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Sessile Serrated Adenomas in the Proximal Colon are Likely to be Flat, Large and Occur in Smokers

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BRIEF ARTICLE

Sessile serrated adenomas in the proximal colon are likely to be flat, large and occur in smokers

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Abstract

AIM: To examine the epidemiology and the morphology of the proximal sessile serrated adenomas (SSAs).

METHODS: We conducted a retrospective study to identify patients with SSAs using a university-based hospital pathology database query from January 2007 to April 2011. Data collected included: age, gender, ethnicity, body mass index, diabetes, smoking, family history of colorectal cancer, aspirin, and statin use. We collected data on morphology of SSAs including site (proximal or distal), size, and endoscopic appearance (flat or protuberant). We also compared proximal SSAs to proximal tubular adenomas detected during same time period.

RESULTS: One hundred and twenty patients with SSAs were identified: 61% were distal and 39% were proximal SSAs. Proximal SSAs were more likely to be flat than distal (100% *vs* 78% respectively; $P = 0.0001$). Proximal SSAs were more likely to occur in smokers (OR = 2.63; 95%CI: 1.17-5.90; $P = 0.02$) and in patients with family history of colorectal cancer (OR = 4.72; 95%CI: 1.43-15.55; $P = 0.01$) compared to distal. Proximal SSAs were statistically more likely to be $\geqslant$ 6 mm in size (OR = 2.94; $P = 0.008$), and also more likely to be large ($\geqslant$ 1 cm) (OR = 4.55; $P = 0.0005$) compared to the distal lesions. Smokers were more likely to have proximal ($P = 0.02$), flat ($P = 0.01$) and large ($P = 0.007$) SSAs compared to non-smokers. Compared to proximal tubular adenomas, proximal SSAs were more likely to be large and occur in smokers.

CONCLUSION: Proximal SSAs which accounted for two-fifths of all SSAs were more likely to present as flat lesions, larger SSAs, and were more likely to occur in smokers and in patients with family history of colorectal cancer. Our data has implications for colorectal cancer screening.

Key words: Proximal; Sessile; Serrated; Adenoma; Colonoscopy; Colorectal cancer; Smoking

Core tip: Sessile serrated adenomas (SSAs) have been implicated in the alternative pathway for colorectal carcinoma. Proximal SSAs might account for higher incidence of interval colorectal cancers (CRC) on the right side given the fact that these are often flat and difficult to detect. Our study is first to compare the morphology and epidemiology of proximal SSAs with distal SSAs.

We found proximal SSAs are more likely to present as flat lesions, larger SSAs, and were more likely to occur in smokers and in patients with family history of CRC. These findings have implications for CRC screening.

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INTRODUCTION

Colorectal cancer is the fourth most common form of cancer and the second most frequent cause of cancer deaths in the United States[1]. The majority of colorectal cancers arise from the adenoma-carcinoma sequence where mutations in the *APC* gene play an early role. However, an alternative pathway exists in which there is an increased frequency of CpG island methylation of gene promoter. These abnormalities are associated with *BRAF* mutations which have been observed in sessile serrated adenomas (SSAs)[2,3] as well as serrated aberrant crypt foci[4]. Large serrated polyps (≥ 1 cm) have been shown to have a strong association with synchronous advanced colorectal neoplasia[5,6]. SSAs are often flat and proximally located. Interval cancers have been shown to be associated with the methylation pathway[7]. In addition to the fact that they may be difficult to detect, SSAs may provide an explanation for the reason why rates of right sided colorectal neoplasia remain high while the left sided lesions have decreased in patients who have had a colonoscopy in the recent past[8,9].

Very few studies have examined the epidemiology of the various types of serrated polyps. A recent study has shown smoking to be strongly associated with SSAs of all sizes, including the clinically important large (≥ 1 cm) lesions[10]. Multivariate logistic regression found that age, smoking and obesity were statistically significant predictive factors for any SSA as compared to controls[10]. Most of the preceding studies have focused on the relatively common left-sided serrated polyps and little is known about the proximal SSAs. Our goal was to examine the epidemiology and the morphology of the proximal SSA in comparison to the distal lesions.

