Predictors of Incident Serrated Polyps: Results from a Large Multicenter Clinical Trial

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ABSTRACT

Background: Serrated polyps (SP) are important colorectal cancer precursors, yet their epidemiology is incompletely understood. We measured risk factors for incident sessile-serrated lesions (SSL) and microvesicular (MVHP) and goblet-cell rich (GCHP) hyperplastic polyp subtypes.

Methods: We conducted a cohort study of patients undergoing colonoscopic surveillance nested within a chemoprevention trial. Outcomes of interest were ≥1 SPs, including SSLs, MVHPs, and GCHPs specifically. Multivariable generalized estimating equation models were used to estimate adjusted risk ratios (RR) and 95% confidence intervals (CI) for different polyp types.

Results: Among 2,102 participants, a total of 1,615 SPs (including 212 SSLs) were found among 758 participants during follow-up. Prior history of SPs was strongly associated with subsequent occurrence of SPs. There was no apparent association between age, sex, or education and risk of SPs. Black participants were at lower risk of SSLs and MVHPs, but higher risk of GCHPs compared with white participants [RR, 0.40; 95% CI, 0.16–0.99); RR, 0.63 (95% CI, 0.42–0.96); and RR, 1.83 (95% CI, 1.23–2.72) respectively]. Alcohol and smoking exposure were also associated with SPs, including hyperplastic polyp subtypes in particular.

Conclusions: In this prospective study, the risk of SP subtypes differed by race, alcohol, and smoking status, and prior history of SPs. Risk factor associations for SPs differ from risk factors for conventional adenomas, supporting the concept of etiologic heterogeneity of colorectal cancer.

Impact: These findings allow for better risk stratification of patients undergoing colorectal cancer screening and could inform screening test selection.

Introduction

Serrated polyps are important colorectal cancer precursors, responsible for up to 25% of sporadic colorectal cancer (1–3). The common histologic feature that links serrated polyps is the serration of the colonic crypt epithelium. This characteristic is found in the hyperplastic polyp (HP), the sessile serrated lesion (SSL, also called sessile serrated polyp or sessile serrated adenoma), and the traditional serrated adenoma (TSA; ref. 3). HPs are the most common serrated lesion, accounting for roughly 60% to 70% of all serrated polyps, and the most innocuous. Most HPs are small, located in the distal colorectum, and have little to no malignant potential. SSLs are less common, occurring in up to 14% of average risk patients undergoing screening colonoscopy (4), and likely generate the most colorectal cancers from this pathway. TSAs are also cancer precursors, but are the least commonly found serrated polyp subtype.

Serrated carcinogenesis involves a unique series of genetic and epigenetic alterations that are distinct from those in the traditional adenoma carcinoma sequence (2, 3). There are at least two different pathways by which serrated lesions can develop into cancer, involving activating mutations in RAS or RAF kinase genes, which can result in the CpG island methylation phenotype (CIMP), leading to inactivation of certain tumor suppressor genes (e.g., *MLH1*, *CDKN2A*) via promoter hypermethylation. These changes can lead to either microsatellite unstable (MSI) or stable (MSS) colorectal cancer (3). Apart from differences in molecular features and histology, serrated lesions also have a different endoscopic appearance, distribution in the colon, growth characteristics, and epidemiology compared with conventional adenomas.

Understanding who is at risk for colorectal cancer and the different types of precursor lesions is important to be able to optimally prevent this deadly disease. Although the epidemiology of conventional adenomas is fairly well elucidated, serrated lesions are comparatively less well studied with respect to both modifiable and nonmodifiable risk factors, preventive influences, and other important associations. In particular, the field lacks longitudinal studies identifying factors that have a clear temporal or causal relationship with serrated lesion outcomes. In addition, there are few published epidemiologic studies examining HP subtypes. Such data are scientifically valuable because some authors suggest that microvesicular (MVHP) and goblet cell-rich (GCHP) HPs could give rise to premalignant SSLs and TSAs (5, 6).

We used data from a large colonoscopy based chemoprevention trial to study the association between baseline participant characteristics and risk of developing serrated lesions, particularly SSLs, during follow up. Because all polyps were removed at baseline, this study is designed to evaluate risk factors for "incident" serrated lesions.

Materials and Methods

Study design and participants

This study used data on baseline participant characteristics and serrated colorectal polyps outcomes among participants in the Vitamin D/Calcium Polyp Prevention Study (VCPPS). The VCPPS parent study was a randomized, multicenter, participant, and

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Clinical Trial Registration: Clinical Trial registration ID: NCT01137552.

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investigator blinded, placebo-controlled chemoprevention trial that took place at 11 geographically diverse centers across the United States. Participants were enrolled in the trial between July 2004 and July 2008, and colonoscopy outcomes were collected up to June 2016. Detailed methods from this trial have been published previously, including the protocol (7). In brief, individuals ages 45 to 75 were invited to participate if they had undergone a clearing colonoscopy with at least one adenomatous polyp (≥2 mm) detected and removed in the preceding 4 months. All participants were scheduled to undergo surveillance colonoscopy at either 3 or 5 years based on the findings of the index examination. Patients with inflammatory bowel disease, kidney dysfunction, known familial colorectal cancer syndromes, or contraindications to receiving the study treatments were excluded.

Following enrollment, participants underwent a run-in period to confirm minimum pill taking adherence of 80% over at least 2 months. Eligible participants were then randomized to receive calcium carbonate (1,200 mg elemental calcium per day), vitamin D_3 (1,000 IU/day), the combination of these agents, or neither agent (placebo). However, eligible women were allowed to choose to receive calcium in their study pills and to be randomized only to vitamin D or placebo. The treatment period continued until the first surveillance colonoscopy at 3 or 5 years. For participants who consented to additional follow-up beyond the treatment phase, data collection continued after the first surveillance colonoscopy (observational period). For this analysis, serrated polyp outcomes were included from any follow-up colonoscopy occurring at least 1-year post-randomization in either the treatment or observational phase. The majority of participants had outcomes determined from a single colonoscopy in both phases.

