Smoking and Other Risk Factors in Individuals With Synchronous Conventional High-Risk Adenomas and Clinically Significant Serrated Polyps

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- BACKGROUND AND AIMS:** Serrated polyps (SPs) and conventional high-risk adenomas (HRAs) derive from two distinct biological pathways but can also occur synchronously. Adults with synchronous SPs and adenomas have been shown to be a high-risk group and may have a unique risk factor profile that differs from adults with conventional HRAs alone. We used the population-based New Hampshire Colonoscopy Registry (NHCR) to examine the risk profile of individuals with synchronous conventional HRAs and SPs.
- METHODS:** Our study population included 20,281 first time screening colonoscopies from asymptomatic NHCR participants 40 years or older between 2004–15. Exams were categorized by findings: (1) normal, (2) HRA only (adenomas $\geq$ 1 cm, villous, high grade dysplasia, multiple adenomas ($>$ 2) and adenocarcinoma), (3) clinically significant SP (CSSP) only (any hyperplastic polyp $\geq$ 1 cm, sessile serrated adenomas/polyps or traditional serrated adenomas), and (4) synchronous HRA + CSSP. Risk factors examined included exposure of interest, smoking (never, past, and current/pack years), as well as age, sex, alcohol, education, and family history of colorectal cancer (CRC). Multivariable unconditional logistic regression tested the relation of risk factors with having synchronous HRA + CSSP versus having a normal exam or HRA alone.
- RESULTS:** Among NHCR participants with 18,354 screening colonoscopies (with complete smoking, sex, bowel preparation data, and adequate preparation) there were 16,495 normal; 1309 HRA alone; 461 CSSP alone, and 89 synchronous HRA + CSSP. Current smoking was associated with an almost threefold increased risk for HRA or CSSP, and an eightfold risk for synchronous HRA + CSSP (aOR = 8.66; 95% CI: 4.73–15.86) compared to normal exams. Adults with synchronous HRA + CSSP were threefold more likely to be current smokers than those with HRA alone (aOR = 3.27; 95% CI: 1.74–6.16).
- CONCLUSIONS:** Our data suggest that current smokers may be at a higher risk for synchronous CSSP + HRA even when compared to having HRA alone.

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INTRODUCTION

Serrated polyps (SPs) are an important focus of colorectal cancer (CRC) screening, accounting for up to 30% of all CRCs [1]. Over the last decade, there has been an increasing awareness about lesions in the serrated pathway. These lesions may be detected in a large proportion of screening exams [2]. SPs represent a heterogeneous group of polyps that includes sessile serrated adeno-

mas/polyps (SSA/P), traditional serrated adenomas (TSA), and hyperplastic polyps (HP). [1, 3–7] While diminutive HPs are believed to have no dysplastic potential, TSAs and SSAs can both exhibit dysplasia. Unfortunately, distinguishing benign HPs from the more dangerous SSA/Ps is challenging due to morphological overlap and issues with inter-observer reproducibility [8–10]. Factors predictive of SSA/Ps include size, location, and histology

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[11, 12]. Based on these factors as well as surveillance recommendations from an expert panel [13] clinically significant serrated polyps (CSSP), may include any SSA/P, TSA, and any hyperplastic polyp ≥ 1 cm anywhere in the colon or potentially any hyperplastic polyp > 5 mm in the proximal colon only. Thus, until histologic classification of SSA/Ps among pathologists becomes more reliable, CSSPs may be a good surrogate for SSA/Ps.

SPs and conventional adenomas can occur synchronously in the same individual, and published data suggest that adults with synchronous SPs and conventional adenomas may represent a different phenotype than adults with high-risk conventional adenomas (HRA) or SPs alone. For example, adults with conventional HRA and CSSPs have a higher risk for metachronous HRA than adults with HRA alone [14, 15]. Identifying risk factors in individuals with CSSPs as well as those with synchronous HRA and CSSP is important for the modification of potentially mutable risk factors such as smoking as well as for tailoring screening recommendations based on risk factors.

