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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia

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In addition to the adenoma to carcinoma sequence, colorectal carcinogenesis can occur via the serrated pathway. Studies have focused on clarification of categories and molecular features of serrated polyps, as well as endoscopic detection and risk assessment. Guidelines from the World Health Organization propose assigning serrated polyps to categories of hyperplastic polyps, traditional serrated adenomas, and sessile serrated lesions (SSLs). Traditional serrated adenomas and SSLs are precursors to colorectal cancer. The serrated pathway is characterized by mutations in RAS and RAF, disruptions to the Wnt signaling pathway, and widespread methylation of CpG islands. Epidemiology studies of serrated polyps have been hampered by inconsistencies in terminology and reporting, but the prevalence of serrated class polyps is 20%–40% in average-risk individuals; most serrated polyps detected are hyperplastic. SSLs, the most common premalignant serrated subtype, and are found in up to 15% of average-risk patients by high-detecting endoscopists. Variations in rate of endoscopic detection of serrated polyps indicate the need for careful examination, with adequate bowel preparation and sufficient withdrawal times. Risk factors for SSLs include white race, family history of colorectal cancer, smoking, and alcohol intake. Patients with serrated polyps, particularly SSLs and traditional serrated adenomas, have an increased risk of synchronous and metachronous advanced neoplasia. Surveillance guidelines vary among countries, but SSLs and proximal hyperplastic polyps require special attention in assignment of surveillance interval—especially in light of concerns regarding incomplete detection and resection.

Keywords: Colon Cancer; Tumor; Colonoscopy.

Approximately 25% of sporadic colorectal cancers (CRCs) arise via serrated precursor lesions, but this was not always well recognized. Before 2010, neoplastic serrated lesions were not well detected by endoscopists and were generally interpreted as harmless hyperplastic polyps (HPs) by pathologists, despite histologic evidence for progression in rare cases.[1,2] There is still a great deal of misunderstanding surrounding serrated polyps with respect to terminology, classification, and risk assessment. In part, this is due to confusing nomenclature, varied and changing pathology criteria, and uncertainties about prognosis. Additionally, knowledge about the importance of serrated neoplasia in CRC prevention has been disseminated relatively slowly to pathologists and gastroenterologists.

Serrated polyps is an umbrella term that encompasses HPs, sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs) (Figure 1*A*). HPs are the most common, comprising approximately 75% all serrated polyps. SSLs (previously called sessile serrated adenomas or sessile serrated polyps) account for approximately 25% of serrated polyps. In general, SSLs are characterized by a larger size (Supplementary Figure 1*A*), location in the proximal colon, and a distinct endoscopic appearance compared with HPs. TSAs are the least-common type of serrated polyp, and are typically polypoid lesions found in the distal colorectum. SSLs and TSAs are each considered precursor lesions for CRC.[3]

We review what we have learned about serrated lesions, the recently updated World Health Organization (WHO) criteria for management of serrated neoplasias, and their molecular features. We discuss the epidemiology of serrated polyps, detection of premalignant serrated polyps by various CRC screening tests (particularly SSLs), and surveillance recommendations for patients with serrated polyps.

Classification of Serrated Polyps

Our increased insight into the development of serrated polyps is reflected in the increasing complexity of the different subtypes identified. Through the 1990s, most polyps with serrated architecture were classified as metaplastic or HPs, but there are now at least 3 well-described serrated polyp entities. With every new edition of the WHO classification system, changes in definitions cause changes in reported distributions and clinical impact (Figure 1*B*).

Hyperplastic Polyps

HPs are identified by exclusion—if in a well-oriented tissue section, the architectural criteria for SSL are not

Abbreviations used in this paper: **CIMP, CpG island methylator phenotype; CRC, colorectal cancer; HP, hyperplastic polyp; MSI, microsatellite instability; MSS, microsatellite stable; NBI, narrow band imaging; SPS, serrated polyposis syndrome; SSL, sessile serrated lesion; SSL-D, sessile serrated lesion with dysplasia; TSA, traditional serrated adenoma; WHO, World Health Organization.**

