Sessile Serrated Polyps and Colon Cancer Prevention
Shahrooz Rashtak1, Rafaela Rego1,2, Seth R. Sweetser1, and Frank A. Sinicrope1,3

Abstract
Evidence suggests that up to one fifth of colorectal carcinomas develop from serrated polyps, named for their pattern of colonic crypts, and include the sessile serrated adenoma/polyp (SSA/P) that has malignant potential. SSA/Ps are typically located in the proximal colon and have molecular features of hypermethylation of CpG islands in gene promoters and activating point mutations (V600E) in the BRAF oncogene. Both of these features are seen in sporadic colorectal carcinomas with microsatellite instability (MSI) which is potentially consistent with an origin of these cancers from precursor SSA/Ps. Dysplasia is detected in a subset of SSA/Ps with a high risk of progression to carcinoma. An uncommon serrated polyp is the traditional adenoma that is typically found in the left colon, has a tubulovillous architecture, and frequently harbors mutant KRAS. To date, the epidemiology of these serrated lesions is poorly understood, and limited observational data suggest a potential chemopreventive benefit of nonsteroidal anti-inflammatory drugs. The current primary strategy to reduce the risk of colorectal carcinoma from serrated polyps is to enhance their detection at colonoscopy and to ensure their complete removal. This review provides insight into the epidemiologic, clinical, histopathologic, and molecular features of serrated polyps and includes data on their endoscopic detection and chemoprevention.

Introduction
Colorectal cancer is the third most common cancer in the United States and the second leading cause of cancer-related mortality (1). The overall incidence of colorectal carcinoma is decreasing in older adults due, in part, to colonoscopic screening with removal of adenomatous polyps that are associated with a reduction in mortality from colorectal carcinoma (2). However, colonoscopy is an imperfect test with an appreciable rate of undetected premalignant lesions and less commonly missed cancers (3). While adenomatous polyps were traditionally considered to be the sole precursor lesions of colorectal carcinomas, an important milestone in our understanding of colorectal carcinogenesis was the recognition of the serrated neoplasia pathway. Approximately 20% of sporadic colorectal carcinomas develop via this pathway with the major precursor lesion being the sessile serrated adenoma/polyp (SSA/P; refs. 4–6).

The term serrated polyp refers to a lesion with a serrated or “sawtooth” appearance of the colonic crypts at microscopy. The most common serrated polyp is the hyperplastic polyp of the rectum and sigmoid colon which accounts for 80% of all serrated polyps and lacks malignant potential. SSA/Ps are estimated to represent up to 20% of all serrated polyps, are typically sessile or flat lesions, and have a predilection for the right colon (6). In contrast to hyperplastic polyps, SSA/Ps can develop classical dysplasia and are considered precursor lesions of colorectal carcinomas. SSA/Ps are difficult to visualize at endoscopy, as they are flat and often have overlying, adherent mucus, making them more likely to be overlooked compared with conventional adenomas (Fig. 1A). SSA/Ps have less distinct borders compared with adenomas and have increased rates of incomplete resection (7). SSA/Ps are believed to be an important contributor to interval colorectal carcinomas, defined as a cancer diagnosed after a screening or surveillance examination, in which no colorectal carcinoma is detected, and before the date of the next recommended examination (8). Traditional serrated adenomas (TSA) are rare and represent only 1% of all serrated polyps. TSAs are typically located in the left colon, are often pedunculated, and have villous morphology with classical dysplasia which confers a malignant potential (9–11). In this article, we review the clinical, endoscopic, and molecular features of SSA/Ps and their association with colorectal carcinoma. In addition, we discuss quantitative estimates of risk, limited data for chemoprevention, and specific approaches to improve endoscopic detection and removal.

