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Colorectal endoscopy, advanced adenomas, and sessile serrated polyps: implications for proximal colon cancer

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Abstract

OBJECTIVES—Colonoscopy is associated with a decreased risk of colorectal cancer but may be more effective in reducing the risk of distal than proximal malignancies. To gain insight into the differences between proximal and distal colon endoscopic performance, we conducted a case-control study of advanced adenomas, the primary targets of colorectal endoscopy screening, and sessile serrated polyps (SSPs), newly recognized precursor lesions for a colorectal cancer subset that occurs most often in the proximal colon.

METHODS—The Group Health-based study population included: 213 advanced adenoma cases, 172 SSP cases, and 1,704 controls ages 50–79, who received an index colonoscopy from 1998–2007. All participants completed a structured questionnaire covering endoscopy history. Participants with polyps underwent a standard pathology review to confirm the diagnosis and reclassify a subset as advanced adenomas or SSPs. Logistic regression analyses were conducted to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between endoscopy and advanced adenomas and SSPs separately; site-specific analyses were completed.

RESULTS—Previous endoscopy was associated with decreased risk of advanced adenomas in both the rectum/distal colon (OR=0.38; 95% CI: 0.26–0.56) and proximal colon (OR=0.31; 95% CI: 0.19–0.52), but there was no statistically significant association between prior endoscopy and SSPs (OR=0.80; 95%CI: 0.56–1.13).

CONCLUSIONS—Our results support the hypothesis that the effect of endoscopy differs between advanced adenomas and SSPs. This may have implications for proximal colon cancer

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prevention and be due to the failure of endoscopy to detect/remove SSPs, or the hypothesized rapid development of SSPs.

Introduction

Colorectal cancer screening is associated with decreased colorectal cancer incidence and mortality; yet it does not prevent all occurrences (1–5). In particular, proximal colon carcinomas may be less affected by screening (4–12). Sigmoidoscopy and colonoscopy are endoscopic procedures used for colorectal cancer screening and primary prevention, but the extent of the colon examined by the respective procedures is different. Sigmoidoscopy examines the rectum and distal portion of the colon, whereas colonoscopy visualizes the rectum and the entire colon.

Given these differences, it was generally assumed that colonoscopy would prevent cancer in the distal and proximal portions of the colon, whereas sigmoidoscopy might prevent only distal disease (13, 14). The results of several observational studies and clinical trials call into question this assumption, suggesting that both sigmoidoscopy and colonoscopy are associated with substantially decreased risks of rectal and distal colon cancer, but they may not modify the risk of proximal colon cancer (4–10). Other studies show reductions in both distal and proximal colon cancer associated with colonoscopy, but report larger effects in the distal colon (11, 12)

Biologic differences between proximal and distal colon polyps and/or cancer, differences in the quality of the colon preparation between the proximal and distal colon, and insufficient endoscopist training have been suggested as possible reasons for the decreased efficacy of endoscopy in the proximal colon (15–17). However, to date there are no published studies examining the association between prior endoscopy and the risk of different types of colorectal cancer precursor lesions. Because different precursor lesions probably represent divergent biologic pathways to colorectal cancer (15), evaluating their association with prior endoscopic exams may shed light on the reasons for reduced efficacy of endoscopy in the proximal colon.

Approximately 75% of colorectal cancers arise from adenomatous polyps (adenomas) and are in the adenoma-carcinoma pathway to colorectal cancer (18). The adenoma-carcinoma pathway usually involves *APC* mutation as an early event, followed by an accumulation of genetic mutations that activate oncogenes and inhibit tumor suppressor genes, which then drive the progression of the adenoma to adenocarcinoma (19). Because of the strong evidence linking adenomas to the risk of subsequent colorectal cancer, the primary targets for colorectal endoscopic procedures are adenomas (13). Detection and removal of adenomas can avert progression of these precursor lesions from pre-malignant to malignant disease, thereby preventing cancer. Most colorectal adenomas, however, will not progress to cancer (20). Large adenomas (> 10mm in diameter) and adenomas with villous histological components (microscopic finger-like projections) have higher rates of progression to cancer than do small adenomas (21, 22). The detection of adenomas with these characteristics, which have been termed advanced adenomas, thus is particularly important for the prevention of colorectal cancer. Advanced adenomas may be used as an indicator of increased risk of colorectal cancer resulting in recommendations to shorten the cancer surveillance interval from 10 years to 3–5 years (13).