Most current article

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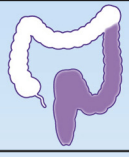
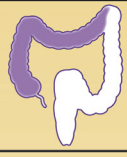
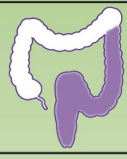
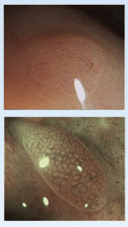
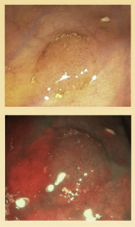
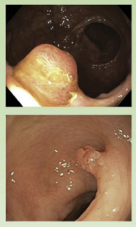
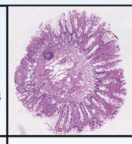
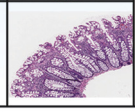
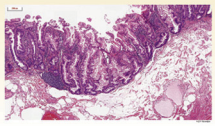
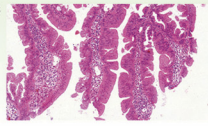
A

Features	Hyperplastic polyps (HPs)	Sessile serrated lesions (SSLs)	Traditional serrated adenomas (TSAs)
Clinical characteristics	• Prevalence: 20%–30% • Size: Usually small or diminutive (≤ 5mm) • Morphology: Flat or sessile	• Prevalence: 5%–15% • Size: Usually larger than HPs, mean diameter= 5–7mm • Morphology: Flat (45%) or sessile	• Prevalence: <1% • Size: Usually larger than SSLs • Morphology: Polypoid or pedunculated
Location	 70%–80% distal	 75%–90% proximal	 Mostly distal
Endoscopic appearance	White light: • Pale or same color as surrounding mucosa • Round or oval shape • Flatten with insufflation • Absent or fine, lacy vessels Narrow band imaging: • NICE type 1 • Uniform dark or white spots 	White light: • Mucus cap • Ring of debris • Cloud-like surface • Irregular shape Narrow band imaging: • NICE type 1 • WASP criteria • Dark spots in crypts 	White light: • Erythematous • Multilobulated • "Pine cone" appearance • Type IV-S pit pattern Narrow band imaging characterisitics not well defined 
Histopathology	Microvesicular HP (MVHP): • Narrow, uniform basal crypt • Serrated upper crypt • Eosinophilic mucin droplets in cytoplasm  Goblet cell rich HP (GCHP): • Goblet cells predominate epithelium • Less serrated than MVHP 	• Serration extending to base of crypts • Dilated and inverted "T" or boot shaped crypts • Crypt branching 	• Pseudostratification • Villous pattern with stretched or pencillate nuclei • Eosinophilic predominant • Ectopic crypts 