Histology and molecular features
The most recent classification of serrated polyps of the colorectum by the World Health Organization categorizes them into 2 main groups based on crypt morphology and the presence or absence of dysplasia. Serrated polyp subtypes include: hyperplastic polyp, SSA/P, SSA/P with dysplasia, and TSA (12, 13), and all but hyperplastic polyps are considered precursors of colorectal carcinoma (14). This classification is important for tailoring surveillance strategies, as each subtype differs in their malignant potential. Hyperplastic polyps are further subclassified into microvesicular, goblet cell–rich, and mucin-poor variants.
The microvesicular hyperplastic polyp (MVHP) is the most common type and often has mutation in the \textit{BRAF} oncogene, suggesting that these polyps may be precursors to SSA/P (15). Compared with SSA/Ps, TSAs can carry either \textit{KRAS} or \textit{BRAF} mutations and with either mutation have similar morphologic features (ref. 16; Fig. 2). SSA/Ps, like hyperplastic polyps, have serrated crypts, but SSA/Ps have characteristic crypts that are distorted with widened and branching bases (ref. 10; Fig. 1B). Before identification of these unique histopathologic features, SSA/Ps were interpreted by pathologists as hyperplastic polyps, and it is likely that under-reading of SSA/Ps continues to occur today in clinical practice. In a retrospective review of polyps initially classified as hyperplastic polyps that were resected between 1980 and 2001 from a single academic center, 81 polyps in 55 patients (5.8%) were reclassified as SSA/P, 40 of these cases had no prior diagnosis of high-grade dysplasia (HGD) or colorectal carcinoma (17). On follow-up, the incidence of subsequent colorectal carcinoma was significantly higher in patients with SSA/P than in those with hyperplastic polypl (12.5% vs. 1.8%). Furthermore, approximately 15% of the SSA/Ps initially misdiagnosed as hyperplastic polyps were found to evolve into lesions with HGD or cancer in the right colon (17). While dysplasia is a universal feature of conventional adenomas, it is not a typical feature of SSA/Ps although conventional dysplasia may develop within an SSA/P indicating neoplastic transformation (10, 18). In a large retrospective study of SSA/Ps removed at colonoscopy, the overall prevalence of dysplasia was 5% (19). SSA/Ps containing dysplastic crypts are classified as SSA/P with dysplasia, which may

\[\text{Figure 1.}\]
\textbf{A}, SSA/P is seen in the right colon (outlined by arrows) at colonoscopy. Note the typical flat appearance of the lesion and common overlying mucus that can obscure its detection. \textbf{B}, Histopathology of a SSA/P shows the characteristic serrated or “sawtooth” appearance of the colonic crypts that are wide and lateral spreading at the base (arrow) of the polyp. \textbf{C}, SSA/P (down arrow) is seen contiguous with a colonic adenocarcinoma (up arrow). The cancer is poorly differentiated with an area of signet ring cells and was found to have MSI and a BRAF mutation.

\[\text{Figure 2.}\]
The precursor of the first pathway (left) is believed to be MVHP, although there is the potential for SSA/P to arise de novo from normal mucosa. This pathway results in BRAF-mutant cancers that are CIMP-high and have MSI-H or are MSS. The second pathway (right) is less well-defined with the potential precursor lesion being the goblet cell hyperplastic polyp leading to the TSA. The end result of this pathway is an MSS and CIMP-low cancer that may have an associated KRAS mutation. Reprinted from ref. 6.
represent an intermediary in the molecular evolution of SSA/P to cancer (20). When SSA/P tissue is found contiguous with carcinoma, a transition zone of dysplasia is frequently present (ref. 11; Fig. 1C).

Most colorectal carcinomas develop from conventional adenomas through a pathway characterized by chromosomal instability (CIN) that is associated with mutations in the APC, TP53, SMAD4, PTEN, and KRAS genes. In addition, genomic profiling revealed other frequently mutated genes (FBXW7, TCF7L2, NRAS, CTNNB1, SMAD2, FAM123B, and SOX9) in these cancers (21). While BRAFV600E mutations are not found in conventional adenomas, they are detected in approximately 8% of colorectal carcinomas and result in activation of the mitogen-activated protein kinase (MAPK) signaling pathway which promote cell proliferation and survival (22). The other major pathway is that of microsatellite instability (MSI) that develops due to deficient DNA mismatch repair (MMR) which is detected in about 15% of all colorectal carcinomas. MSI is most often sporadic and as a consequence of epigenetic inactivation of the MLH1 MMR gene that occurs in a background of hypermethylation at CpG islands in the promoter regions of cancer-associated genes that is termed CIMP (CpG island methylator phenotype) with frequent BRAFV600E mutations. Data indicate that the mutant BRAF oncoprotein functions through the transcriptional repressor MAFG as the pivotal factor required for MLH1 silencing and CIMP in colorectal carcinomas containing BRAFV600E mutations (23). In addition to BRAFV600E, other frequent targets of mutation in MSI tumors include ACVR2A, APC, TGFBR2, MSH3, MSH6, SLC9A3, and TCF7L2 (24). Recently, a consortium was formed to resolve inconsistencies among the reported gene expression–based colorectal carcinoma classifications. This effort identified 4 consensus molecular subtypes (CMS) with distinguishing features: CMS1 (14%) hypermutated, MSI, and immune activation; CMS2 (37%), epithelial, WNT, and MYC signaling activation; CMS3 (13%), epithelial, and metabolic dysregulation; and CMS4 (23%), mesenchymal with TGFβ activation, stromal invasion, and angiogenesis (24).