Many studies have examined risk factors in individuals with SPs or adenomas alone [16–25]. Although SPs and adenomas derive from two distinct biological pathways, many of these studies show that smoking is a shared risk factor [16–21, 26–29]. It is not surprising that smoking is a particularly strong risk for SSA/P since smoking is linked with mutations observed in these lesions [30]. However, very few studies have examined the risk factor profile of individuals with synchronous HRAs and SPs [22, 25]. The few such studies evaluated non-screening individuals undergoing colonoscopy for symptoms or previous history of adenomas, and were therefore limited by selection bias [22, 25]. Another limitation of existing studies is the evaluation of risk factors for all SPs broadly, without accounting for subtypes. Since some subsets of SPs may have more clinical significance (i.e., risk of progressing to CRC) than others, evaluating risk factors without accounting for SP subtype is a significant limitation. Thus, examining the risk factors for specific clinically relevant subgroups, such as CSSP, may provide more useful data that could improve tailoring of screening guidelines based on risk profiles.

Our goal was to examine the risk profile of individuals with synchronous HRAs and CSSPs and compare them to those with normal exams, those with HRAs alone or CSSPs alone. To achieve sufficient sample size for examining the risk profile for each of these four groups, we used the large population-based New Hampshire Colonoscopy Registry (NHCR). Our hypothesis was that current smoking would be more strongly associated with having synchronous HRA and CSSP as compared to having HRA alone.

METHODS

The design and development of the NHCR is described in detail elsewhere. [31–33] Briefly, NHCR, founded in 2004, is a population-based, statewide registry collecting data from endoscopy sites throughout New Hampshire (NH). Prior to colonoscopy, consenting patients complete a self-administered patient questionnaire, which is a double sided one page form. The questionnaire, which has been used since the registry's inception in 2004

[34], collects data on demographic factors (e.g., age, sex, marital status, education), behaviors (e.g., smoking, alcohol intake, aspirin use, and exercise), and family history of CRC.

With respect to exam level data, the endoscopists complete the NHCR Procedure Form and the clinical endoscopy report immediately after the exam has been completed. The endoscopist may complete form unassisted or dictate the information to the endoscopy nurse. The endoscopist is responsible for completing both forms at the same time. The NHCR Procedure Form collects detailed information about the indication for screening colonoscopy, including screening exam (no symptoms or family history), screening exam for family history of polyp(s), or screening exam for family history of CRC with specification of first degree relative(s). Exams with any of the above screening indications were included in this analysis. Surveillance colonoscopies (personal history of CRC and/or personal history of polyps, surveillance exam for familial polyposis/HNPCC, or surveillance for IBD) and all diagnostic exams were not included in this analysis [35]. Other data collected include findings (location, size, and specific treatment of polyps, cancer, or other findings), type, and quality of bowel preparation, sedation medication, anatomical location reached during the procedure, withdrawal time, follow-up recommendations, and immediate complications.

The NHCR requests pathology reports for all colonoscopies with findings directly from the pathology laboratory used by each participating endoscopy facility. Trained NHCR staff Nabstrack and enter these pathology reports, including location, size, and histology of each polyp, into the NHCR database, linking individual polyp level data to information from the Procedure Form. [33] All data collection and study procedures were approved by the Committee for the Protection of Human Subjects at Dartmouth College (study #00015834), as well as by other relevant human subjects reviewing bodies at participating sites.

Cohort

Our analysis included screening colonoscopies (both average-risk and those with family history of CRC) included within the NHCR among patients 40 years or older from 1/04/2004 to 6/15/2015 at 27 endoscopy facilities, including hospitals, ambulatory surgery centers, and community practices across NH. We excluded exams performed for the indication of surveillance or diagnostic indications such as bleeding, change in bowel habits, or anemia. We also excluded exams with poor bowel preparation and incomplete exams, as well as exams with missing key variables: sex, smoking status (current, past, and never), and bowel preparation quality.