The VCPPS study was conducted in accordance with recognized ethical guidelines (Declaration of Helsinki) and was approved by the institutional review boards of the central coordinating site (Dartmouth) and all participating clinical sites. All participants provided written informed consent prior to enrollment. The trial was registered at ClinicalTrials.gov (no. NCT00153816).

Measurement of outcomes, exposures, and covariates

At enrollment, trained research staff collected baseline data in a standardized fashion, including demographics, medical history, family history, concomitant medications, health habits, and diet (Block Brief 2000 questionnaire). We collected and systematically abstracted all baseline colonoscopy reports and pathology reports to record data on all polyps found on the baseline (pre-enrollment) exam. The diagnosis for all baseline polyps, adenoma or serrated, was determined per local diagnosis. Height and weight were determined by self-report or measurement, and used to calculate body mass index (BMI). Throughout the trial, patients were contacted by a study coordinator periodically to verify adherence, adverse events, concomitant medications, and receipt of colonoscopy or other colorectal imaging.

All polyps found during post-randomization colonoscopies were reviewed centrally by an expert gastrointestinal pathologist. For this study, the outcomes of interest included all SPs, subtyped as HPs (MVHP and GCHP), SSLs (with or without cytologic dysplasia), and TSAs, classified according to the 2010 WHO criteria (8). Polyp location was categorized as right-sided if proximal to the splenic flexure, and lesions more distal were categorized as left-sided.

Statistical analysis

The primary outcomes for this *post hoc* analysis of the VCPPS study were one or more serrated polyps (any type) overall, as well as SSLs and HPs specifically. We were unable to assess TSAs as an outcome in modeling due to their rarity. Multivariable generalized estimating equation (GEE) models were used to estimate risk ratios (RR) and 95% confidence intervals (CI) for different serrated polyp types. Separate models were run for each exposure of interest, which included age, sex, race, education, BMI, physical activity level, smoking status and duration, baseline alcohol use, aspirin or NSAID exposure, and baseline polyp findings (categories and referent groups indicated in tables). Models were adjusted for several covariates, including randomization variables (age, sex, race (white, black, other), center [grouped geographically into southeast (Georgia, North Carolina, South Carolina, and Puerto Rico), north (Ohio, New Hampshire, Iowa, and Minnesota), and west (Colorado, Texas, and California)], vitamin D study treatment (placebo, active), and calcium study treatment (placebo, active—this includes women who elected to receive calcium and were not randomized to it), and potential confounding factors (study phase of the outcome (treatment or observational), and either number of serrated polyps at baseline for any serrated polyp and HP outcomes, or baseline SSL or proximal serrated polyps for SSL outcome. *P* for trend was calculated using a continuous ordinal variable for the categories of the exposure variable.

Two-sided *P* values of <0.05 were considered statistically significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute).

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Participants and baseline characteristics

A total of 2,813 participants were enrolled and 2,259 underwent randomization. Among these, 2,102 participants had a colonoscopy at least 1 year after randomization and had sufficient pathology data to determine polyp outcomes during the initial treatment phase; these individuals were included in the analysis presented here. Because of cessation of funding before all subjects reached their second surveillance colonoscopy, only approximately half of the participants (n = 1,127) had at least one colonoscopy with complete data from the observational phase (Supplementary Fig. S1).

The majority of included participants were male (64%) and white race (89%; **Table 1**). Most participants were ages 55 or older (65%). At baseline, most participants had one or two low-risk tubular adenomas, but 384 (19%) had advanced adenomas. There were 502 participants who had synchronous serrated polyps at baseline including 335 (17%) with a single serrated polyp and 167 (8%) with 2 or more. Most baseline serrated polyps were HPs, but 155 (8%) of participants had either an SSL or proximal serrated polyp at baseline.

Occurrence of serrated polyps

A total of 1,040 serrated polyps (including 132 SSLs) were found during the treatment phase, and an additional 575 serrated polyps (including 80 SSLs) were found during the observational phase. On the participant level, 565 (27%) participants had at least one serrated polyp in the treatment phase, including 494 (24%) with HPs, 100 (5%) with SSLs, and 8 (0.4%) with TSAs (**Table 2**). During the observational phase, 327 (30%) participants had serrated polyps during this period, including 269 (25%) with HPs, 62 (6%) with SSLs, and 6 (0.6%) with TSAs. 11 of 62 (18%) observational phase participants with SSLs also had a prior SSL during the treatment phase. Most SSLs (67%) were located in the proximal colon.

Table 1. Characteristics for all included subjects.