The initiating molecular event in the SSA/Ps to colorectal carcinoma sequence is believed to be mutational activation of the BRAF oncogene, detected in about 80% of these lesions, which is followed by CIMP (5). CIMP is believed to promote the transition of MGHVs to SSA/Ps, and hypermethylation of MLH1 may be a key event in the development of dysplasia within an SSA/P that may promote progression to cancer (ref. 25; Fig. 2). Molecular profiling indicates that dysplastic foci within SSA/Ps are likely to be the immediate precursors of colorectal carcinoma in these lesions (4). Since BRAFV600E mutations and CIMP are characteristic of sporadic colon cancers with MSI, these data suggest that SSA/Ps are precursor lesions of sporadic MSI cancers (26). These findings are supported by a mechanistic animal model of SSA/P that was generated by conditional BRAF knock-in mice that were crossed to Villin-Cre transgenic mice with restriction of the oncogene to small intestinal and colonic epithelia (27). The resulting double mutant mice developed serrated polyps that were characterized by hyperproliferation and activation of ERK and WNT signaling pathways. In an age-dependent manner, hyperplasia progressed to dysplasia and TSAs, but not SSA/Ps which the authors speculated was due to predilection for polyps in the mouse small intestine, as SSA/Ps in humans are colonic. The authors referred to the small intestinal lesions as murine serrated adenomas which showed either low-grade or high-grade dysplasia. In 16% (5 of 31) of the mice, dysplasia progressed to invasive carcinoma, and importantly, nearly 40% (13 of 33) of the BRAF-mutated serrated adenomas and cancers were MSI-high (MSI-H). Progression to carcinoma was shown to be accelerated by p53 mutation or p16Ink4a inactivation. Therefore, overexpressing p16Ink4a and p53 tumor suppressor functions is likely critical for ultimate progression to cancer (28). This study confirms that a BRAF oncogenic mutation can induce formation of murine SSA/Ps with ability to progress to carcinoma. In an model of oncogenic KrasG12D expression driven by a transgenic Villin promoter, epithelial hyperplastic changes were seen but not development of TSA or SSA/Ps. Deletion of Cdh1a (the locus encoding p16Ink4a and p19Arf) in KrasG12D–expressing mice prevented senescence and led to invasive carcinomas (29, 30). However, unlike the oncogenic BRAF-driven tumors, these tumors neither were MSI-H nor showed WNT pathway activation.

Using an unsupervised classification strategy involving more than 1,100 colon cancers, established CIN and MSI were identified in addition to a third subtype that was largely microsatellite stable (MSS) and contained relatively more CIMP-positive carcinomas. This colon cancer subtype is related to SSA/Ps which show very similar gene expression profiles, including upregulation of genes involved in matrix remodeling and epithelial–mesenchymal transition (31). However, factors responsible for driving distinct subtypes of colorectal carcinoma are incompletely understood. In contrast to adenomas where the predominant response to TGFβ was apoptosis, TGFβ treatment induced a mesenchymal phenotype in a genetically engineered organoid culture carrying a BRAFV600E mutation which represents a model system for SSA/Ps (32). These data suggest that TGFβ signaling may be a key factor in directing SSA/Ps to the mesenchymal subtype of colorectal carcinoma. In another study, RNA sequencing (RNA-Seq) was performed on 21 SSA/Ps, 10 hyperplastic polyps, 10 adenomas, 21 uninvolved colon, and 20 control colon specimens to define a gene signature of SSA/Ps. This SSA/P gene signature was then evaluated in colon cancer RNA-Seq data from The Cancer Genome Atlas (21) to identify a subtype of colon cancers that may develop from SSA/Ps. A total of 1,422 differentially expressed genes were found in SSA/Ps relative to controls. A 51-gene panel in SSA/P showed similar expression to a subset of colon cancers with MSI from TCGA. A smaller 7-gene panel showed high sensitivity and specificity in identifying BRAF-mutant, CIMP-H, and MLH1-silenced colon cancers that are likely to develop through the serrated neoplasia pathway (33). These data suggest that a key event is epigenetic inactivation of MLH1, often in a background of CIMP, which confers the MSI-associated subtype.