Recent research suggests that, in addition to advanced adenomatous polyps, other colorectal polyps play a significant role in colorectal cancer development. In particular, certain serrated polyps may be precursors for colorectal cancers that develop via a “serrated polyp pathway” (23–27). Serrated polyps are distinct from conventional adenomas and represent a heterogeneous group of polyps with varying histology and malignant potential. Until

recently, most serrated polyps were considered hyperplastic, and were thought to have no malignant potential. Now, histologic differences between hyperplastic polyps and sessile serrated polyps (SSPs), also known as sessile serrated adenomas, have been recognized. SSPs are characterized by basal crypt distortion and by being usually located in the proximal colon (28). Cross-sectional studies of molecular markers suggest a link between SSPs and colorectal cancers characterized as having a CpG Island Methylator Phenotype (CIMP), which denotes a subgroup of colorectal cancers that carry an excessively high proportion of aberrantly methylated genes (25, 29–31). The prevalence of CIMP-positive cancer is much higher in the proximal colon than in the distal colon; 30–32% of proximal colon cancers are CIMP-positive, compared to 3–5% of distal colon and rectal cancers (32, 33). Thus, precursors of CIMP-positive colorectal cancer, such as SSPs, have been proposed to play a particularly important role in proximal colon cancer development.

Colonoscopy is most sensitive for detecting large and polypoid adenomas (34). Because SSPs tend to be flat (sessile) lesions, they are more difficult to detect endoscopically compared to pedunculated and/or protruding polyps, such as advanced adenomas (35–37). Thus, the objective of this study was to test the hypothesis that the reduced efficacy of endoscopy in the proximal colon may be due, in part, to the endoscopic failure to detect, resect, and thus prevent advanced “serrated pathway” polyps.

Methods

We conducted a case-control study of advanced adenomas and SSPs. Previous history of sigmoidoscopy and/or colonoscopy was evaluated in relation to advanced adenomas and SSPs, overall, and stratified by anatomic site.

Study population

We utilized a previously described study population recruited in two phases (38–41) consisting of enrollees of Group Health, a large integrated-health plan in Washington state, who underwent colonoscopy for any indication between 1998–2007. This colonoscopy was considered their “index” colonoscopy. To better represent the population of individuals undergoing colorectal cancer screening, our analyses were restricted to participants aged 50–79 at the index exam. Protocols for eligibility and data collection were applied uniformly to both study phases and were approved by Institutional Review Boards at Group Health and the Fred Hutchinson Cancer Research Center. All participants provided written informed consent.

Patients diagnosed with adenomas, hyperplastic polyps, or who had normal findings at the index exam (*i.e.* no colorectal disease detected) were potentially eligible to participate. We excluded those with current or previous colorectal cancer, inflammatory bowel disease, familial adenomatous polyposis, or Lynch Syndrome, and those with prior colectomy. We also excluded potentially eligible participants who had had a colonoscopy within the 12 months prior to the index colonoscopy, those with incomplete index colonoscopies (*i.e.*, the cecum was not reached by the colonoscope or bowel preparation was poor), and enrollees of Group Health for less than 3 years.

Data Collection

Study participants completed a standardized questionnaire with information on: previous endoscopy, demographic characteristics, family history of colorectal cancer, height, weight, physical activity, alcohol consumption, smoking, aspirin use, and, for women, reproductive history and hormone use. Approximately 74% (N=2,485) of potentially eligible study participants consented to answer the questionnaire, and the majority of these participants

completed the questionnaire within 3–4 months of their index exam. Among participants who completed questionnaires, 399 were excluded due to missing data on previous endoscopy procedures or missing pathology data on polyp size.