Characteristics	*n* (%)
Total participants	2,102 (100)
Age	
<55	743 (35.4)
55–59	542 (25.8)
60–64	398 (18.9)
≥65	419 (19.9)
Sex	
Male	1,334 (63.5)
Female	768 (36.5)
Race	
White	1,788 (88.7)
Black	160 (7.9)
Other	69 (3.4)
Education	
<High school graduate	105 (5.0)
High school graduate	284 (13.6)
Some college	1,205 (57.6)
Graduate school	497 (23.8)
Body mass index	
<25 kg/m^2	487 (23.2)
25–29.9 kg/m^2	857 (40.8)
≥30 kg/m^2	757 (36.0)
Activity level	
Low	497 (23.9)
Medium	664 (32.0)
High	916 (44.1)
Smoking status	
Never	1,122 (53.4)
Former	783 (37.3)
Current	197 (9.4)
Pack years	
0	1,122 (53.5)
>0 to 13	310 (14.8)
>13 to 34	333 (15.9)
>34	331 (15.8)
Maximum amount smoked for 1+ year	
0	1,122 (53.4)
>0 to <1 pack	292 (13.9)
1 pack	366 (17.4)
> 1 pack	321 (15.3)
Duration smoked	
0	1,122 (53.5)
>0 to 15 years	299 (14.3)
16–34 years	444 (21.2)
>34 years	232 (11.1)
Baseline alcohol use	
None	639 (32.7)
0.1–1 drink/day	793 (40.5)
>1 drink/day	524 (26.8)
Baseline aspirin use	*n* (%)
None	932 (44.3)
<1 day/week	301 (14.3)
1–6 days/week	178 (8.5)
7 days/week	691 (32.9)
Baseline non-aspirin NSAID use	
None	796 (37.9)
<1 day/week	787 (37.4)
1–6 days/week	361 (17.2)
7 days/week	158 (7.5)
Baseline advanced adenoma	
No	1,682 (81.4)
Yes	384 (18.6)
Baseline serrated polyp	
0	1,524 (75.2)
1	335 (16.5)
2+	167 (8.2)
Baseline SSL or proximal serrated polyp	
No	1,821 (92.2)
Yes	155 (7.8)
Menopausal status	
Pre	155 (20.5)
Post	603 (79.6)
Baseline HRT status	
Never	407 (53.5)
Former	242 (31.8)
Current	112 (14.7)
Ever used contraceptives	
No	133 (17.4)
Yes	633 (82.6)
Age at menarche	
≤11	142 (18.8)
12	193 (25.5)
13	249 (32.9)
≥14	172 (22.8)
Number of pregnancies	
0	79 (10.3)
1	84 (11.0)
2	204 (26.6)
3	206 (26.9)
≥4	194 (25.3)
Number of live births	
0	114 (14.9)
1	106 (13.8)
2	273 (35.6)
3	169 (22.0)
≥4	105 (13.7)

(Continued on the following column)

Table 1. Characteristics for all included subjects. (Cont'd)

Note: *N*s for a variable may not sum to the total due to missing data. Percentages are based on nonmissing data. Data for menopausal status, HRT and contraceptive use, menarche, pregnancies, and births limited to female participants only.
Abbreviation: HRT, hormone replacement therapy.

Risk factor associations

Table 3 presents results for associations of baseline participant characteristics with various serrated polyp outcomes. No apparent association was seen between age or sex and risk of serrated polyps. However, non-white participants, specifically those who identified as black, were at lower risk of SSLs and MVHPs [RR (95% CI) compared with white individuals: 0.40 (0.16–0.99) and 0.63 (0.42–0.96), respectively]. In contrast, black participants appeared to be at increased risk of GCHPs compared with white participants [RR, 1.83; 95% CI, 1.23–2.72; **Fig. 1A**). In this analysis, we found no association between physical activity, presence of advanced adenoma at baseline, use of NSAIDs or aspirin and serrated polyp outcomes. We also did not identify any meaningful associations between menopausal status, use of hormone replacement, or use of contraceptives and occurrence of serrated polyps overall (**Table 4**). However, an increasing number of pregnancies and live births were associated with a higher risk of HPs. For example, women with four or more pregnancies had roughly twice the risk of HPs compared with nulliparous women (RR, 2.24; 95% CI, 1.23–4.08; P_{trend} = 0.05). A similar pattern was observed for four or more live births

Table 2. Number of participants with each outcome by study phase.

Polyp outcomes	Treatment phase *n* with outcome/*N*[a] (%) *N* with exam = 2,102	Observational phase *n* with outcome/*N*[a] (%) *N* with exam = 1,127
Any serrated polyp	565/2,058 (27.5)	327/1,100 (29.7)
Sessile serrated lesion	100/2,014 (5.0)	62/1,078 (5.8)
>1 SSL	24/2,012 (1.2)	11/1,075 (1.0)
SSL ≥ 1 cm	17/2,013 (0.8)	15/1,075 (1.4)
SSL with dysplasia	4/2,013 (0.2)	3/1,077 (0.3)
Traditional serrated adenoma	8/2,013 (0.4)	6/1,076 (0.6)
Any hyperplastic polyp	494/2,056 (24.0)	269/1,095 (24.6)
Microvesicular HP	304/2,038 (14.9)	153/1,087 (14.1)
Goblet cell–rich HP	215/2,033 (10.6)	115/1,084 (10.6)
HP not subclassified	65/2,021 (3.2)	43/1,079 (4.0)

[a]*N* = number with exam and sufficient pathology to determine outcome status.

versus none. However, there was no clear association between number of pregnancies or births and risk of SSLs.

A history of serrated polyps at baseline was the strongest risk factor for serrated polyps during follow-up [RR (95% CI) for 1 or 2+ serrated polyps at baseline vs. none: 1.91 (1.53–2.39) and 4.47 (3.34–6.00), respectively, $P_{trend} < 0.0001$; **Fig. 1B**]. Smoking status was also significantly associated with serrated polyps. Current smokers at baseline exhibited the highest risk of serrated polyps during follow-up for all serrated polyp subtypes [current smoker vs. never smoker RR (95% CI) for MVHPs: 1.58 (1.10–2.28); GCHPs: 2.36 (1.59–3.52); and SSLs: 1.70 (1.00–2.86); **Fig. 1C**]. We also observed a dose-related trend with respect to duration smoked and maximum amount smoked and HP occurrence, although a clear relationship between these variables and SSL risk was not demonstrated. Alcohol use was associated with an increased risk of HPs and MVHPs specifically [RR (95% CI) for >1 drink/day vs. none: 1.30 (1.01–1.69) and 1.61 (1.18–2.18), respectively], but was not associated with risk of GCHPs. Obesity was associated with an elevated risk of HPs, and GCHPs specifically [RR (95% CI) for BMI ≥30 vs. <25 kg/m^2: 1.31 (1.03–1.68) and 1.54 (1.07–2.21), respectively], although no clear association between obesity and either SSLs or MVHPs was identified.