In colorectal specimens from patients with colorectal carcinoma containing serrated polyps, the cancer was more likely to show MSI-H (34). These data were often obtained before recognition of SSA/Ps as a distinct entity, and re-review of their histology indicates that many of these lesions were SSA/Ps. In a review of the pathology database at Mayo Clinic from 2006 to 2012, 2,646 colorectal carcinomas were identified of which 33 cancers arose within or contiguous with an SSA/P. By histopathology, SSA/Ps that were associated with colon carcinomas contained frequent dysplasia (48%). Most of these cancers (94%) had mutated BRAF, loss of MLH1 (79%), and were predominantly located in the proximal colon (6, 35). Taken together, data indicate that SSA/Ps are likely the predominant precursor lesion of sporadic colorectal carcinomas with MSI (36).
SSA/Ps and Risk of Colorectal Carcinoma

The natural history of SSA/Ps is not well understood and estimates of cancer risk remain limited. SSA/Ps may be relatively indolent lesions, but a subset may have the potential for rapid progression once dysplasia develops (37). The overall prevalence of dysplasia in SSA/P is estimated to be 5% on the basis of a large retrospective study of SSA/Ps removed at colonoscopy that were not associated with cancer (19). A large cross-sectional study found that 85% of 2,416 SSA/Ps were nondysplastic, 14% had low- or high-grade dysplasia, and 1% had adenocarcinoma (38). The frequency of dysplasia in this series, however, may be an overestimate, as it may be biased towards larger lesions identified at colonoscopy. Other reports have shown that the prevalence of SSA/Ps without dysplasia is about 7.4%, whereas the prevalence of SSA/Ps with dysplasia is 0.6%, accounting for total SSA/P prevalence of 8.1% in average risk screening population (39). The relatively low prevalence of dysplasia in SSA/Ps suggests that only a small subset of these lesions have the potential for progression to cancer. This is supported by longitudinal observations on 23 large SSA/Ps found at screening colonoscopy that were left in situ and did not progress to cancer over a median of 11 years (40). In a multicenter study, SSA/Ps that were 1 cm or larger were significantly associated with a higher risk of developing colorectal carcinoma (OR, 4.79). The anatomic location of serrated polyps has been associated with the risk of colorectal carcinoma (41). Recently, a predictive model was developed to identify large, proximal, or dysplastic serrated polyps on the basis of clinical factors that include age above 50 years OR, 2.2; 95% confidence interval (CI), 1.3–3.8), history of serrated polyps (OR, 2.6; 95% CI, 1.3–4.9), current smoking (OR, 2.2; 95% CI, 1.4–3.6), or lack of regular nonsteroidal anti-inflammatory drug (NSAID) use (OR, 1.8; 95% CI, 1.1–3.0). An elevated risk score of more than 3 was associated with a 3-fold higher chance of detecting a large, proximal SSA/P with dysplasia compared with individuals with a lower score (42). This scoring system can potentially alert endoscopists to be especially vigilant for SSA/Ps in certain groups of patients having a high pretest probability for SSA/Ps. Post-polypectomy surveillance is recommended after removal of SSA/Ps or large and/or proximal hyperplastic polyps. While the presence of a hyperplastic polyp is not associated with an increased risk of cancer (43), large (>10 mm) serrated polyps in the proximal or distal colon has been shown to be associated with synchronous advanced neoplasia (44).