Outcome measures

From the screening colonoscopy cohort, we identified those with the following findings on colonoscopy: normal (no polyps or other pathology), HRAs alone, CSSPs alone, and synchronous HRAs + CSSPs. Normal exams had no findings including no adenomas or any SPs (HPs, SSA/Ps, or TSAs). Exams with HRA had at least one advanced adenoma (large (≥ 1 cm), adenoma with villous component, high grade dysplasia or adenocarcinoma) or at least 3 small (< 1 cm) tubular adenomas. By definition, exams with HRA alone had no CSSPs. In our database, size of polyps

were binned into <5 mm, 5–9 mm, and ≥ 1 cm. Thus, NHCR participants with CSSP alone had at least one large (≥ 1 cm) HP anywhere in the colon, or an SSA/P or TSA of any size and no adenomas. Last, those with synchronous HRA and CSSP had at least one HRA and one CSSP.

Exposure variable

The main exposure variable of interest was smoking status. Smoking was self-reported and categorized as never, past and current smoking. We also examined smoking exposure using cutoff exposures of 20 pack years (0 pack years, 1–19 pack years, and ≥ 20 pack years) as suggested by ACG CRC screening guidelines [36] for NHCR participants by smoking status classification (never, past, and current) and risk group.

Covariates

The covariates examined were age, sex, body mass index (BMI), family history of CRC (defined as at least one first-degree relative with CRC), aspirin use (never, any dose 1–2 times per week, any dose 3 or more times per week), educational level (high school or less, at least some college or more), marital status, exercise (never, light (1–2x per week or active lifestyle or 3 or more times per week), and alcohol intake (never, 1–8 servings per week, ≥ 9 servings per week). All variables were considered categorical except for age and BMI, which were used as continuous variables.

Analysis

We used descriptive statistics, χ^2 test for trend and Fisher's exact test to evaluate categorical variables. Wilcoxon rank sum and Mann-Whitney tests were used for non-parametric continuous variables. We performed univariate analyses and multivariable logistic regression models comparing predictors of HRA, CSSP, and HRA + CSSP on screening exam as compared to having a normal exam. We also compared predictors of having synchronous HRA + CSSP on screening colonoscopy as compared to having HRA alone. The multivariable model included all co-factors listed above; age (continuous), sex (M versus F), BMI (continuous), first degree relative with CRC (yes versus no), exercise (none versus light versus 3 or more times per week), aspirin use (never versus any dose 1–2 times per week and 3 or more times per week), education level (some college or more versus less education), and alcohol intake (never versus 1–8 servings per week versus 9 or more per week). For the multivariate analyses, we performed listwise deletion in which any person with missing non key variables was deleted from the model. The analyses were conducted in SPSS 25 (IBM NY).

To examine the possible effect of exam indication on the outcomes, we repeated the above analyses using data from all exams regardless of exam indication, in other words surveillance and diagnostic in addition to screening.

RESULTS

Population analyzed

In the NHCR database there were 28,184 first time screening colonoscopies in individuals 40 years or older. After excluding those

adults with low risk adenomas ($n=4365$), small HPs (<10 mm) ($n=3490$), HRA with 5–9 mm HPs ($n=48$), those with incomplete smoking ($n=928$), bowel preparation data (654) or poor bowel preparation ($n=290$) and missing sex ($n=55$), there were 18,354 exams in our analyses (16,495 with normal exams, 1309 with HRA only, 461 with CSSP only and 89 with HRA + CSSP). These data are shown in Figure 1. There were no significant differences for prevalent index findings between the sample included in our analyses ($n=18,354$) and the sample excluded based on missing data and poor bowel preparation ($n=1927$) (data not shown).

Baseline characteristics

The mean ($\pm$ SD) age was 55.5 (± 7.1) years, mean BMI was 27.8 (± 5.8), 57.8% were female and nearly all were Caucasian (96.1%). Nearly half (44.7%) of the participants were current or past smokers. Subject demographic and risk factor summary statistics stratified by colonoscopy findings are shown in Table 1.