Discussion

In this study using data from a large, multicenter, prospective study, we found that patients who reported smoking at baseline had an increased risk of incident serrated polyps of all types, and specifically HPs. Nonwhite participants had a lower risk of developing SSLs and MVHPs, but had a higher risk of developing GCHPs. Not surprisingly, those with a prior history of serrated polyps at their baseline colonoscopy exhibited an increased risk of developing serrated polyps and specifically SSLs during the follow-up period. We did not find evidence that baseline use of NSAIDs or aspirin reduced the risk of serrated polyps in contrast to prior work (9–11).

A limited number of studies have examined risk factors for serrated polyps, both in aggregate and for serrated polyp subtypes of more clinical importance, namely SSLs and TSAs. We did not find a relationship between age or sex and risk of serrated polyps, which is consistent with most prior literature demonstrating minimal or no increased risk of SSLs beyond age 50, and roughly equivalent risk of SSLs among men and women (4, 12, 13). This is not necessarily in conflict with findings that women are at higher risk of *BRAF*-mutated cancers than men (14, 15), because female sex is inversely associated with risk of conventional adenomas and *KRAS-mutated* cancers, which are more common.

A meta-analysis of modifiable risk factors for serrated polyps published in 2017 (comprising six studies with data on SSLs) found that smoking and alcohol intake were associated with SSLs in particular (16). In addition, an analysis of pooled data from two large cohort studies ($n = 141{,}143$) also found that smoking and alcohol (as well as BMI) were associated with serrated polyps (17). A prior study by our group found that smoking was associated with increased risk of serrated polyps, particularly in the left colon (18). Similar to these other reports, we found that smoking and alcohol were associated with serrated class polyps. In particular, we found that smoking (including smoking duration and maximum amount smoked) was most strongly related to HP occurrence, but this effect was attenuated for SSLs. The implications of this finding are not entirely clear, as HPs are generally not thought to be premalignant lesions.

Smoking has been associated with serrated pathway cancers as well as polyps. Studies of invasive colorectal cancer have consistently identified a stronger relationship between cigarette smoking and risk of MSI, CIMP, and/or *BRAF*-mutated cancers compared with conventional (*WNT*/*KRAS* driven) cancers (19, 20). Although the reasons for this are not entirely clear, cigarette smoke has direct immunomodulatory effects in the colon, which promote Th1 inflammation and impede T-cell memory capacity (21–23). Smoking may also increase immune checkpoint expression, thereby perhaps decreasing immune surveillance in early colorectal carcinogenesis (24).

Regarding race, our finding that black individuals appear to be at lower risk of SSLs (and conversely that white individuals are at higher risk of SSLs) is also consistent with prior work (10, 25–28). Reasons for this finding are uncertain. As race is largely a social construct, it is possible that this relationship is confounded by other factors such as colonoscopy quality or socioeconomic status. However, a prior study demonstrated that even within a low-income and uninsured colonoscopy screening population, black individuals were still at lower risk of serrated polyps, suggesting that socioeconomic status alone does not explain these differences (29). One prior study found that higher levels of education were associated with serrated polyps (and SSLs specifically; ref. 30), but we did not see a clear association between education levels and serrated polyp outcomes in our analysis. The contrasting associations between race and MVHPs and GCHPs is

Table 3. Association of selected personal characteristics and serrated polyp outcomes.