Direct evidence that SSA/Ps can be precursors of colorectal carcinoma is shown by the demonstration of an SSA/P contiguous with a colorectal carcinoma at surgical resection (Fig. 1C). Among 33 colon cancers that arose within or contiguous with an SSA/P, 16 (48%) were found to contain dysplasia. The presence of focal dysplasia within a contiguous SSA/P supports a dysplasia to carcinoma sequence for these lesions (35). The timing of the transition from serrated lesion to cancer is often longer compared with adenomas; however, progression of an SSA/P to an early invasive cancer has been documented to occur within 8 months (37). The presence of dysplasia with a propensity for rapid progression may account for the paucity of colon cancers found in association with SSA/Ps at surgical resection because the carcinoma likely overgrows and replaces the SSA/P. In contrast, colorectal carcinomas are more commonly found to contain residual adenomatous tissue in endoscopic biopsies and surgical resection specimens (45).

Epidemiology

The natural history of SSA/Ps and risk factors for progression to malignancy are poorly understood. SSA/Ps are more commonly seen in individuals of advanced age, in women, and in smokers (46, 47). In colonoscopy studies and in pathology database reviews, women represent up to 65% of individuals with detected SSA/Ps (22, 46, 48–52). In addition, women have a higher proportion of advanced serrated lesions including SSA/Ps with low- or high-grade dysplasia and SSA/Ps with invasive adenocarcinoma (38). A recent analysis of several studies of serrated polyps found that risk is associated with different lifestyle factors (53). When the highest and lowest categories of exposure were compared, factors found to significantly increase risk for serrated polyps included tobacco smoking [relative risk (RR), 2.47; 95% CI, 2.12–2.87], alcohol intake (RR, 1.33; 95% CI, 1.17–1.52), high BMI (RR, 1.40; 95% CI, 1.22–1.61), and high intake of fat or meat. However, conflicting data exist as to the association of SSA/Ps with obesity (46, 49, 54), such that this association remains uncertain. Direct associations for smoking and alcohol tended to be stronger for SSA/Ps than hyperplastic polyps (53). In contrast, factors found to significantly decrease risks for serrated polyps included use of NSAIDs (RR, 0.77; 95% CI, 0.65–0.92) or aspirin (RR, 0.81; 95% CI, 0.67–0.99), as well as high intake of folate, calcium, or fiber. No significant associations were detected between serrated polyp risk and physical activity or hormone replacement therapy. The most consistent data are for tobacco as a risk factor for SSA/Ps (46, 49, 55), particularly those located in the proximal colon (42, 56). Some (47, 57, 58), but not other (59, 60), studies found cigarette smoking to be associated with MSI-H colorectal carcinomas including a large population-based, case–control study (61); however, this association may be limited to tumors showing CIMP, regardless of MSI status (62). In addition to smoking, other risk factors for serrated lesions with CIMP included white race and a history of polyps (63).

The gut microbiome is being increasingly recognized as a contributor to colorectal tumorigenesis and evidence suggests the role of *Fusobacterium nucleatum*. The presence of *F. nucleatum* was analyzed in tissues from 343 serrated lesions, 122 non-serrated adenomas, and 511 colorectal carcinomas. In this report, the presence of *F. nucleatum* was similar among SSA/Ps (35%), TSAs (30%), and non-serrated adenomas (33%) and was significantly more frequent in colorectal carcinomas (56%; ref. 64). Interestingly, the investigators found that *F. nucleatum* was significantly associated with CIMP-high versus CIMP-low or CIMP-negative premalignant lesions. In a smaller study, the relative abundance of *Fusobacteria* in tissue did not differ significantly between the tubular adenomas and SSA/P groups but was again higher in the colorectal carcinoma group (65). Another study detected invasive *F. nucleatum* in the majority of proximal hyperplastic polyps and SSA/Ps which was significantly higher than found in tubular adenomas (66). Detection of *F. nucleatum* showed a predilection for proximal versus distal colorectal carcinomas. These studies suggest that *F. nucleatum* may play a role in the serrated neoplasia pathway of colon tumorigenesis. Further studies are needed examine microbial composition and metabolites associated with these lesions including their relationship to the tumor immune microenvironment.