B

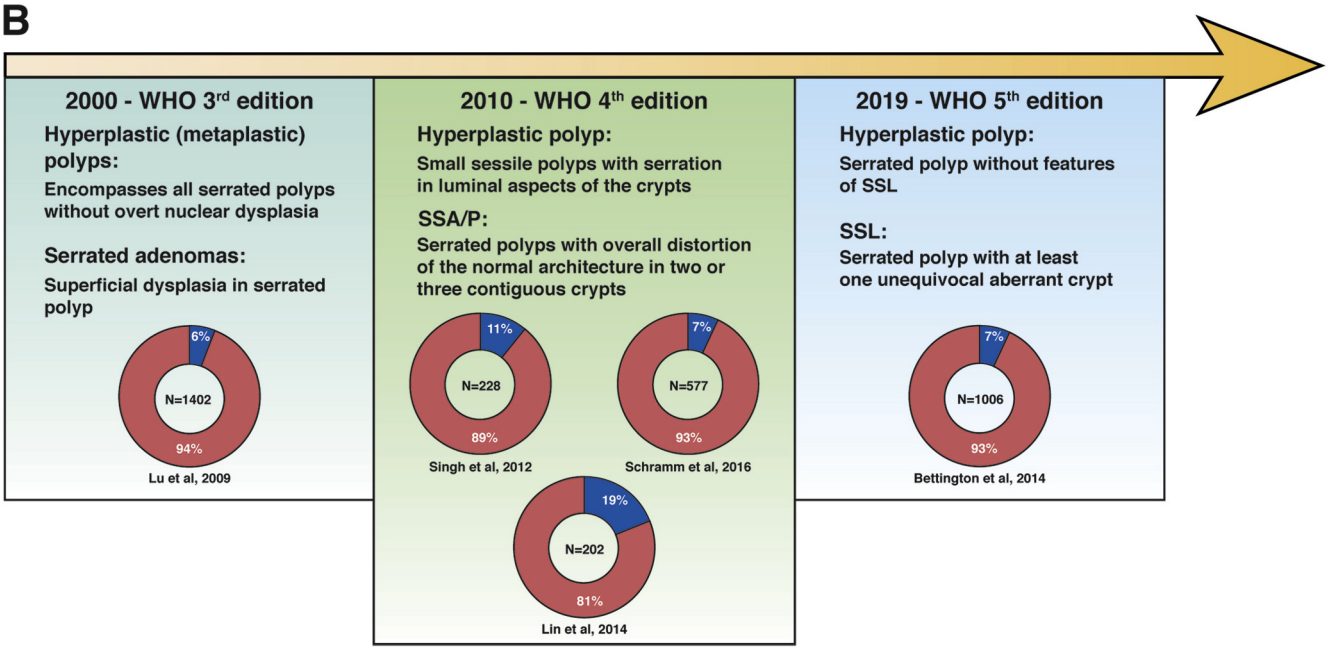


Figure 1. Classification of serrated polyps. (*A*) Clinical, endoscopic, and histologic characteristics of the different serrated polyps. (*B*) Development of definitions for SSLs and HPs over time and subsequent changes in prevalence of diagnostic categories. Studies of expert pathology review of HPs using each definition are shown in *pie charts*. The percentage of HPs re-diagnosed as SSLs is shown in *blue*, the unchanged cases are *red*. GCHP, goblet cell–rich hyperplastic polyp; WASP, workgroup serrated polyps and polyposis.

met.[3] Because the characteristics of SSLs are mainly observed in the deeper parts of the crypts, the orientation of biopsies is essential for an adequate diagnosis. The overall architecture of HP is unchanged compared with the normal colonic mucosa, and crypts remain evenly spaced. The superficial epithelium shows serration, which might cover the

upper two-thirds of the crypts (Figure 1*A*). Two variants of HPs are the microvesicular type and the goblet cell–rich hyperplastic polyps. Goblet cell–rich hyperplastic polyps have subtle morphologic alterations, such as surface tufting and increased numbers of goblet cells, resulting in small polyps. Microvesicular hyperplastic polyp are easily recognized and characterized by microvesicular epithelial cells with abundant cytoplasm, with clear stellate lumina in cross-sectioned crypts. A third subtype was described (the mucin-poor type), but it is no longer considered a separate subtype—these lesions are caused by regenerative changes in damaged microvesicular hyperplastic polyps.[3]

Sessile Serrated Lesions

The WHO recommends use of the term *sessile serrated lesion* vs other terms, such as *sessile serrated adenoma*, *sessile serrated polyp*, or *sessile serrated adenoma/polyp*.[3] The major feature that distinguishes SSLs from HPs is architectural distortion, which is most likely a result of alterations in the proliferative zone of the crypts. According to the updated WHO criteria, the presence of a single unequivocally distorted crypt is considered diagnostic for SSL.[3] Crypt distortion can be present in different forms, such as horizontal crypts, dilated crypts (basal third of the crypt), and/or crypts that have serrations extending in the crypt base. Branching crypts are no longer considered diagnostic of SSL, although these frequently occur in combination with other crypt abnormalities. Clinical features, such as size, location, and endoscopic appearance can support identification of SSL, but are not sufficient for identification. Other features that support identification are the presence of mucosal prolapse or stromal proliferations.

Mucosal prolapse is also known as herniation through the muscularis mucosa, pseudoinvasion, epithelial misplacement, or inverted crypts. It is rare in patients with HP.[4] The exact etiology is unknown, so this phenomenon has not been given a name yet. Stromal proliferation includes perineural proliferation as well as lipomatosis. More than 6% of SSLs have perineural-like stromal proliferations that can be detected during histology analysis[5] and do not share the BRAF mutations present in the epithelial component.[6] The clinical implications of these minor histologic features are not clear.