With regards to smoking, individuals with HRA + CSSP were more likely to be current smokers (32.6%) than those with normal exams (7.7%) or those with HRA (18.0%) or those with CSSP (17.8%) alone ($p < 0.001$ for all comparisons). In addition, those with HRA + CSSP were more likely to have a 20 pack-year or greater exposure (58.0%) than those with normal exams (20.2%) or those with HRA (35.5%) or CSSP alone (32.7%) ($p < 0.001$ for all comparisons).

Fig. 1 Flow diagram showing exclusion of New Hampshire Colonoscopy Registry participants for current analysis

Table 1 Characteristics of 18,354 NHCR participants as stratified by colonoscopy findings

	Normal exam <i>N</i> = 16,495	HRA alone <i>N</i> = 1309	CSSP alone <i>N</i> =461	HRA+CSSP <i>N</i> =89
	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
Age in years (mean ± S.D.)	55.3 (±7.0)	57.1 (±7.9)	54.3 (±5.5)	57.5 (±7.7)
Sex (%male)	6661 (40.4)	818 (62.5)	196 (42.5)	64 (71.9)
Race (%caucasian)	(15,646) (96.1)	(<i>n</i> = 1245) (96.4)	443 (96.9)	81 (95.3)
Married	12,240 (76.7)	921 (72.5)	329 (73.8)	64 (74.4)
Mean BMI (mean ± S.D.)	27.6 (±5.8)	29.1 (±5.9)	28.7 (±6.2)	29.4 (±6.7)
Family history of CRC (First degree relative)	2299 (14.5)	207 (16.2)	79 (17.7)	14 (16.1)
Aspirin (any dose at least 3 times per week)	3984 (25.5)	319 (25.7)	85 (19.2)	28 (32.6)
Smoking				
Never	9338 (56.6)	559 (42.7)	222 (48.2)	25 (28.1)
Past	5890 (35.7)	517 (39.5)	156 (33.8)	35 (39.3)
Current	1267 (7.7)	233 (17.8)	83 (18.0)	29 (32.6)
Smoking exposure ≥ 20 pack years	3184 (20.2)	440 (35.5)	145 (32.7)	47 (58.0)
Smoking exposure pack years	9.1 (±16.8)	16.0 (±21.9)	13.7 (±19.7)	25.2 (±24.8)
Education (at least some college)	12,552 (78.3)	893 (70.0)	331 (74.4)	61 (71.8)
Alcohol use (nine or more drinks per week)	1745 (10.7)	211 (16.4)	55 (12.1)	15 (17.2)
Exercise (at least three times per week)	6657 (40.8)	391 (30.1)	152 (33.3)	29 (34.5)
Missing data: Age = (<i>n</i> =0), smoking status (<i>n</i> =0), sex = <i>n</i> =0, BMI (<i>n</i> =324), marital status (<i>n</i> =588), education (<i>n</i> =514), alcohol (<i>n</i> =264), education (<i>n</i> =929), aspirin use (<i>n</i> =954), family history (<i>n</i> =658), race (<i>n</i> =237), smoking (20 pack-year categories) (<i>n</i> =853), and exercise (<i>n</i> =190)				

Finally those with HRA + CSSP had a greater total pack-year smoking exposure (25.2 ± 24.8) than those with normal exams (9.1 ± 16.8) or those with HRA (16 ± 21.9) or CSSP alone (13.7 ± 19.7) ($p < 0.001$ for all comparisons). These data are in Table 1.