Association with interval cancers

SSA/Ps may contribute disproportionately to interval colon cancers which are defined as cancers diagnosed before the next

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Endoscopic detection

It is important to recognize that newer generation colonoscopes with increased optical resolution permit the detection of subtle and flat mucosal lesions and likely contribute to the increased recognition of SSA/Ps over the past several years. A high-quality bowel preparation with meticulous mucosal inspection is needed to optimize the detection of SSA/Ps (71). SSA/Ps commonly have an adherent mucus-cap which may be a clue to its presence. Careful examination of the right colon is critical, as the majority of SSA/Ps are proximally located. Colonoscopy has been shown to be significantly less effective at detecting as well as reducing mortality from cancers of the right versus left colon (72). Given limitations of conventional white light colonoscopy, enhanced endoscopic methods are being studied that include narrow-band imaging (NBI) and chromoendoscopy that utilizes a mucosal contrast agent (73) for differentiating hyperplastic polyps from SSA/Ps polyps (74). In a study from Japan that used magnifying colonoscopy, the type II open-shape pit pattern (Type II-O) was reported to be specific to SSA/Ps with BRAF mutation and CIMP (75). Complete removal of SSA/Ps is critical to reducing colorectal carcinoma incidence. In a study by Pohl and colleagues, 50% of SSA/Ps that were at least 1 cm in size were incompletely resected at colonoscopy which underscores the need for proper polypectomy technique (7). Incomplete polypectomy and lack of adherence to follow-up surveillance are strongly associated with colorectal carcinoma risk after colonoscopic polyp detection (76). An expert-panel consensus conference recommends complete removal of all serrated lesions proximal to the sigmoid colon and all serrated lesions in the rectosigmoid which are larger than 5 mm in size given their risk of malignancy (77).

Multitarget stool DNA testing is an FDA-approved molecular assay that is an available option for colorectal carcinoma screening in patients at average risk (78). This technology probes shed DNA in feces to identify selected biomarkers and also includes a quantitative fecal immunochemical test (FIT; ref. 79). Stool DNA testing was shown to detect 42% of SSA/Ps of at least 1 cm in size and may, therefore, have the potential to improve the detection of SSA/Ps (80).

Serrated polyp syndrome

Serrated polyp syndrome (SPS) is characterized by multiple serrated polyps in the colon of patients who fulfill WHO criteria and is associated with a high risk of colorectal carcinoma. Gene expression profiling indicates that serrated polyps from those meeting criteria for the SPS completely overlap with those found in non-syndromic patients (81). According to American College of Gastroenterology (ACG) clinical guidelines, genetic testing is not routinely recommended for SPS, as a clear genetic etiology has yet to be defined for this condition. However, SPS patients with concurrent personal or family history of adenomas can be considered for analysis for MUIYH mutations (82). A low frequency of MUIYH mutations has been found among patients with multiple adenomatous and serrated polyps. This phenotype frequently includes patients with serrated polyps, especially when the G396D mutation was present. Colonoscopy every 1 to 3 years with attempted removal of all polyps >5 mm diameter for patients with SPS has been recommended by ACG. Colectomy and ileorectal anastomosis is indicated in those who develop cancer or in those where controlling the growth of serrated polyps cannot be achieved endoscopically (82).

Preventive approaches

Intake of aspirin was found to significantly decrease the risk of serrated polyps in an analysis of pooled data from 3 randomized chemopreventive trials examining the effect of aspirin on adenoma recurrence. In this study, daily aspirin intake was associated with a reduced risk of serrated polyps in the right colon (81 mg; RR, 0.56; CI, 0.34–0.91; 325 mg RR, 0.58; 95% CI, 0.36–0.95), whereas it had no effect on left-sided or advanced lesions compared with placebo (ref. 54; Table 1). The study included all types of serrated polyps and of note, a family history of polyps or folate intake was each associated with increased risk for serrated polyps diagnosed during each trial’s main treatment period of approximately 3 to 4 years (54). Another report utilized data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) that included 4,017 subjects with a biopsy-proven polyp in the left colon or rectum to study the association of NSAIDs (aspirin and ibuprofen) use with risk of polyp and cancer development. This study showed that regular use of aspirin was inversely associated with adenomas and hyperplastic polyps (OR, 0.8; 95% CI, 0.7–0.9 for both); however, it did not specify the proportion of SSA/P among those with hyperplastic polyps (ref. 83; Table 1). Concurrent use of aspirin and ibuprofen was associated with even lower risk of developing hyperplastic polyps (OR, 0.7; 95% CI, 0.6–0.9), adenomas (OR, 0.8; 95% CI, 0.7–0.9), and advanced adenomas (OR, 0.8; 95% CI, 0.7–1.0; ref. 83). In a recent meta-analysis that included 43 observational studies, factors found to significantly decrease risk for serrated polyps included use of NSAIDs (RR, 0.77; 95% CI, 0.65–0.92) or aspirin (RR, 0.81; 95% CI, 0.67–0.99), with suggestion that the reduction in risk may be even stronger for SSA/Ps (53).
Serrated Polyps and Cancer Prevention