MATERIALS AND METHODS

Patient selection and data collection

The retrospective study was approved by the Institutional Review Board of the University of Connecticut Health Center. We defined cases as patients diagnosed to have SSAs from January 2007 to April 2011, identified by a pathology database query. We identified all lesions diagnosed by our pathologists as SSA. We excluded the traditional serrated adenomas or the subgroup of serrated polyps that not only share serrated crypt architecture with hyperplastic polyps, but also have cytologic dysplasia. SSAs were those serrated polyps with abnormal proliferation and/or abnormal architecture, but without the cytological dysplasia seen in adenomatous polyps. All of the SSAs were confirmed or had a clinical description that alerted the pathologist that the endoscopist was suspecting a SSA. We defined a large SSA as any SSA of size greater than or equal to 1 cm in diameter.

We collected the following data from the patient's charts: age, gender, ethnicity, height, weight, clinically diagnosed type Ⅱ diabetes mellitus, smoking exposure, a family history of colorectal cancer, lipid profile, use of aspirin, calcium, hormone replacement therapy and statin use. From an electronic database at our University Hospital, we were able to use several different primary care and sub specialty notes to collect and confirm the data. Thus, most of our information had at least one source.

With regard to smoking, we calculated the exposure in the form of pack-years (*i.e.*, number of packs smoked per day multiplied by the number of years smoked). We defined a smoker as someone who smoked at least 20 pack-years or more regardless of whether they quit smoking. Family history of colorectal cancer was defined as having at least one first degree relative or two second degree relatives with the disease. Obesity was defined as a body mass index ≥ 30 kg/m^2. We also randomly selected patients with adenomas who had colonoscopies during the same time period as the patients with serrated lesions.

High-definition (1080i signal) wide-angle (170° field of view) Olympus 180-series colonoscopes (Olympus America, Center Valley, PA, United States) were used to perform all of the colonoscopies. All polyps were photo documented next to a snare catheter for *in vivo* measurement and retrieved for histology, and morphology was classified according to the Japanese Research Society for Cancer of Colon and Rectum guidelines[11,12]. We used a standard method to visualize the polyp for morphologic classification. Specifically, the colon was insufflated so that the polyp was visualized and photo documented in this setting. Any lesion that was determined to be Ip, Is, or Ips was considered to be polypoid or protuberant, and those that were Ⅱa, Ⅱb, or Ⅱc were considered to be flat or non-polypoid. Adenoma size was confirmed by the pathology report[13]. One experienced endoscopist (Anderson JC) confirmed the morphology from the photodocumentation for a representative group of adenomas that were randomly selected from our analyzed sample. The colon was divided into proximal and distal by the splenic flexure which was considered proximal. A colonoscopy was considered complete if the following criteria were fulfilled: transillumination of the right lower quadrant, visualization of the ileocecal valve, or appendiceal orifice.

Statistical analysis

Our main outcomes were detection of SSAs, and proximal SSAs. SPSS version 20.0 (Chicago, IL, United States)

Table 1 Comparison of patient characteristics among proximal and distal sessile serrated adenoma group *n* (%)

	Proximal SSA (*n* = 47)	Distal SSA (*n* = 73)	Univariate OR (95%CI)	*P* value	Multivariate OR (95%CI)
Race (CC)	37 (78.7)	54 (74.0)	1.30 (0.54-3.12)	0.66	-
Gender (male)	21 (44.7)	27 (37.0)	1.38 (0.65-2.90)	0.45	-
Age (yr) (≥ median)	28 (59.6)	40 (54.8)	1.22 (0.58-2.56)	0.71	-
Obesity	22 (46.8)	36 (49.3)	0.90 (0.43-1.88)	0.85	-
Family history	11 (23.4)	5 (6.8)	4.16 (1.34-12.89)	0.01	4.72 (1.43-15.55) *P* = 0.01
Diabetes mellitus	14 (29.8)	23 (31.5)	0.92 (0.42-2.05)	1.00	-
Smoking	30 (63.8)	30 (41.0)	2.53 (1.19-5.39)	0.02	2.63 (1.17-5.90) *P* = 0.02
Triglyceride (mean ± SD, mg/dL)	124.9 ± 63.9	129.7 ± 67.9	-4.80 (-29.38-19.78)	0.69	-
Cholesterol (mean ± SD, mg/dL)	179.1 ± 45.8	180.9 ± 43.8	-1.80 (-18.31-14.71)	0.83	-

SSA: Sessile serrated adenoma.

was used for all statistical analysis. Univariate analyses were performed using Fisher's test or χ^2 for dichotomous variables and unpaired *t*-test for non-parametric continuous variables. After univariate analyses, all variables with a *P* value of 0.10 or less were entered into the equation and only those variables with $P < 0.10$ were used in the final multivariate logistic regression equation to estimate Odds ratios and 95% confidence intervals for proximal SSAs. We considered results to be significant if the *P* value was < 0.05.