Sessile Serrated Lesions With Dysplasia

Progression of SSLs into SSLs with dysplasia (SSL-D) is not frequent—approximately 4%–8% of SSLs contain dysplasia.[7,8] At least 3 different morphologic types of dysplasia have been described in SSL-D,[9,10] which often occur within the same lesion. Intestinal dysplasia is similar to the dysplasia observed in conventional adenomas, and is relatively rare. There is no loss of MLH1 staining, and there seems to be no progression to CRC in these lesions, especially when there is low-grade dysplasia.[9,10] Serrated dysplasia is more common and is characterized by eosinophilic cytoplasm and tightly packed small glands, and its presence can be considered to represent progression to a TSA.[11] Nuclear atypia and mitotic activity are pronounced, and loss of MLH1 staining is infrequent. The third pattern is the minimal deviation dysplasia, with limited changes compared to SSL, and characteristic loss of MLH1. Most SSL-Ds, however, have an undefined pattern of dysplasia, with loss of MLH1 expression in up to 80% of cases.[9] Immunohistochemical analysis for MLH1 is important for determining the presence of clinically important dysplasia in SSLs—loss of MLH1 staining confirms the presence of dysplasia. However, the normal staining pattern can be retained in some cases of evident dysplasia. The different types of dysplasia have limited diagnostic value, but are increasingly studied in research into progression of SSLs, in combination with their molecular features. It is important to be aware of these different SSL-D in clinical practice.

Traditional Serrated Adenomas

TSAs are villous polyps with cells that contain prominent eosinophilic cytoplasm and pencillate nuclei. The pattern of serration is different from that of SSLs or HPs, and features narrow slits (Figure 1*A*). Ectopic crypts, a diagnostic features of TSAs, are found mainly in larger, distally located lesions.[11] Ectopic crypts develop orthogonally to the crypt axis and therefore have no connection to the muscularis mucosae. They contain actively proliferating cells that have aberrant expression of *GREM1*. Variants in the *GREM1* gene have been associated with hereditary mixed polyposis syndrome.[12] Lesions with characteristics of SSLs and TSAs should be classified as TSAs.

Pathology Interpretation and Reclassification of Serrated Polyps

Older clinical specimens and studies included serrated polyps that were misidentified, compared with modern criteria. Studies have evaluated the effects of reviewing these specimens, to establish the accuracy of identification based on histologic features, and mainly focused on the distinction between HP and SSL. This distinction is a significant challenge—multiple studies have reported considerable inter-observer variability in identification of HPs, and of SSLs in particular.[13–15] See Figure 1 for the variations in identification attributable to modifications in WHO definitions. Revision of cases performed from 2000 to 2010 indicate the increasing recognition of SSLs. One study during this time period reviewed more than 1400 HPs, and reclassified 6% of HPs as SSLs.[16] After SSLs (then called SSA/Ps) were included in the WHO classification of 2010, 8%–19% of HPs were reclassified as SSLs.[17–19] When only larger HPs were taken into account, the proportion of reclassified HPs was as high as 28%.[20,21] Application of the 1 crypt rule, per the recent revised WHO criteria, likely increases the sensitivity of detection of SSLs further. Bettington et al[22] reported that the application of this criterion resulted in a 7% increase in the proportion of serrated polyps classified as SSLs. An additional benefit of this new definition is improved inter-observer agreement compared with the 4th edition WHO criteria.[23,24] Inter-observer agreement can be further improved by better orientation of polyps[25] and by training.[26]

To acknowledge ongoing research, the category "serrated adenoma not classified" has been introduced by the WHO. This category should only be used for lesions that cannot be classified as TSAs or SSLs.

Serrated Adenocarcinoma

In analogy to serrated precursor lesions, serrated adenocarcinoma is increasingly recognized as a distinct CRC subtype. Studies found that 10%–15% of colorectal tumors could be classified as serrated adenocarcinomas, based on histologic features.[27] These tumors have glandular serration, with or without mucinous areas. Based on molecular features, researchers proposed that approximately 25% of colorectal tumors develop along the serrated pathway, although these tumors do not all necessarily have serrated morphology.