The mechanism underlying the potential chemopreventive efficacy of NSAIDs against development of serrated polyps is unclear. NSAIDs inhibit cyclooxygenase enzymes that regulate the synthesis of prostaglandins and related eicosanoids. Compared to adenomas, SSA/Ps have been shown to infrequently overexpress COX2; however, COX2 overexpression is more frequent with neoplastic progression (84). Data from observational studies suggest that regular aspirin use was not associated with decreased risk of BRAF-mutated colorectal carcinomas (85) which may arise via the serrated pathway. Of note, aspirin intake (600 mg/d for a mean of 25 months) was shown to significantly reduce the incidence of colorectal carcinoma in Lynch Syndrome gene mutation carriers (86) whose tumors overexpress COX2; however, COX2 overexpression is more prevalent. 

Calcium supplementation was not associated with a reduced risk of developing serrated polyps (ref. 54; Table 1). Folic acid is an essential micronutrient in the process of DNA synthesis, and a low folate-containing diet has been associated with an increased risk of colorectal carcinoma (88). In a large observational cohort (Nurses’ Health Study), supplemental folic acid was significantly associated with a lower risk of colorectal carcinoma (RR, 0.25; 95% CI, 0.13–0.51) that was apparent only after 15 years of intake (89). In contrast, a randomized controlled trial revealed that 1 mg/d of supplemental folic acid was associated with higher risk of developing colorectal adenomas and advanced proximal serrated polyps (RR, 2.07; 95% CI, 1.14–3.77) with failure to reduce the risk of colorectal carcinoma (refs. 90, 91; Table 1). A pooled analysis of 3 large chemoprevention studies found that folate treatment was associated with an increased risk for right-sided serrated polyps diagnosed during each trial’s main treatment period of 3 to 4 years (54). In these studies, serrated polyps were broadly defined and subsets were not specifically examined. Pooled data from a randomized trial showed a modest effect of supplemental antioxidant vitamins C and E and β-carotene in decreasing the risk of serrated polyps that did not achieve statistical significance (92). With regard to hormone replacement therapy, usage failed to reduce the risk of serrated polyps, including SSA/Ps (49).

**Table 1. Chemoprevention for serrated polyps**

<table>
<thead>
<tr>
<th>Chemopreventive strategy</th>
<th>Preventive effect</th>
<th>Follow-up duration</th>
<th>Proposed mechanism</th>
<th>Site of action</th>
<th>Magnitude</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin 81 mg/d</td>
<td>Yes</td>
<td>3 y</td>
<td>Inhibition of prostaglandins/eicosanoids</td>
<td>Proximal serrated polyps</td>
<td>RR, 0.56 (0.34–0.91)</td>
<td>(54)</td>
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<tr>
<td>Aspirin 325 mg/d</td>
<td>Yes</td>
<td>3 y</td>
<td>Inhibition of prostaglandins/eicosanoids</td>
<td>Proximal serrated polyps</td>
<td>RR, 0.58 (0.36–0.95)</td>
<td>(54)</td>
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<tr>
<td>Aspirin (&gt; 4 times/mo)</td>
<td>Yes</td>
<td>1 y</td>
<td>Inhibition of prostaglandins/eicosanoids</td>
<td>Hyperplastic polyps</td>
<td>OR, 0.8 (0.7–0.9)</td>
<td>(83)</td>
</tr>
<tr>
<td>Aspirin + Ibuprofen</td>
<td>Yes</td>
<td>1 y</td>
<td>Inhibition of prostaglandins/eicosanoids</td>
<td>Hyperplastic polyps</td>
<td>OR, 0.7 (0.6–0.9)</td>
<td>(83)</td>
</tr>
<tr>
<td>Folic acid, 1 mg/d</td>
<td>No</td>
<td>3 y</td>
<td>Involved in DNA synthesis</td>
<td>Proximal advanced* serrated polyps</td>
<td>RR, 2.07 (1.14–3.77)</td>
<td>(54, 90)</td>
</tr>
<tr>
<td>Calcium 1,200 mg/d</td>
<td>No</td>
<td>4 y</td>
<td>Inhibition of colonic epithelial proliferation</td>
<td>Serrated polyps</td>
<td>RR, 0.98 (0.61–1.57)</td>
<td>(54, 95, 96)</td>
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<tr>
<td>β-Carotene</td>
<td>No</td>
<td>4 y</td>
<td>Presumed antioxidant effect</td>
<td>Serrated polyps</td>
<td>1.09 (0.76, 1.57)</td>
<td>(49)</td>
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<tr>
<td>Vitamin C</td>
<td>No</td>
<td>1-9 years</td>
<td>Unknown</td>
<td>Serrated polyps</td>
<td>0.36 (0.15–0.86)</td>
<td>(93)</td>
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<tr>
<td>Vitamin E</td>
<td>No</td>
<td>1-9 years</td>
<td>Unknown</td>
<td>Serrated polyps</td>
<td>1.09 (0.76, 1.57)</td>
<td>(49)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>No</td>
<td>1-9 years</td>
<td>Unknown</td>
<td>Serrated polyps</td>
<td>1.09 (0.76, 1.57)</td>
<td>(49)</td>
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Any serrated lesion >1 cm, SSA/P or TSA, or mixed polyps.