Characteristic	Any serrated polyp RR (95% CI)	Sessile serrated lesion RR (95% CI)	Any hyperplastic polyp RR (95% CI)	Microvesicular HP RR (95% CI)	Goblet cell–rich HP RR (95% CI)
Age					
<55	Reference	Reference	Reference	Reference	Reference
55–59	1.11 (0.89–1.40)	0.94 (0.59–1.50)	1.10 (0.87–1.40)	1.33 (1.02–1.75)	0.80 (0.57–1.12)
60–64	1.18 (0.92–1.51)	1.48 (0.95–2.32)	1.13 (0.87–1.47)	1.25 (0.91–1.73)	0.89 (0.63–1.26)
≥65	1.17 (0.91–1.50)	1.29 (0.81–2.07)	1.05 (0.81–1.37)	1.08 (0.79–1.47)	1.04 (0.73–1.48)
P_{trend}	0.16	0.11	0.57	0.50	0.91
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	1.02 (0.84–1.24)	0.86 (0.59–1.26)	1.01 (0.83–1.25)	1.03 (0.80–1.31)	0.95 (0.71–1.27)
Race					
White	Reference	Reference	Reference	Reference	Reference
Black	0.88 (0.64–1.22)	0.40 (0.16–0.99)	1.08 (0.78–1.49)	0.63 (0.42–0.96)	1.83 (1.23–2.72)
Other	1.06 (0.67–1.66)	0.19 (0.03–1.38)	1.30 (0.82–2.05)	0.57 (0.29–1.14)	1.38 (0.70–2.71)
Education					
<High school graduate	1.20 (0.68–2.11)	2.32 (0.90–5.98)	1.14 (0.63–2.03)	1.65 (0.85–3.21)	0.64 (0.27–1.57)
High school graduate	Reference	Reference	Reference	Reference	Reference
Some college	0.92 (0.70–1.21)	1.32 (0.78–2.25)	0.92 (0.69–1.21)	1.08 (0.77–1.50)	0.69 (0.49–0.98)
Graduate school	0.91 (0.67–1.24)	1.49 (0.82–2.70)	0.82 (0.60–1.13)	0.97 (0.67–1.42)	0.62 (0.41–0.94)
P_{trend}	0.35	0.72	0.13	0.28	0.10
Body mass index					
<25 kg/m^2	Reference	Reference	Reference	Reference	Reference
25–29.9 kg/m^2	0.97 (0.77–1.23)	0.87 (0.56–1.34)	1.00 (0.78–1.29)	0.86 (0.64–1.15)	1.43 (1.00–2.03)
≥30 kg/m^2	1.19 (0.94–1.51)	0.75 (0.48–1.19)	1.31 (1.03–1.68)	1.15 (0.87–1.54)	1.54 (1.07–2.21)
P_{trend}	0.08	0.22	0.01	0.15	0.03
Physical activity level					
Low	Reference	Reference	Reference	Reference	Reference
Medium	0.93 (0.73–1.18)	0.73 (0.47–1.14)	1.11 (0.86–1.43)	1.11 (0.82–1.49)	0.93 (0.66–1.30)
High	0.94 (0.75–1.18)	0.75 (0.49–1.14)	1.05 (0.83–1.34)	1.09 (0.82–1.45)	0.92 (0.67–1.26)
P_{trend}	0.65	0.23	0.79	0.60	0.61
Smoking status					
Never	Reference	Reference	Reference	Reference	Reference
Former	1.60 (1.32–1.95)	1.01 (0.69–1.48)	1.71 (1.39–2.10)	1.77 (1.38–2.26)	1.77 (1.33–2.36)
Current	1.74 (1.28–2.35)	1.70 (1.00–2.86)	1.86 (1.37–2.52)	1.58 (1.10–2.28)	2.36 (1.59–3.52)
P_{trend}	<0.0001	0.15	<0.0001	<0.0001	<0.0001
Pack years					
0	Reference	Reference	Reference	Reference	Reference
>0 to 13	1.51 (1.17–1.95)	1.06 (0.64–1.75)	1.57 (1.20–2.05)	1.75 (1.29–2.37)	1.56 (1.06–2.29)
>13 to 34	1.49 (1.16–1.92)	1.54 (0.98–2.42)	1.49 (1.14–1.95)	1.48 (1.08–2.03)	1.68 (1.16–2.42)
>34	1.91 (1.48–2.45)	0.88 (0.52–1.50)	2.21 (1.70–2.87)	1.94 (1.42–2.64)	2.63 (1.88–3.68)
P_{trend}	<0.0001	0.70	<0.0001	<0.0001	<0.0001
Maximum amount smoked for 1+ year					
0	Reference	Reference	Reference	Reference	Reference
>0 to < 1 pack	1.41 (1.08–1.84)	1.39 (0.84–2.29)	1.37 (1.04–1.81)	1.31 (0.95–1.81)	1.93 (1.33–2.80)
1 pack	1.71 (1.35–2.16)	1.11 (0.68–1.80)	1.84 (1.44–2.35)	1.89 (1.42–2.52)	1.75 (1.24–2.47)
>1 pack	1.73 (1.33–2.25)	1.00 (0.61–1.63)	1.98 (1.51–2.60)	1.89 (1.37–2.62)	2.07 (1.44–2.96)
P_{trend}	<0.0001	0.84	<0.0001	<0.0001	<0.0001
Duration smoked					
0	Reference	Reference	Reference	Reference	Reference
>0 to 15 years	1.51 (1.16–1.97)	1.17 (0.72–1.89)	1.60 (1.22–2.11)	1.76 (1.29–2.40)	1.40 (0.93–2.11)
16–34 years	1.56 (1.24–1.96)	1.08 (0.68–1.72)	1.67 (1.31–2.12)	1.68 (1.26–2.23)	1.90 (1.38–2.61)
>34 years	1.98 (1.49–2.63)	1.25 (0.73–2.14)	2.10 (1.57–2.82)	1.78 (1.26–2.51)	2.76 (1.89–4.02)
P_{trend}	<0.0001	0.44	<0.0001	<0.0001	<0.0001
Baseline alcohol use					
None	Reference	Reference	Reference	Reference	Reference
0.1–1 drink/day	1.09 (0.88–1.34)	1.20 (0.79–1.81)	1.06 (0.85–1.33)	1.29 (0.98–1.70)	0.94 (0.68–1.29)
>1 drink/day	1.17 (0.92–1.50)	1.05 (0.65–1.70)	1.30 (1.01–1.69)	1.61 (1.18–2.18)	1.10 (0.77–1.57)
P_{trend}	0.24	0.89	0.03	0.005	0.44
Baseline aspirin use					
None	Reference	Reference	Reference	Reference	Reference
<1 day/week	0.90 (0.68–1.19)	1.37 (0.82–2.27)	0.84 (0.62–1.13)	0.73 (0.50–1.06)	0.79 (0.52–1.21)
1–6 days/week	1.04 (0.75–1.45)	1.00 (0.50–1.99)	1.06 (0.74–1.50)	1.08 (0.72–1.62)	0.82 (0.50–1.33)
7 days/week	1.21 (0.99–1.49)	1.41 (0.93–2.13)	1.15 (0.93–1.43)	1.09 (0.85–1.39)	1.28 (0.95–1.72)
P_{trend}	0.06	0.14	0.16	0.40	0.12

(Continued on the following page)

Table 3. Association of selected personal characteristics and serrated polyp outcomes. (Cont'd)