Case-control classification

For polyp cases, standardized pathology reviews were completed, and medical records were reviewed to ascertain the size and anatomic site of each polyp. Participants were classified as advanced adenoma cases if they had at least one adenomatous polyp ≥ 10 mm in diameter, with $\geq 20\%$ villous components or with high-grade dysplasia. SSPs were distinguished from hyperplastic polyps if they displayed exaggerated crypt serration, crypt dilatation, crypt branching, horizontal crypt extensions at the base, or other distortion of architectural organization and maturation (28). Participants with one or more SSP were considered SSP cases. Controls included those who had no colorectal pathology identified during the index colonoscopy, and those who had hyperplastic polyps of any size or tubular adenomas <10 mm in diameter at the index exam and no advanced adenomas or SSPs. The final study population included 213 adenoma cases, 172 SSP cases and 1,704 controls.

Statistical Analysis

We performed logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI) comparing endoscopy history between each case group and controls (STATA 10.1, StataCorp LP, College Station, TX). We evaluated separate regression models for: 1) all advanced adenoma cases; 2) all SSP cases; 3) rectal or distal advanced adenomas; 4) rectal or distal SSPs; 5) proximal advanced adenomas; and 6) proximal SSPs. Each model had a common reference group that included participants who reported no colonoscopy or sigmoidoscopy at least 2 years prior to the index exam. The other exposure categories included participants who reported a prior endoscopy 2 or more years before the index exam according to type of prior endoscopy (sigmoidoscopy only; colonoscopy only; both sigmoidoscopy and colonoscopy). Logistic regression models were also used to compare advanced adenoma cases to SSP cases, and the Wald p-value for the comparison between these case groups was presented for each type of endoscopy.

Statistical models included the following potential confounders, chosen *a priori* based on the literature: age at the index exam, sex, race, BMI (kg/m^2), physical activity (minutes/week), history of colorectal cancer in a first degree relative, alcohol intake (drinks/week), cigarette smoking status (never, former, current), regular non-steroidal anti-inflammatory drug use (ever/never), and for women, hormone therapy (ever/never). We also adjusted for the phase of the study in which participants were recruited. Multiple imputation was conducted to supply missing adjustment variables (42), using the *ice* command in STATA 10.1.

Because endoscopy is an intervention designed to prevent advanced colorectal lesions and cancer, but not smaller lesions, our control group included not only polyp-free patients, but also those with non-advanced polyps. Given the objective of this study, this is the most appropriate comparison group. However, we conducted sensitivity analyses restricting controls to those who were polyp-free at the index colonoscopy to determine if point estimates were affected by the composition of the control group. Additionally, we examined whether associations varied by the amount of time between the prior endoscopy and index colonoscopy.

Results

Table 1 displays selected characteristics by case-control status. Compared to controls, advanced adenoma cases were more likely to be male or to be obese, and they were less

likely to exercise 60 minutes per week or to use NSAIDs. SSP cases were more likely to report a family history of colorectal cancer than controls.

Prior endoscopy was common in this population, with 54% having 1 prior sigmoidoscopy (26%), colonoscopy (13%), or both (15%). Prior colon/rectal endoscopy was associated with a decreased risk of advanced adenomas (OR=0.36; 95% CI: 0.26–0.50), but there was not a statistically significant association between prior endoscopy and SSPs (OR=0.80; 95% CI: 0.56–1.13) (Table 2). Analyses comparing advanced adenomas to SSPs, suggested that the association with endoscopy was statistically significantly different between advanced adenomas and SSPs (P -value=0.001). This finding of decreased risk for advanced adenomas and no statistically significant association for SSPs was consistent across each category of previous endoscopy (i.e. sigmoidoscopy only, colonoscopy only, or both sigmoidoscopy and colonoscopy (Table 2). Further, associations did not vary substantially by anatomic site (Table 3). For advanced adenomas, any prior endoscopy was associated with decreased risks for these lesions in both the rectum/distal colon (OR=0.38; 95% CI: 0.26–0.56) and proximal colon (OR=0.31; 95% CI: 0.19–0.52). Sigmoidoscopy only, as well as colonoscopy only, was associated with a decreased risk of advanced adenoma for both regions of the colon. For SSPs, all OR estimates were <1; however, no statistically significant associations were observed for SSPs regardless of anatomic site or type of endoscopy.