Predictors of endoscopic findings

Univariate analyses for the association between risk factors and exam findings are shown in Table 2. Multivariate analyses are shown in Table 3. After adjusting for key co-variables, current smoking was associated with an almost 3-fold increased risk for HRA (aOR = 2.82, 95% CI 2.35–3.39) or CSSP (aOR = 2.79, 95% CI 2.10–3.70), and an even greater risk (8 fold) for synchronous HRA and CSSP (aOR = 8.66 95% CI: 4.73–15.86) as compared to having a normal exam (no SPs or adenomas) (Table 3). Furthermore, adults with HRA and CSSP were more likely to be current smokers than those with HRA alone (aOR = 3.27 95% CI: 1.74–6.16). Higher BMI was associated with a higher risk for HRA (aOR = 1.03, 95% CI 1.02–1.04), CSSP (aOR = 1.03, 95% CI 1.00–1.04) as well as synchronous HRA + CSSP (aOR = 1.06, 95% CI 1.02–1.10). Older age was a risk factor for HRA (aOR = 1.05, 95% CI 1.04–1.06) and HRA + CSSP (aOR = 1.06, 95% CI 1.03–1.09). Female sex was associated with a lower risk of HRA alone, (aOR = 0.41, 95% CI 0.36–0.47) and synchronous HRA + CSSP (aOR = 0.28, 95% CI 0.17–0.48).

Light exercise (aOR = 0.79, 95% CI 0.64–0.97) and exercise at least 3 ×/week (aOR = 0.66, 95% CI 0.52–0.83) were associated with a reduced risk of HRA compared to normal exam. Taking

any dose of aspirin 3 or more times per week was associated with a reduced risk of HRA (aOR = 0.68, 95% CI 0.59–0.80) and CSSP (aOR = 0.71, 95% CI 0.53–0.94). Having at least one first degree relative with CRC was associated with an increased risk for HRA (aOR = 1.23, CI 95% 1.04–1.46).

After re-examining our data with all exams regardless of indication, we observed similar results to those with screening as an indication. Specifically, current smoking was associated with an approximately ninefold increased risk for HRA + CSSP versus normal exams (aOR = 9.43 95% CI: 5.66–15.72) and an adjusted risk of 3.80 (2.23–6.47) as compared to HRA only. These data are shown in supplementary tables 1 and 2.

DISCUSSION

The goal of this analysis was to examine risk factors associated with having synchronous CSSP + HRA, with a particular focus on smoking. Published data suggest that individuals with both lesions may be at high risk for metachronous conventional high-risk adenomas and thus perhaps for developing CRC [15]. In this analysis, we observed that adults undergoing colonoscopy found to have synchronous HRA and CSSPs were more likely to be current smokers when compared to those who had normal exams without adenomas or SPs. In fact, smoking had a significantly stronger association in individuals with synchronous HRAs and CSSPs when compared to even those with HRA on screening colonoscopy. The finding regarding smoking and individuals with

Table 2 Univariate analysis of risk Factors for adults with HRA only ($n=1309$), CSSP only ($n=461$) and both HRA and CSSP ($n=89$) (reference = adults with normal exam ($n=16,495$))