Characteristic	Any serrated polyp RR (95% CI)	Sessile serrated lesion RR (95% CI)	Any hyperplastic polyp RR (95% CI)	Microvesicular HP RR (95% CI)	Goblet cell–rich HP RR (95% CI)
Baseline non-aspirin NSAID use					
None	Reference	Reference	Reference	Reference	Reference
<1 day/week	1.12 (0.91–1.37)	0.91 (0.61–1.34)	1.14 (0.92–1.42)	1.15 (0.89–1.49)	1.21 (0.90–1.63)
1–6 days/week	1.30 (1.00–1.68)	1.14 (0.71–1.84)	1.33 (1.01–1.75)	1.44 (1.05–1.99)	1.17 (0.81–1.71)
7 days/week	0.89 (0.62–1.27)	0.48 (0.20–1.13)	1.03 (0.71–1.49)	1.06 (0.68–1.64)	1.01 (0.61–1.68)
P_{trend}	0.46	0.43	0.18	0.13	0.59
Baseline advanced adenoma					
No	Reference	Reference	Reference	Reference	Reference
Yes	1.03 (0.82–1.28)	1.49 (1.01–2.20)	0.96 (0.76–1.21)	1.16 (0.89–1.51)	0.69 (0.49–0.98)
Baseline serrated polyp[a]					
0	Reference	Reference	Reference	Reference	Reference
1	1.91 (1.53–2.39)	1.94 (1.26–2.99)	1.81 (1.43–2.29)	1.78 (1.35–2.34)	1.77 (1.27–2.46)
2+	4.47 (3.34–6.00)	3.32 (2.08–5.30)	4.16 (3.10–5.58)	4.10 (3.02–5.56)	3.92 (2.77–5.55)
P_{trend}	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Baseline SSL or PSP[b]					
No	Reference	Reference	Reference	Reference	Reference
Yes	2.36 (1.75–3.18)	3.11 (1.97–4.93)	1.84 (1.35–2.52)	2.02 (1.43–2.85)	1.74 (1.15–2.64)

Note: Each serrated polyp phenotype was investigated in a separate GEE model, adjusted for age, sex, center [grouped geographically into southeast (Georgia, North Carolina, South Carolina, and Puerto Rico), north (Ohio, New Hampshire, Iowa, and Minnesota), and west (Colorado, Texas, and California)], race (white, black, other), study phase (treatment, observational), vitamin D study treatment (placebo, active), calcium study treatment (placebo, active—this includes women who elected to receive calcium and were not randomized to it), and either number of serrated polyps at baseline (0, 1, 2+) for any serrated polyp and hyperplastic polyp outcomes or baseline SSL/right-sided serrated polyp (no, yes) for SSL outcome.

Abbreviations: PSP, proximal serrated polyp; SSL, sessile serrated lesion.

[a]Not adjusted for number of serrated polyps at baseline.

[b]Not adjusted for SSL or proximal serrated polyps at baseline.

somewhat puzzling. Interestingly, this finding has also been reported by other researchers as well. In a single-center US cross-sectional study of over 3,500 patients undergoing colonoscopy, Qazi and colleagues found that compared with white participants, black participants were at a decreased risk for MVHPs but an increased risk of GCHPs [OR (95% CI) 0.55 (0.40–0.75) and 1.82 (1.37–2.45), respectively], a pattern consistent with our findings for risk of incident lesions (5). These polyps have different molecular features: MVHPs are frequently *BRAF* mutated, whereas GCHPs are not, and *KRAS* mutation is more common in GCHPs than MVHPs (31). This raises the possibility that differences in genetic ancestry (measured by race as a proxy) could explain why black individuals appeared to be at higher risk of GCHPs, despite a lower risk of MVHPs and SSLs. Indeed, *KRAS* mutation rates appear to be 10% to 15% higher in colorectal cancers among black patients compared with white patients (32–36). Furthermore, differences in immune responses have been observed in black individuals that may influence the risk, growth, and pathway trajectory of serrated neoplasia (37–41). Parenthetically, multiple studies have shown that black individuals have a higher prevalence of proximal (nonserrated) adenomas and advanced adenomas compared with white individuals, which suggests possible biologic differences related to conventional pathway lesions as well (29, 42–44). These findings could be important to explore along with mutational profiles of different polyp types in future studies.

Similar to others, we found that prior history of serrated polyps predicts future occurrence (45, 46). In contrast, presence of advanced adenomas at baseline did not predict occurrence of serrated polyps during follow-up in this study. These findings support the concept that the traditional adenoma-carcinoma sequence and serrated pathway(s) are distinct, with differing risk factors, although patients can certainly harbor both types of polyps (12).

We previously published an analysis of the treatment effects of calcium and vitamin D on serrated polyp outcomes (47). That study found that calcium and the combination of calcium and vitamin D led to increased risk of SSLs, particularly in the later years of the study. Because of this, we carefully controlled for treatment assignment in this study, so as to isolate nontreatment participant characteristics associated with the development of serrated polyps and particularly SSLs. Furthermore, because treatment was randomized, this is unlikely to be a significant confounder of our results.

Strengths of this study include the use of data from a relatively large number of participants from a multicenter trial. We examined incident serrated polyps within a prospective trial, which is an advantage with respect to studying causal associations compared with cross-sectional studies. Although pathology interpretation of serrated polyps can be a pitfall of epidemiology studies of this kind, we performed central path review by an expert GI pathologist who helped author the WHO criteria for serrated polyps. Furthermore, the fact that participants were included from multiple geographically dispersed sites across the US contributes to the external validity of our results. However, we had relatively few outcomes, particularly with respect to SSLs and TSAs, which is common among studies of these lesions given their relatively low incidence compared with conventional adenomas. We were unable to perform detailed analyses on TSA risk factors given their rarity. We aimed to perform a broad analysis of possible serrated polyp risk factors, but given the multiple comparisons performed, it is possible that some positive associations occurred by chance alone. Despite use of multivariable modeling, residual confounding is also possible.