Sensitivity analyses restricting the control group to polyp-free participants, did not substantially affect the point estimates for endoscopy and advanced adenomas or for SSPs. For advanced adenomas, when the control group was restricted to polyp-free participants, OR=0.36; 95% CI: 0.26–0.51; for SSPs, OR=0.78; 95% CI: 0.53–1.12.

When restricting analyses to those who had endoscopy >10 years ago and those who had never had endoscopy, a statistically significant inverse association between endoscopy and advanced adenomas was still observed (OR=0.41; 95% CI: 0.27–0.62). Further, those with their last endoscopy >5 years ago had similar associations when compared to patients who had endoscopy 5 years ago. For the association between advanced adenomas and endoscopy >5 years ago, OR=0.36; 95% CI: 0.25–0.53; and for endoscopy 2–5 years ago, OR=0.38; 95% CI: 0.26–0.56. For the association between SSPs and endoscopy >5 years ago, OR=0.73; 95% CI: 0.48–1.09; and for endoscopy 2–5 years ago, OR=0.86; 95% CI: 0.58–1.29.

Discussion

Colorectal cancer studies indicate that endoscopy is effective for decreasing the incidence and mortality of rectal and distal colon cancer, but it has reduced efficacy for proximal colon malignancies (4–7, 9–12). Our data suggest that unlike the results observed for colorectal cancer, the effectiveness of endoscopy for advanced adenomas and for SSPs does not vary by anatomic site. Rather, endoscopy has very different consequences dependent on polyp type, with advanced adenomas having a strong inverse association with prior endoscopy but SSPs having no statistically significant association with prior endoscopy. Because advanced adenomas and SSPs are precursor lesions for divergent colorectal cancer pathways (15), and because SSPs tend to arise in the proximal colon (26, 27), our results suggest that differences in the biology or microanatomy between proximal and distal colon cancer may play a role in the reduced efficacy of endoscopy for proximal colon cancer prevention.

Although this is the first study to evaluate the association between prior endoscopy and SSPs, there are previous studies that report biologic differences between colon cancers identified within 3–5 years of colonoscopy (termed interval colon cancer) and other colon

cancers. In a case-case comparison study of 63 interval and 131 age- and sex-matched non-interval colon cancer cases, interval cancers were more likely to be proximally located (OR=1.9; 95% CI: 1.0–3.8), CIMP-high (OR=2.4; 95% CI: 1.2–4.9), and to exhibit microsatellite instability (MSI), which is often associated with CIMP (OR=2.7; 95% CI: 1.0–6.8) (43). These tumor characteristics are all associated with the serrated pathway to colorectal cancer, in which SSPs are an important precursor lesion (26, 27). Proximal location was associated with interval colorectal cancer in two additional studies (5, 44), and MSI was reported as a predictor of interval colorectal cancer in one of these studies (44). MSI cancers have been proposed to arise from an accelerated polyp to cancer progression sequence, which may explain their increased frequency in interval cancers.