Molecular Features of the Serrated Pathway

The serrated pathway is characterized by a sequence of genetic and epigenetic changes that accompany polyp progression, tracked by histologic features (Figure 2*A*). In most serrated polyps, the first step of the pathway is believed to be acquisition of a mutation in a gene that regulates mitogen-activated protein kinase pathway (such as in *KRAS* or in most cases *BRAF*).[28] Activating mutations in BRAF result in widespread methylation of CpG islands, called the a CpG island methylator phenotype (CIMP).[29,30] CIMP results in silencing of many genes, including some tumor suppressor genes. Hypermethylation of *CDKN2A* (which encodes P16) occurs more frequently in TSAs than SSLs, in particular in the advanced lesions with *BRAF* mutations.[11] Hypermethylation of the promoter of the *MLH1* occurs only in SSLs and is associated with specific polymorphisms in *MLH1* (*MLH1-93AA*).[31] Approximately 75% of SSL-D[32] have microsatellite instability (MSI), resulting from this specific hypermethylation. Thus, immunostaining for MLH1 protein can identify dysplasia.[9]

Progression of serrated polyps is associated with activation of the WNT signaling pathway (Figure 2*B*). The development of conventional adenomas also involves activation of the WNT pathway, which is usually an early step in carcinogenesis. Truncating mutations in *APC* gene are found in >90% of adenomas. In contrast, similar *APC* mutations are found in only 10%–15% of SSL-D and 36% of TSAs.[33] Activation of the WNT pathway in SSLs is caused mainly by mutations in the RNF43–ZNRF3 complex[34,35]; these can be as frequent as 86% in cases with *MLH1* promoter hypermethylation. Mutations in this receptor prevent normal regulation of WNT by RNF43-mediated stimulation of endocytosis of the frizzled–LRP5–LRP6 complex.[36] Alternatively, approximately 30% of TSAs have fusions of genes in the R-spondin family (RSPO fusions), resulting in R-spondin overexpression, and down-regulation of *RNF43*.[37,38] This occurs more frequently in *KRAS*-mutated TSAs.

Colorectal tumors arising from serrated lesions can exhibit different molecular features, likely dependent on the precursor polyps and pathways. There are at least 3 subgroups of CRCs, based on molecular features (Figure 2). CRCs with *BRAF* mutations have high levels of CpG island methylation (CIMP-high), MSI, and are mainly found in the right colon.[39–42] MSI is found in conventional adenomas only in patients with Lynch syndrome (Dabir et al, unpublished data), so it is reasonable to assume that CRCs with *BRAF* mutations (3%–8% of CRCs)[39–42] are of only serrated origin, and are derived from SSLs. Morphologically, medullary, mucinous, and signet ring cell carcinomas are overrepresented in this tumor group.[43] These tumors are called CMS1 in the common molecular subtype classifications of CRC,[44] and are characterized by a hypermutator phenotype and favorable patient outcomes. A second group of colorectal tumors, which is more rare (account for 2%–6%), have mutations in *BRAF*, are CIMP high, but are microsatellite stable (MSS).[39–42] *BRAF* mutations are rare in conventional adenomas,[45,46] so most of these tumors are of serrated origin (from either SSLs or TSAs). The third group of colorectal tumors is characterized by *KRAS* mutations and MSS. These account for 25%–33% of colorectal tumors.[39–42] Only a small proportion of these tumors are likely to be of serrated origin, given the relative rarity of the TSA precursor, and the fact that *KRAS* mutations are found more frequently in conventional adenomas.[45] However, most colorectal tumors (53%–70%) do not fall into any of these categories.

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS) is characterized by multiple serrated polyps throughout the colorectum and increased risk of CRC. Updated WHO criteria for SPS include: at least 5 serrated lesions or polyps proximal to the rectum, all ≥5 mm, with 2 or more that are ≥10 mm, or more than 20 serrated lesions or polyps of any size distributed throughout the large bowel, with at least 5 proximal to the rectum.[3] It is important to note that any serrated polyp subtype (HP, SSL, TSA, or serrated adenoma not classified) is included in the final polyp count, and that polyp count is cumulative over multiple colonoscopies. The WHO criteria used to include: any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS, but this item was eliminated from the most recent criteria (Supplementary Table 1). However, SPS phenotypes vary, and because little is known about the genetic alterations that contribute to their development, SPS might result from more than 1 disorder. A small proportion of patients with SPS have mutations in *RNF43*, which regulates the WNT pathway (Figure 2*B*). However, most cases of SPS are not associated with any specific genetic variants.[47]

