with none of the traditional risk factors having a significant association with interval PCCRC. Further research on the biology and molecular factors in this important subgroup is clearly indicated. Despite the suggestion that biology may be playing a significant role, a high percentage of PCCRC can be attributed to quality. This would be amenable to endoscopic quality improvement, which has been previously shown to reduce PRCCRC. In this study, nonadherence to CRC screening surveillance guidelines was a major, yet novel, risk factor for PCCRC—interval PCCRC specifically—and should be further investigated in larger studies.

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Received September 9, 2021. Accepted January 7, 2022.

Correspondence:
Address correspondence to: Eric K. Ganguly, MD, 111 Colchester Ave, Burlington, Vermont 05401. e-mail: Eric.ganguly@uvmhealth.org.

Authors' Contributions:
Sonja P. Dawsey contributed to IRB approval, obtained data from the tumor registry, extracted patient data from the electronic medical record, carried out literature search, wrote the manuscript, made tables, and made figures and was secondary in study design. Pamela M. Vacek helped with study design, ran statistics, and helped with writing methods and results. Eric K. Ganguly was primary in study design and edited the manuscript.

Conflicts of Interest:
The authors disclose no conflicts.

Funding:
The authors report no funding.

Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytic methods, and study materials will not be made available to other researchers.