In contrast to studies suggesting that biologic differences account for differences in the efficacy of endoscopy, two large cohort studies and one case-case comparison study suggest that endoscopist specialty and proficiency are associated with the risk of colorectal cancer following colonoscopy (5, 45, 46). In a cohort study of over 110,000 individuals with a negative index colonoscopy, the risk of colorectal cancer during the 15 years following the index colonoscopy was 27–39% higher in those patients examined by an endoscopist who was not a gastroenterologist compared to those who were evaluated by a gastroenterologist (46). In a study of over 45,000 individuals from the National Colorectal Cancer Screening Program in Poland, the risk of colorectal cancer during the interval between the index colonoscopy and the next scheduled screening colonoscopy was increased among patients who had endoscopists who had a history of low adenoma-detection rates (OR=12.5; 95% CI: 1.5–103.4 comparing those with an adenoma detection rate <11% to those with adenoma detection rate ≥20%) (45). Finally, a case-case comparison study of 4,883 colorectal cancer cases from the Manitoba Cancer Registry, reported a 38% increase in the odds of colorectal cancer during the 6–36 months following colonoscopy comparing those who had a family-practice physician as their endoscopist to those who were evaluated by a gastroenterologist (5).

There are two predominant theories of why there are variations in the effectiveness of endoscopy for colon cancer prevention by anatomic site. One cites biologic differences, and the other points towards differences in endoscopists' training. Although these explanations seem independent, they may actually be complementary and overlapping. SSPs are flat colonic lesions that are difficult to visualize and resect (35–37). These lesions were first widely recognized by the medical community in 2003 (28), and consensus about their importance as a potential precursor to a subset of colorectal cancer has been emerging ever since (26, 27). Therefore, specialists may be more likely than general practitioners to visualize SSPs at endoscopy and to be aware of their clinical significance.

The index colonoscopy for this study occurred between 1998 and 2007. These dates preceded the 2008 guidelines from the United States Multi-Society Task Force on Colorectal Cancer and the American Cancer Society, which recommended complete resection of SSPs (47). Awareness about the importance of SSPs has been increasing over time, and a recent retrospective cohort study of colonoscopy patients at a single medical center reported that detection rates of SSPs in the proximal colon increased by 4.5-fold from 2006–2008 (37). This increased recognition of SSPs may lead to better effectiveness for SSP prevention via colonoscopy, which would have implications for future proximal colon cancer prevention. Therefore, future studies analyzing the effects of endoscopy may detect significant inverse associations between SSPs and endoscopy that was not observed during the timeframe for this study.

Prior sigmoidoscopy was associated with a 52% decrease in the risk of distal and rectal advanced adenomas and a 62% decrease in the risk of proximal advanced adenomas. This

finding may seem counterintuitive because sigmoidoscopy does not image the proximal colon. However, some studies suggest that patients with no polyps found at sigmoidoscopy have a lower risk of developing both proximal and distal colon cancer than the general population (48, 49); although other studies report statistically significantly lower risk for distal malignancies only (50). Also, distal polyps may predict proximal neoplasia (51–53), and those individuals with polyps identified at sigmoidoscopy are usually referred for further evaluation via colonoscopy. Therefore, the majority of those with only prior sigmoidoscopy and no prior colonoscopy probably were polyp-free at their prior sigmoidoscopy. Thus, they may comprise a low-risk group for developing colorectal neoplasia.

Our study results should be interpreted in the light of several limitations. First, because our study population is predominantly white and well-educated, our results may not be generalizable to minority populations or those with less education. Several studies have demonstrated differences in compliance with follow-up screening and procedures among people of different ethnic and racial backgrounds (54, 55). Therefore, the association between colonoscopy and advanced adenomas may be attenuated in groups who have lower compliance with recommendations. Second, data on the endoscopists performing the index colonoscopy and prior endoscopy procedures were not collected. However, for the index colonoscopy, everyone in this study population was evaluated at a gastrointestinal clinic. Although there is still variation in polyp detection rates among gastroenterologists, this variation is less than the variation observed between specialists and family-practice physicians (5), and we do not anticipate endoscopist proficiency at the index exam to be associated with the probability of a prior endoscopy. Thus, any bias introduced would likely be non-differential, resulting in conservative estimates of the association between prior endoscopy and advanced polyp risk. Finally, because SSPs are rare, particularly in the distal colon and rectum, our study power was limited to detect significant associations between endoscopy and SSPs. However, we were still able to detect statistically significantly different associations with endoscopy comparing advanced adenomas to SSPs (P -value=0.001).