Risk factors	HRA alone vs. normal	CSSP alone vs. normal	Synchronous HRA+CSSP vs. normal	Synchronous HRA+CSSP vs. HRA alone
	Unadjusted OR (95% CI)	Unadjusted OR (95% CI)	Unadjusted OR (95% CI)	Unadjusted OR (95% CI)
Age (continuous)	1.03 (1.02–1.04)	0.98 (0.96–0.99)	1.04 (1.01–1.07)	1.01 (0.98–1.03)
Sex (F versus M)	0.41 (0.36–0.46)	0.92 (0.76–1.10)	0.27 (0.17–0.42)	0.65 (0.50–1.05)
BMI (continuous)	1.04 (1.03–1.05)	1.03 (1.01–1.04)	1.04 (1.01–1.08)	1.01 (0.97–1.04)
Family history (First degree relative)	1.23 (1.04–1.46)	1.27 (0.99–1.62)	1.13 (0.64–12.01)	0.99 (0.55–1.79)
Smoking				
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Past	1.47 (1.29–1.66)	1.11 (0.91–1.11)	2.22 (1.32–3.71)	1.51 (0.89–2.56)
Current	3.07 (2.61–3.62)	2.76 (2.12–3.57)	8.55 (4.99–14.64)	2.78 (1.60–4.85)
Aspirin use				
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1–2/week	1.29 (1.13–1.48)	1.07 (0.86–1.33)	2.12 (1.30–2.71)	1.71 (1.00–2.92)
>2/week	1.13 (0.98–1.30)	0.72 (0.54–0.92)	2.07 (1.20–3.58)	1.84 (1.05–3.23)
Activity/exercise				
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Light	0.73 (0.60–0.88)	0.80 (0.58–1.11)	0.93 (0.42–2.05)	1.27 (0.56–2.87)
3×/week	0.48 (0.39–0.58)	0.60 (0.42–0.84)	0.72 (0.31–1.64)	1.51 (0.65–3.51)
Alcohol				
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1–8/week	0.73 (0.62–0.87)	1.04 (0.85–1.27)	0.92 (0.57–1.47)	1.27 (0.78–2.06)
1–8/week	0.53 (0.45–0.63)	1.16 (0.85–1.59)	1.65 (0.89–3.06)	1.21 (0.64–2.29)
Education (some college vs less)	0.65 (0.57–0.73)	0.81 (0.65–1.00)	0.71 (0.44–1.13)	1.09 (0.67–1.77)

HRA high-risk adenomas, CSSP clinically significant serrated Polyp

synchronous HRA and CSSPs has not been previously described in published studies examining risk factors in people with both conventional adenomas and SPs [29].

One case control study [22], observed a trend ($p=0.07$) for a stronger association for smoking and having both SPs and adenomas as compared to adenomas alone. However, that analysis examined all adenomas as opposed to more clinically important lesions like HRAs, and included adults presenting for surveillance of prior polyps and symptoms. The inclusion of these non-screening exams could have introduced a selection bias. Finally, that study examined all SPs as one group as opposed to distinguishing clinically important subgroups as our analysis did. Another study examining pooled data from intervention trials found that current smoked had an increased risk for having SPs and adenomas [25]. This analysis was also conducted in non-screening adults and did not examine HRA or subgroups of potentially clinically significant SPs [25]. In addition, they did not directly compare the risk factor profile of those with adenomas to those with synchronous adenomas and

SPs. Finally a study that combined data from the Nurses' Health Study (NHS), the NHS2 and the Health Professionals Follow-up Study observed that smoking was strongly associated with adults who had synchronous SPs and conventional adenomas. Like the above studies, that analysis did not exclude diagnostic exams, and did not examine high-risk adenomas or SPs [37].

In contrast, this current study included only asymptomatic individuals presenting for screening colonoscopy and examined risk factors for synchronous HRAs and CSSPs. We defined CSSP based on published data regarding classification of SPs [11, 12] as well as recommendations from an expert panel [13]. Specifically, we included those SPs that were classified as SSA/Ps or TSAs as well as those HPs that were large (≥ 1 cm). The latter polyp-based factors have been shown to be predictive of SPs being classified as SSA/Ps in published studies [11, 12]. Thus, the CSSPs in our sample represent SPs that are more likely to be SSA/Ps than the more benign HPs and may provide more useful data than studies examining all SPs a group.

Table 3 Multivariate analyses of risk factors for adults with HRA only ($n=1309$), CSSP only ($n=461$) and both HRA and CSSP ($n=89$) (reference = adults with normal exam ($n=16,495$))