Multiple studies have demonstrated variable detection of serrated polyps and SSLs specifically (4, 48), and this could have also affected

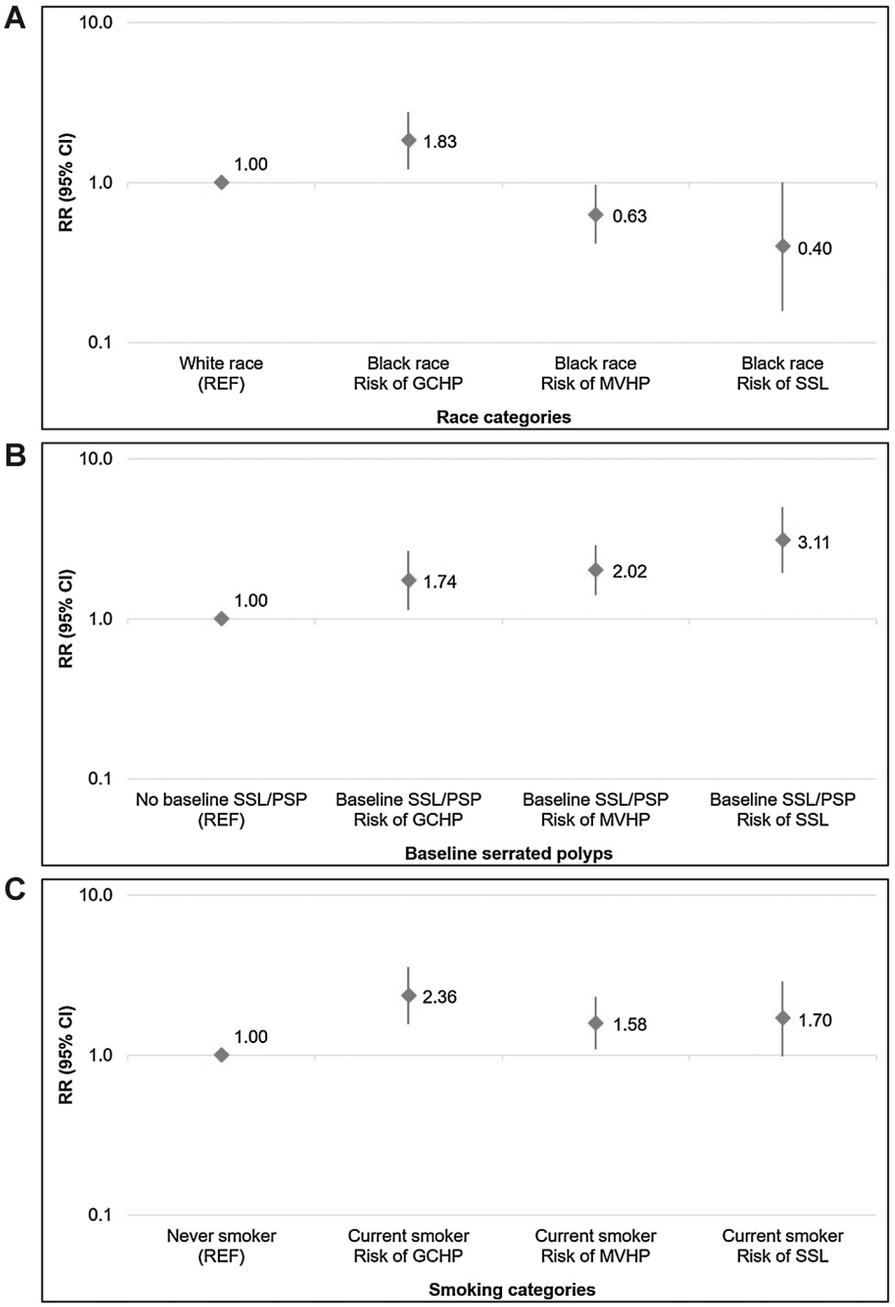

Figure 1.
Risk of different serrated polyp subtypes by race (**A**), presence of sessile serrated lesions or proximal serrated polyps on baseline exam (**B**), and smoking status (**C**). GCHP, goblet cell hyperplastic polyp; MVHP, microvesicular hyperplastic polyp; REF, referent category; SSL, sessile serrated lesion.

our study. If SSLs were underdetected at baseline, lesions detected during follow-up would not be truly "incident" but rather pre-existing lesions. This should not materially affect our results regarding risk factor associations. If SSLs were underdetected during follow-up (a form of measurement bias), it could bias results though imperfect sensitivity of outcome measures is generally thought to have minimal effects on risk ratios when specificity is high (49). We used local pathologist diagnoses for baseline results, which could have been inaccurate given known variability in pathology diagnosis of serrated lesions among non-expert pathologists (50). We attempted to minimize the potential impact of imperfect baseline diagnoses of serrated polyps by combining SSLs with proximal hyperplastic polyps in our analyses. Finally, all participants in the VCPPS trial had to have at least one adenomatous polyp on baseline exam, so this study did not include patients with isolated serrated polyps. Prior research suggests that roughly half of patients with SSLs have synchronous conventional adenomas (51). Although we have no reason to believe that risk factor associations for serrated class polyps would be different in this group, it is possible that this feature of the study design impacts the external validity of our findings.