RESULTS

From January 2007 to April 2011, 120 patients (mean age: 59.72 ± 10 years, males: 40%) with SSAs were identified. This included 90 patients searched through the same pathology database query that were part of the earlier study focused on identifying risk factors associated with any SSAs[10]. Thirty additional patients were added to this database between October 2010 and April 2011. Proximal SSAs constituted two-fifths (47/120) of all SSAs. Fifty-seven (78%) of the distal lesions were flat as compared to the 47 (100%) proximal lesions which were all flat ($P = 0.0001$). Proximal SSAs were more likely to occur in smokers compared to distal (30/47 *vs* 30/73; $P = 0.02$) as shown in Table 1. Similarly, smokers were more likely to have proximal SSAs compared to non-smokers (30/60 *vs* 17/60; $P = 0.02$). Compared to non-smokers, smokers were also more likely to have flat SSAs (57/60 *vs* 47/60; $P = 0.01$). Proximal SSAs were more likely to be found in subjects with a family history of colorectal cancer compared to distal SSAs (11/47 *vs* 5/73; $P = 0.01$) as shown in Table 1.

We also examined the site of the SSA in relation to the adenoma size and morphology. Proximal SSAs were more likely to be ≥ 6 mm in size and also more likely to be large (≥ 1 cm) compared to the distal lesions, as shown in Table 2. Smokers were significantly more like to have large SSAs (23/60 *vs* 9/60; $P = 0.007$; multivariate OR = 3.93; 95%CI: 1.52-10.17) compared to non-smokers.

We compared SSA group to a control group consisting of 122 patients with conventional tubular adenomas identified from the same time period. Proximal tubular adenoma constituted 64% of all tubular adenomas compared to proximal SSA which constituted 39% of all SSAs. Proximal SSAs were significantly more likely to be flat, large (≥ 1 cm), and occur in smokers compared to the proximal tubular adenomas, as shown in Table 3.

DISCUSSION

Our data suggest that proximal SSAs are more likely to occur in smokers and in patients with family history of colorectal cancer. Proximal SSAs are also more likely to present as large lesions, including the significant (≥ 6 mm) adenomas and clinically important large (> 1 cm) adenomas. In addition, we found proximal SSAs to be more likely to present as flat lesions. To our knowledge, this is the first study examining the morphology of SSAs specifically, and their association with smoking with respect to anatomical location.

We found smokers to have proximal, flat and large SSAs. Smoking has been associated with key mutations in cancer-related genes such as *hMLH1*, CPG island methylation phenotype (CIMP) and *BRAF* mutation, with multiple studies establishing a definitive link between smoking and microsatellite instability-high (MSI-H) colorectal cancers[14-19]. Molecular studies have shown serrated polyps including SSAs to be associated with a higher frequency of CIMP and *BRAF* mutations[3,20-22]. Several large studies have reported the association of serrated adenoma- carcinoma pathway *via* the microsatellite instability[23-28]. With respect to the link between smoking and serrated lesions, multiple studies have shown that cigarette smoking has a stronger association with serrated polyps than it does with adenomatous polyps[29-34]. Wallace *et al*[35] identified smoking as one of the major risks for serrated polyps. Current smokers were found more likely to have proximal nondysplastic serrated polyps in a study by Schreiner *et al*[6]. A recent study by Anderson *et al*[10] demonstrated smoking to be a major risk factor for the presence of SSAs. Our current study further links smoking strongly with proximal SSAs compared to distal lesions. Thus, smoking is not only a major risk factor for all SSAs, but is a much stronger predictor of proximal SSAs. Our study demonstrates smoking to be strongly

Table 2 Comparison of adenoma characteristics in the proximal and distal sessile serrated adenoma *n* (%)

	Proximal SSA (*n* = 47)	Distal SSA (*n* = 73)	Univariate OR (95%CI)	*P* value
Flat SSA	47 (100.0)	57 (78.0)	-	0.0001
⩾ 6 mm SSA	31 (66.0)	29 (39.7)	2.94 (1.37-6.31)	0.0080
⩾ 1 cm SSA	21 (44.7)	11 (15.0)	4.55 (1.92-10.77)	0.0005

SSA: Sessile serrated adenoma.