In summary, we observed a strong, statistically significant inverse association between advanced adenomas and prior endoscopy, and unlike colorectal cancer studies, this association did not vary according to anatomic site. However, there was not a statistically significant association between SSPs and prior endoscopy. Because SSPs are important precursors in the proximal colon, these results may help to explain why several colorectal cancer studies report poor effectiveness for endoscopy in preventing proximal colon cancer. There is now a growing awareness of the importance of SSPs, and future studies should assess if this increased vigilance for SSPs results in better effectiveness of endoscopy for the prevention of SSPs, and more importantly, proximal colon cancer.

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What is current knowledge

- Advanced adenomas are well-established precursor lesions and targets of colorectal cancer surveillance.
- Sessile serrated polyps are newly recognized lesions that are more common in the proximal colon, and mounting evidence indicates that these polyps may also be important precursors for a subset of colon cancer.
- Even though colonoscopy images the entire colon, risk reduction associated with colonoscopy is significantly greater in the distal than in the proximal colon, and interval colon cancer is more common in the proximal than in the distal colon. The reasons for the differing effects of endoscopy in the proximal vs. the distal colon remain unclear.

What is new here

- In contrast to colorectal cancer, the association between endoscopy and advanced colorectal polyps did not vary by anatomic site.
- The association between endoscopy and advanced colorectal polyps varied according to polyp type; prior endoscopy was strongly associated with a reduced risk of advanced adenomas in both the distal and proximal colon, but there was not a significant association between sessile serrated polyps and prior endoscopy.
- These results support the hypothesis that biologic and microanatomic differences between precursors for proximal and distal colon cancer may contribute to the reduced efficacy of endoscopy for proximal colon cancer prevention.

Table 1

Characteristics of patients with advanced adenoma, sessile serrated polyps, and controls^a: Group Health Enrollees 1998–2007

	Controls ^a (n=1704) N (%)	Advanced Adenomas (n=213) N (%)	Sessile Serrated Polyps (n=172) N (%)
Age (years)			
50–59	771 (45)	91 (43)	77 (45)
60–69	638 (38)	79 (37)	73 (42)
70–80	295 (17)	43 (20)	22 (13)
Men	765 (45)	134 (63)	69 (40)
Race/Ethnicity			
Caucasian	1477 (87)	179 (84)	148 (86)
African American	49 (3)	8 (4)	1 (1)
Asian American	69 (4)	13 (6)	9 (5)
Other	109 (6)	13 (6)	14 (8)
Family history of colorectal cancer (Yes)	351 (21)	37 (17)	49 (28)
Education			
High school graduate or less	247 (15)	35 (16)	18 (11)
Some college/vocational school	445 (26)	55 (26)	43 (25)
College graduate	432 (25)	46 (22)	47 (27)
Post-college graduate school	580 (34)	77 (36)	64 (37)
BMI (kg/m²)			
<25	644 (38)	62 (29)	71 (41)
25–29.9	672 (40)	85 (40)	60 (35)
30	377 (22)	64 (30)	41 (24)
Physical Activity (≥ 60 min/wk)	722 (42)	72 (34)	74 (43)
Smoking Status			
Never	882 (52)	101 (47)	92 (54)
Former	711 (42)	99 (47)	61 (35)
Current	111 (6)	13 (6)	19 (11)
Alcohol consumption (≥ 1 drink/wk)	973 (57)	119 (54)	97 (56)
NSAIDs use (Yes)	957 (56)	103 (48)	89 (52)
Hormone therapy use^b (Yes)	567 (60)	47 (59)	57 (55)

^a Controls include participants with no colorectal pathology, participants with non-advanced adenomas, and participants with hyperplastic polyps

^b Among women only

Adjusted^a regression analyses of the association between previous endoscopy, advanced adenomas, and sessile serrated polyps: Group Health enrollees 1998–2007.