In conclusion, using data from a large, multicenter prospective trial, we found evidence that smoking, presence of serrated polyps at baseline, and white race were associated with incident SSLs. We also

Table 4. Association of selected reproductive variables and serrated polyp outcomes.

Characteristic	Any serrated polyp RR (95% CI)	Sessile serrated lesion RR (95% CI)	Any hyperplastic polyp RR (95% CI)	Microvesicular HP RR (95% CI)	Goblet cell–rich HP RR (95% CI)
Menopausal status					
Pre	Reference	Reference	Reference	Reference	Reference
Post	1.01 (0.68–1.48)	1.32 (0.61–2.85)	0.89 (0.60–1.33)	1.07 (0.66–1.74)	0.67 (0.38–1.16)
Baseline HRT status					
Never	Reference	Reference	Reference	Reference	Reference
Former	1.05 (0.76–1.47)	2.04 (1.11–3.75)	0.92 (0.65–1.31)	1.06 (0.70–1.59)	0.64 (0.38–1.07)
Current	0.69 (0.45–1.05)	0.44 (0.13–1.53)	0.66 (0.42–1.03)	0.63 (0.36–1.11)	0.66 (0.34–1.29)
P_{trend}	0.13	0.89	0.07	0.12	0.15
Ever used contraceptives					
No	Reference	Reference	Reference	Reference	Reference
Yes	0.97 (0.66–1.42)	2.12 (0.84–5.36)	0.79 (0.53–1.18)	1.04 (0.64–1.71)	0.72 (0.41–1.27)
Age at menarche					
11	Reference	Reference	Reference	Reference	Reference
12	1.10 (0.72–1.69)	1.92 (0.77–4.76)	1.09 (0.69–1.72)	1.27 (0.74–2.20)	0.91 (0.47–1.74)
13	1.12 (0.75–1.67)	1.51 (0.61–3.77)	1.04 (0.68–1.61)	1.35 (0.80–2.29)	1.13 (0.63–2.02)
≥14	0.74 (0.45–1.19)	0.78 (0.25–2.40)	0.77 (0.46–1.29)	0.89 (0.47–1.70)	0.88 (0.44–1.76)
P_{trend}	0.29	0.61	0.33	0.89	0.95
Number of pregnancies					
0	Reference	Reference	Reference	Reference	Reference
1	1.30 (0.68–2.46)	0.65 (0.18–2.33)	1.81 (0.92–3.58)	1.08 (0.46–2.54)	3.44 (1.20–9.86)
2	1.48 (0.85–2.58)	0.98 (0.35–2.73)	1.92 (1.06–3.48)	1.60 (0.82–3.13)	2.52 (0.94–6.78)
3	1.33 (0.76–2.31)	0.85 (0.30–2.42)	1.63 (0.90–2.97)	1.23 (0.61–2.49)	2.44 (0.93–6.42)
≥4	1.61 (0.92–2.81)	0.60 (0.20–1.78)	2.24 (1.23–4.08)	1.79 (0.91–3.53)	3.34 (1.27–8.75)
P_{trend}	0.16	0.36	0.05	0.14	0.07
Number of live births					
0	Reference	Reference	Reference	Reference	Reference
1	1.50 (0.87–2.58)	1.15 (0.39–3.39)	1.67 (0.94–2.94)	0.78 (0.37–1.65)	2.20 (0.99–4.88)
2	1.32 (0.84–2.09)	1.10 (0.44–2.76)	1.50 (0.93–2.43)	1.14 (0.65–1.98)	1.53 (0.75–3.11)
3	1.39 (0.84–2.28)	1.05 (0.38–2.93)	1.41 (0.83–2.38)	1.09 (0.60–2.00)	1.37 (0.63–2.97)
≥4	1.86 (1.05–3.27)	0.76 (0.23–2.52)	2.24 (1.24–4.04)	1.78 (0.92–3.46)	2.16 (0.95–4.89)
P_{trend}	0.08	0.58	0.05	0.11	0.28

Note: Analysis limited to female participants. Each characteristic is run in a separate GEE model, adjusted for age, center [grouped geographically into southeast (Georgia, North Carolina, South Carolina, and Puerto Rico), north (Ohio, New Hampshire, Iowa, and Minnesota), and west (Colorado, Texas, and California), race (white, black, other), study phase (treatment, observational), vitamin D study treatment (placebo, active), calcium study treatment (placebo, active—this includes women who elected to receive calcium and were not randomized to it)], and either number of serrated polyps at baseline (0, 1, 2+) for any serrated polyp and hyperplastic polyp outcomes or baseline SSL/right-sided serrated polyp (no, yes) for SSL outcome. Men were included in the models and treated as a separate group; they were dropped from the model to obtain *P* for trend.
Abbreviation: HRT, hormone replacement therapy.

saw that black participants were at higher risk of GCHPs, and white participants were at higher risk of MVHPs, for reasons that are unclear. Additional research is needed to explore the underlying mechanisms for these findings. Understanding these risk factors could allow for better risk stratification of patients undergoing colorectal cancer screening, and could potentially guide screening test selection, as serrated class polyps are less-well detected by noninvasive screening tests (52). Furthermore, risk factor associations for SPs differ from known risk factors for conventional adenomas, which supports the concept of etiologic heterogeneity of colorectal cancer.

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Authors' Contributions

S.D. Crockett: Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing. **E.L. Barry:** Conceptualization, data curation, formal analysis, methodology, writing–original draft, project administration, writing–review and editing. **L.A. Mott:** Data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **D.C. Snover:** Investigation, writing–review and editing. **K. Wallace:** Writing–review and editing. **J.A. Baron:** Conceptualization, resources, supervision, funding acquisition, investigation, methodology, writing–review and editing.

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