Risk factors	HRA alone vs. normal	CSSP alone vs. normal	Synchronous HRA + CSSP vs. normal	Synchronous HRA + CSSP vs. HRA alone
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Age (continuous)	1.05 (1.04–1.06)	0.99 (0.97–1.00)	1.06 (1.03–1.09)	1.02 (0.98–1.05)
Sex (F versus M)	0.41 (0.36–0.47)	0.92 (0.74–1.13)	0.28 (0.17–0.48)	0.65 (0.38–1.11)
BMI (continuous)	1.03 (1.02–1.04)	1.03 (1.00–1.04)	1.06 (1.02–1.10)	1.03 (0.99–1.08)
Family history (First degree relative)	1.23 (1.04–1.46)	1.24 (0.95–1.61)	01.18 (0.63–2.20)	0.95 (0.50–1.81)
Smoking				
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Past	1.29 (1.12–1.48)	1.10 (0.87–1.38)	1.85 (1.05–3.26)	1.39 (0.78–2.48)
Current	2.82 (2.35–3.39)	2.79 (2.10–3.70)	8.66 (4.73–15.86)	3.27 (1.74–6.16)
Aspirin use				
Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1–2/week	1.14 (0.98–1.32)	1.08 (0.86–1.35)	1.68 (0.97–2.94)	1.43 (0.81–2.54)
>2/week	0.68 (0.58–0.80)	0.71 (0.53–0.94)	1.03 (0.57–1.88)	1.49 (0.80–2.79)
Activity/exercise				
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Light	0.79 (0.64–0.97)	0.95 (0.65–1.32)	1.40 (0.58–3.41)	1.65 (0.67–4.02)
3×/week	0.66 (0.52–0.83)	0.76 (0.52–1.13)	1.54 (0.59–4.02)	2.49 (0.95–6.49)
Alcohol				
None	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1–8/week	0.84 (0.73–0.97)	1.15 (0.92–1.44)	1.01 (0.61–1.70)	1.19 (0.70–2.04)
>8/week	1.09 (0.90–1.32)	1.29 (0.92–1.80)	1.21 (0.62–2.36)	1.07 (0.53–2.15)
Education (some college vs less)	0.87 (0.75–0.99)	0.94 (0.74–1.19)	1.07 (0.64–1.81)	1.16 (0.68–1.97)

HRA high-risk adenomas, CSSP clinically significant serrated Polyp
Cases included in the models: (1) HRA versus normal; 1151 HRA and 14,255 normal, (2) CSSP versus normal; 403 CSSP and 14255 normal, (3) HRA + CSSP versus normal; 77 HRA + CSSP and 14255 Normal, (4) HRA + CSSP versus HRA alone; 1151 HRA and 77 HRA + CSSP

Our findings for individuals with HRA alone or CSSP alone support previously published studies regarding smoking. We observed that smoking was strongly associated with HRAs [3, 17–19, 21]. Smoking was also strongly associated with CSSP in our analysis. Smoking has been linked with an elevated risk for lesions in the serrated pathway [26], especially sessile serrated adenomas/polyps [16, 20]. In fact, two case control studies demonstrated that smoking was associated with a higher risk for SSA/Ps than for adenomas [20, 23]. For both pathways, the link between polyps and smoking has biologic plausibility. Smoking cigarettes is associated with exposure to many carcinogens including aromatic amines, nitrosamines, and heterocyclic amines, all of which can be associated with mutations that are observed in CRC [24, 38]. The link with SSA/Ps is perhaps more direct as smoking has been linked with specific mutations observed in the serrated pathway including BRAF mutations [39], microsatellite instability and increased CpG island methylation (CIMP) [30, 38]. Thus, it is

not surprising that the link between SSA/P and smoking is strong [40], perhaps even stronger than for HRA. A greater amount of smoking exposure likely puts one at risk for having lesions from both pathways. Indeed, adults with synchronous HRA + CSSP were more likely to have a 20 pack-year history exposure than those with HRA alone.

Our findings have many implications. A recent NHCR study has shown that compared with those without any polyps, people with synchronous HRA and SSA/Ps are more likely to have metachronous HRA [15]. The absolute risk was about 50%, almost 4 times as high as the risk for people with HRA alone. Identifying people at risk for synchronous HRA and CSSPs may further tailor screening recommendations and improve the overall effectiveness of CRC screening programs, especially in settings with limited colonoscopy resources. In addition, since smoking is a modifiable risk factor, smoking cessation counseling and pharmacotherapy should be promoted to reduce an individual's CRC risk.