**Conclusion**

Recognition of the serrated neoplasia pathway provides an opportunity to further reduce the incidence of colorectal carcinoma. The SSA/P is a polyp with malignant potential, and a subset shows classical dysplasia indicating the potential to progress via a dysplasia-to-carcinoma sequence. While uncommon among serrated polyps, TSAs are known to have malignant potential. Interobserver variability remains an issue in the histopathologic diagnosis of SSA/Ps (93), although pathologists with gastrointestinal subspecialty training and those who have gained familiarity with these lesions through the literature were shown to be more likely to make an accurate diagnosis (94). Given interobserver variation in pathologic interpretation, guidelines of the American Gastroenterological Association recommend that all proximal colon serrated lesions ≥10 mm in size should be considered sessile serrated polyps, even if the pathologic interpretation is hyperplastic polyp (82).

Given limited data, large-scale genomic analysis is needed to further molecularly characterize SSA/Ps including the subset with dysplasia and/or carcinoma. As with adenomas, it is likely that only a subset of serrated polyps will ever progress to develop dysplasia, yet factors governing such progression remain unknown. SSA/Ps have molecular features of BRAF mutations and CIMP that also characterize sporadic colorectal carcinomas with MSI which supports the origin of these cancers from precursor SSA/Ps. However, gene expression profiling data suggest that SSA/Ps may also be precursors of a mesenchymal subtype of colorectal carcinoma that have a poor prognosis (24). The identification of patients at risk of serrated polyps including lifestyle factors that influence this risk remain an important unmet need. A greater insight into the epidemiology of serrated polyps has the potential to enhance primary and secondary prevention strategies.
While limited data suggest that NSAIIDs may protect against serrated polyps, further studies are needed to confirm this finding and to provide mechanistic insight. Evidence indicates that SSA/PSs may be important contributors to interval colorectal cancers, especially in the right colon. Accordingly, efforts to enhance the endoscopic detection of SSA/PSs and ensure their complete removal are an immediate need and important for reducing colorectal cancer incidence. Guidelines for the management of patients with serrated polyps are based upon consensus opinion and are expected to continue to evolve.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**References**


**Authors’ Contributions**

Conception and design: S. Rashak, S.R. Sweetser, F.A. Sinicrope
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F.A. Sinicrope
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Rego, F.A. Sinicrope
Writing, review, and/or revision of the manuscript: S. Rashak, R. Rego, S.R. Sweetser, F.A. Sinicrope
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F.A. Sinicrope
Study supervision: F.A. Sinicrope

Received October 14, 2016; revised November 21, 2016; accepted March 15, 2017; published OnlineFirst March 21, 2017.
Serrated Polyps and Cancer Prevention


www.aacrjournals.org Cancer Prev Res; 10(5) May 2017

Published OnlineFirst March 21, 2017; DOI: 10.1158/1940-6207.CAPR-16-0264

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Shahrooz Rashtak, Rafaela Rego, Seth R. Sweetser, et al.


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