Table 3 Comparison of patient and adenoma characteristics among proximal sessile serrated adenoma and proximal tubular adenoma groups *n* (%)

	Proximal SSA (*n* = 47)	Proximal TA (*n* = 78)	Univariate OR (95%CI)	*P* value
Family history	11 (23.4)	14 (18.0)	1.40 (0.57-3.40)	0.4900
Smoking	30 (63.8)	26 (33.3)	3.53 (1.65-7.54)	0.0010
Adenoma size ⩾ 1 cm	21 (44.7)	11 (14.1)	4.92 (2.08-11.61)	0.0002
Flat morphology	47 (100.0)	46 (59.0)	-	< 0.00001

SSA: Sessile serrated adenoma; TA: Tubular adenoma.

linked with flat and proximal SSAs, which were more likely to present as large lesions having higher neoplastic potential.

Several studies have explored the association between smoking and anatomical site-specific lesions. Colorectal cancers arising from the serrated pathway that are *BRAF*-mutated, CIMP-high and MSI-H, and are specifically associated with smoking[17,18] occur most often in the proximal colon[36,37]. Limsui *et al*[16] also reported an association between proximal colon cancer and cigarette smoking in a large cohort study of over 37000 women. However, few studies, including a meta-analysis of the association between colorectal cancer and smoking, suggest a specific association with distal/rectal neoplasia[15,38,39]. A recent case-control study by Burnett-Hartman *et al*[29] also reported a stronger association between distal/rectal colorectal polyps and smoking. Botteri *et al*[40] showed a strong association between smoking and cancers in the rectum and proximal colon. They postulated that this could be due to the differential anatomical location of serrated colorectal cancers. Although non-serrated polyps tend to have no site predilection[40-42], studies have reported that serrated neoplasia arise more frequently in the proximal colon and in the rectum[43-45]. Microsatellite instability has been associated with proximal lesions[46,47] and has been shown to develop late in serrated adenoma-carcinoma pathway[3]. This could possibly explain our observation of large and proximal SSAs in smokers. As with microsatellite instability, studies have shown that tumors involving *BRAF* mutations arise more frequently in the proximal colon than in the distal colon[7,48-50]. Our study shows proximal SSAs comprise two-fifths of all SSAs, but are clinically more important given the finding that they are larger and all have flat morphology compared to the distal lesions which were more common. Smoking was found to be a much stronger risk factor for proximal SSAs compared to proximal tubular adenomas, likely due to high frequency of CIMP and *BRAF* mutations which are involved in serrated lesions.

Another interesting observation was the link between family history of colorectal cancer and proximal SSAs on both univariate and multivariate analyses. Family history of colorectal cancer has been shown to be a predictor of proximal significant adenomas on previous studies[51]. Schreiner *et al*[6] also found patients with family history of colorectal cancer to be more likely to have proximal non-dysplastic serrated polyps. However, this study did not include an analysis that distinguished hyperplastic polyps and SSAs. Our study is the first to show similar association of family history of colorectal cancer with proximal SSAs. Anderson and colleagues did not find family history of colorectal cancer to be a risk factor for SSAs compared to controls[10]. This might be because of the relatively small sample size and the fact that distal lesions accounted for two-third of all SSAs. Our results show family history of colorectal cancer is associated with proximal and not distal SSAs. Patients with family history of colorectal cancer might have an alternative involvement of *BRAF*-serrated pathways predisposing them to proximal SSA, which might account for the increased risk of adenoma and colorectal neoplasia.