We also found that BMI was positively correlated with HRA and CSSP, alone or synchronous. Although we examined BMI as a continuous variable in our analysis, our findings linking increasing BMI and HRA and CSSP support other studies that identify obesity as another risk factor for SSA/P²⁰ and conventional adenomas [41, 42]. In fact, based on many studies [17, 18, 41, 42], recent ACG CRC Screening Guidelines identify adults who are obese as well as smokers as being at a higher risk for colorectal neoplasia than average-risk individuals without these risk factors [36].

There are several strengths in our analysis. Our main exposure variable, smoking, has been identified in several models as predicting the presence of advanced adenomas and SSA/P in previously published studies [43, 44]. The large database of the NHCR, with nearly 20,000 screening colonoscopies included in this analysis, provided excellent power to examine the impact of smoking colonoscopy findings. Specifically, we had enough exams that we could divide NHCR participants into those with normal exams or no adenomas or SPs, those with HRA and no SPs, those that had CSSP and no adenomas and finally those that had both CSSP and HRA. This allowed us to accurately assess the risk of smoking with large numbers for each of the 4 subsets of exam findings separately. In addition, we included other factors in our models such as alcohol intake which has been associated with risk for both conventional adenomas [45] and SPs [46]. In a recent large meta-analysis, alcohol was observed to be the strongest risk factor for SPs (RR = 1.33; 95% CI, 1.17–1.52) after obesity (RR = 1.30 95% CI 1.22–1.61) and smoking (RR = 2.47; 95% CI 2.12–2.87) [29]. Another strength is the population-based nature of our study sample, the screening colonoscopies were performed by 104 endoscopists practicing at 27 diverse facilities including community and academic practices, both urban and rural, thereby increasing the generalizability of the results. Furthermore, the detailed exam and specimen level data of the NHCR, including quality of bowel preparation and completeness of exam, allowed this analysis to exclude incomplete exams and those with poor bowel preparation. Finally, comprehensive pathology capture with matching to the individual polyp level [33] enabled accurate assessment of adenoma or SP status.

We acknowledge certain limitations of this study. There may be misclassification of polyp histology by the multiple pathology labs evaluating polyp tissue among these 29 endoscopy sites. However, since NHCR is a population-based registry, our findings reflect “real life practice”. Information on smoking was self-reported and it is possible that patients under reported or over reported tobacco use; however, this is no different than clinical practice. The patient cohort lacks diversity and is predominantly white, which limits generalizability to clinical practices across the United States and thus the results should be confirmed in another patient population. Finally, our analysis did not include other potentially important CRC risk factors such as red meat consumption and other co-morbidities.

In summary, this study demonstrates that current smoking is associated with a higher risk of synchronous HRA and CSSP. Given the high risk for metachronous HRA, among those with synchronous HRA and CSSP [14, 15], smoking should be considered a risk factor in surveillance guidelines such that those who smoke

may need more frequent surveillance compared to non-smokers. Furthermore, since smoking is a modifiable risk factor, primary care practitioners and endoscopists should counsel patients on the importance of smoking cessation. Future studies should examine the pathways of this elevated risk, including evaluation of molecular mutations and whether more intense surveillance among those who smoke results in a decrease in CRC.

Disclaimer

The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government.

CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Smoking is associated with serrated polyps
- ✓ Smoking is associated with conventional high-risk adenomas
- ✓ Individuals with clinically significant serrated polyps (CSSP) and high-risk adenomas (HRA) are at a higher risk for metachronous HRA than even those with HRA and thus may have unique risk profile

WHAT IS NEW HERE

- ✓ Smoking was strongly associated with individuals with HRA + CSSP as compared to individuals with normal exams
- ✓ Smoking was more closely linked with HRA + CSSP than with HRA.

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