Table 2

	Controls ^b		Advanced adenomas		Sessile serrated Polyps		p-value ^c Adv AD vs. SSP
	N (%)	N (%)	N (%)	OR ^a (95% CI)	N (%)	OR ^a (95% CI)	
No prior endoscopy	740 (43)	136 (64)	1.00 (ref)	1.00 (ref)	81 (47)	1.00 (ref)	
Any Endoscopy ^d	964 (57)	77 (36)	0.36 (0.26–0.50)	0.80 (0.56–1.13)	91 (53)	0.80 (0.56–1.13)	0.001
Sigmoidoscopy Only ^e	464 (27)	45 (21)	0.46 (0.32–0.67)	0.80 (0.52–1.20)	41 (23)	0.80 (0.52–1.20)	0.040
Colonoscopy Only ^e	233 (14)	15 (7)	0.31 (0.18–0.54)	0.84 (0.51–1.38)	25 (15)	0.84 (0.51–1.38)	0.009
Sigmoidoscopy and Colonoscopy ^e	267 (16)	17 (8)	0.24 (0.13–0.42)	0.76 (0.46–1.26)	25 (15)	0.76 (0.46–1.26)	0.006

^a Adjusted for age, sex, race, education, BMI, physical activity, family history of colorectal cancer, alcohol intake, smoking status, NSAIDs use, hormone therapy use, and study phase.

^b Controls include participants with no colorectal pathology, participants with non-advanced adenomas, and participants with hyperplastic polyps

^c Wald p-value from the regression model comparing advanced adenoma cases to sessile serrate polyp cases

^d Prior sigmoidoscopy, colonoscopy, or a history or both exams 2 years prior to the index colonoscopy

^e Previous exam 2 years prior to the index colonoscopy

Table 3

Adjusted^a logistic regression analyses of the association between previous endoscopy, advanced adenomas, and sessile serrated polyps by anatomic site: Group Health enrollees 1998–2007.

	Controls ^b		Rectal and Distal Advanced adenomas		Proximal Advanced adenomas		Rectal and Distal Sessile serrated polyps		Proximal Sessile serrated polyps	
	N (%)	N (%)	OR ^a (95% CI)	N (%)	OR ^a (95% CI)	N (%)	OR ^a (95% CI)	N (%)	OR ^a (95% CI)	
No prior endoscopy	740 (43)	93 (65)	1.00 (ref)	49 (62)	1.00 (ref)	28 (52)	1.00 (ref)	65 (49)	1.00 (ref)	
Any Endoscopy ^c	964 (57)	50 (35)	0.38 (0.26–0.56)	30 (38)	0.31 (0.19–0.52)	26 (48)	0.64 (0.35–1.15)	69 (51)	0.75 (0.50–1.11)	
Sigmoidoscopy Only ^d	464 (27)	30 (21)	0.48 (0.31–0.76)	16 (21)	0.38 (0.21–0.71)	12 (22)	0.67 (0.32–1.38)	30 (22)	0.71 (0.44–1.14)	
Colonoscopy Only ^d	233 (14)	12 (8)	0.36 (0.19–0.69)	7 (9)	0.28 (0.12–0.64)	9 (17)	0.81 (0.36–1.82)	18 (14)	0.76 (0.43–1.36)	
Sigmoidoscopy and Colonoscopy ^d	267 (16)	8 (6)	0.21 (0.10–0.45)	7 (9)	0.24 (0.10–0.56)	5 (9)	0.42 (0.15–1.14)	21 (15)	0.80 (0.46–1.39)	

^a Adjusted for age, sex, race, education, BMI, physical activity, family history of colorectal cancer, alcohol intake, smoking status, NSAIDs use, hormone therapy use, and study phase.

^b Controls include participants with no colorectal pathology, participants with non-advanced adenomas, and participants with hyperplastic polyps

^c Prior sigmoidoscopy, colonoscopy, or a history or both exams 2 years prior to the index colonoscopy

^d Previous exam 2 years prior to the index colonoscopy

Note: 9 study participants had advanced adenomas in both the distal and proximal portions of the colon and were included in both groups

16 study participants had advanced SSPs in both the distal and proximal portions of the colon and were included in both groups