There are many implications for our findings with respect to colorectal screening. The majority of our SSAs were flat. Those located proximally were all flat as opposed to the distal lesions. These lesions may be difficult to detect and may be associated with synchronous advanced neoplasia[5,6]. Proximal SSAs would be theoretically much more difficult to detect given their location: incomplete colonoscopies, variation in cecal intubation rates, variation in detection of proximal serrated polyps[52]. Given the potential for malignancy of SSAs as well as their proclivity to a flat morphology, these lesions may explain the lack of protection of colonoscopy in the proximal colon. Studies have shown the limitations of colonoscopy in reduction of right sided colon cancers[8,9]. Interval colorectal cancers are three times as likely to occur in the right colon[53] and proximal SSAs might account for significant proportion of these interval colorectal cancers. Recent study by Arain *et al*[7] also found interval cancers to be more likely to arise in the proximal colon and found both CIMP and MSI to be independently associated with interval cancers. This might pose an important concern from a screening perspective. Proximal SSAs are more likely to occur in smokers which may require special screening techniques to identify these lesions in this high risk group. We further divided our SSAs into the larger lesions due to their malignant potential and those > 6 mm. We chose the latter measurement since lesions of this size are considered important clinically with regard to optical colonoscopy as well as computer tomographic colonography (CTC)[54,55]. We observed that most of these lesions were found proximal to the splenic flex-

ure. Therefore, if chromoendoscopy is found to be beneficial in detecting flat adenomas, the entire colon, with special attention to the right side, would be important in smokers and in patients with family history of colorectal cancer. Therefore, great attention to the proximal colon with a detailed evaluation for flat adenomas should be undertaken. Perhaps different techniques, such as special high-definition colonoscopes, narrow band imaging or chromoendoscopy may be required to detect these flat adenomas[56]. The role of CTC in screening smokers for colorectal cancer may also change as it may be more difficult to identify lesions with a flat morphology by this method of screening.

We acknowledge that the retrospective design of the study is a potential limitation for our results. Our retrospective data collection included data regarding known colorectal neoplasia risk factors such as smoking history, family history of colorectal cancer and obesity in addition to medication use, dietary intake, lipid profile and patient demographics. However, we acknowledge that there may have been factors that were missed. Another limitation of this study is the relatively small sample size and single center study.

In conclusion, our study is the first to suggest that proximal SSAs are more likely to present as flat and large adenomas, and also more likely to occur in smokers and in patients with family history of colorectal cancer compared to distal SSAs. Smokers are more likely to have proximal, flat, and large SSAs. Increased malignant potential from larger size and difficulty in detection given their flat morphology might contribute to higher risk of interval colorectal cancer in the proximal colon, particularly in smokers.

COMMENTS

Background

Sessile serrated adenomas (SSAs) have been implicated in the alternative pathway for colorectal carcinoma (CRC) and might account for significant proportion of interval CRC given the fact that these are often flat and difficult to detect. Lesions in this pathway and interval cancers share a common proximal location as well as molecular mutations. Many of the epidemiological studies have focused on the relatively common left-sided serrated polyps and little is known about proximal SSAs.

Research frontiers

Smoking, age, obesity, diabetes have been identified as risk factors for SSAs. Proximal serrated polyps have attracted more attention based on their premalignant potential and their association with synchronous and metachronous lesions.

Innovations and breakthroughs

Their results show differences in risk factors, epidemiology and morphology between proximal and distal SSAs. These novel data show that proximal SSAs are all flat and more likely to present as larger lesions. Proximal SSAs are more likely to occur in smokers and in patients with family history of CRC.

Applications

Smokers are more likely to have proximal SSAs which are flat and larger. This might have implications for CRC screening, recommending use of new or different techniques such as chromoendoscopy in smokers for detection of these lesions which account for significant proportion of interval cancers in the right colon. Future studies should focus on techniques and procedure-related factors to enhance the detection of these clinically important proximal SSAs.

Terminology

Sessile serrated adenoma are characterized by the presence of a disorganized and distorted crypt growth pattern that is usually easily identifiable upon low-power microscopic examination. Crypts, particularly at the basal portion of the polyp, may appear dilated and/or branched, particularly in the horizontal plane, which leads to the formation of "boot", "L", or "anchor"-shaped crypts. The terms "SSAs" and "sessile serrated polyp" are considered synonyms, and both are acceptable. Proximal colon location is defined as proximal to the splenic flexure (transverse colon, ascending colon, cecum, ileocecal valve).

Peer review

This is a nice and well written retrospective case-control study showing that SSAs in the proximal colon were more associated with smoking compared to distal SSAs and tubular adenoma in the proximal colon.

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