The prevalence of SPS in average-risk populations undergoing colonoscopy ranges from 0.03% to 0.5%, depending on screening vs surveillance indication.[48] Patients with SPS typically receive their diagnosis when they are 40–60 years old, and the disorder is equally common among men and women.[49,50] Studies from cohorts of patients SPS report overall cancer risk in the range of 15%–30%, though cancer risk varies with patient age, polyp burden and phenotype, and presence of high-risk histologic features.[50,51] Close endoscopic surveillance is recommended

for patients with confirmed SPS, with annual colonoscopies (or occasionally longer intervals in individuals with lower polyp burden and absence of high-risk features).[52] Endoscopic management can reduce the risk of cancer development in many patients with SPS, so referral to a specialized center or endoscopist should be considered following diagnosis.[53]

Epidemiology

It is a challenge to make conclusions from epidemiologic studies of serrated polyps, due to inconsistent terminology and nomenclature, the changing taxonomy, variations in detection and resection practices, and a preponderance of single-center studies with limited external validity. Also, the most common serrated polyps are distal HPs (which are generally thought to be harmless), so it is difficult to draw conclusions from epidemiology studies that group all serrated class lesions together. Many authors and groups have addressed these limitations by using surrogate definitions for important or clinically significant serrated polyps, namely larger and/or proximally located lesions. However, such classification schemes are neither particularly sensitive nor specific for the entire group of premalignant serrated polyps. For example, most SSLs are <1 cm in size, as many as 25% are located in the distal colorectum,[54,55] and most TSAs are distally located. Furthermore, true (presumably low-risk) HPs exist in the proximal colon in significant numbers of individuals.[56] For this reason, more recent studies that classify serrated polyps per 2010 WHO taxonomy are the most informative regarding epidemiology.

Serrated neoplasia appears to be a universal human phenomenon; SSLs and other serrated lesions are found in many disparate populations and ethnic groups. Although most epidemiology studies of SSLs were performed in the United States or Europe, serrated polyps have been reported worldwide, in studies from Korea,[57] Japan,[58,59] China,[60,61] Australia,[62] Peru,[63] Argentina,[64] Russia,[65] Turkey,[66] India,[67] and Nigeria,[68] among other countries. In general, countries that do not screen the population for CRC, or that perform colonoscopies primarily for diagnostic purposes, report lower prevalence values for adenomatous polyps and serrated polyps.

Prevalence Based on Endoscopic Data

A number of cross-sectional studies have measured the endoscopic prevalence of serrated polyps overall and SSLs and TSAs specifically. Older studies (those published or containing colonoscopy data before 2010) generally provide less-reliable information, so it is important to focus on contemporary studies for more accurate epidemiologic data. Furthermore, given substantial variation in serrated polyp detection (especially SSL detection), prevalence estimates depend on the endoscopists who perform the colonoscopies. Furthermore, many endoscopists do not remove obvious diminutive distal HPs, given lack of malignant potential, so prevalence estimates for total serrated polyps, and HPs in particular, are likely to be underestimated from analyses of colonoscopy and pathology data.

In pathology series studies, serrated polyps accounted for 30%–40% of polyps removed from unselected adult patients undergoing colonoscopy for screening, surveillance, or diagnostic indications.[69–72] An estimated 20%–40% of screening-age adults have at least 1 serrated polyp—most are small, distal HPs.[45,62,73]

Reviews of recently published colonoscopy series studies found that an average 2%–8% of SSLs are detected (akin to prevalence) in average-risk patients undergoing colonoscopy.[8,54,58,62,73–82] Among high-detecting endoscopists and centers, however, the reported prevalence values are 13%–20% (Figure 3*A*, Supplementary Table 2).[45,54,62,74,78] It is a reasonable assumption that detection of SSLs among high detectors is the best estimate of the true prevalence of these lesions. Dysplastic SSLs are uncommon, occurring in roughly 0.5% of average-risk patients (approximately 4%–8% of all SSLs).[7,8,54]

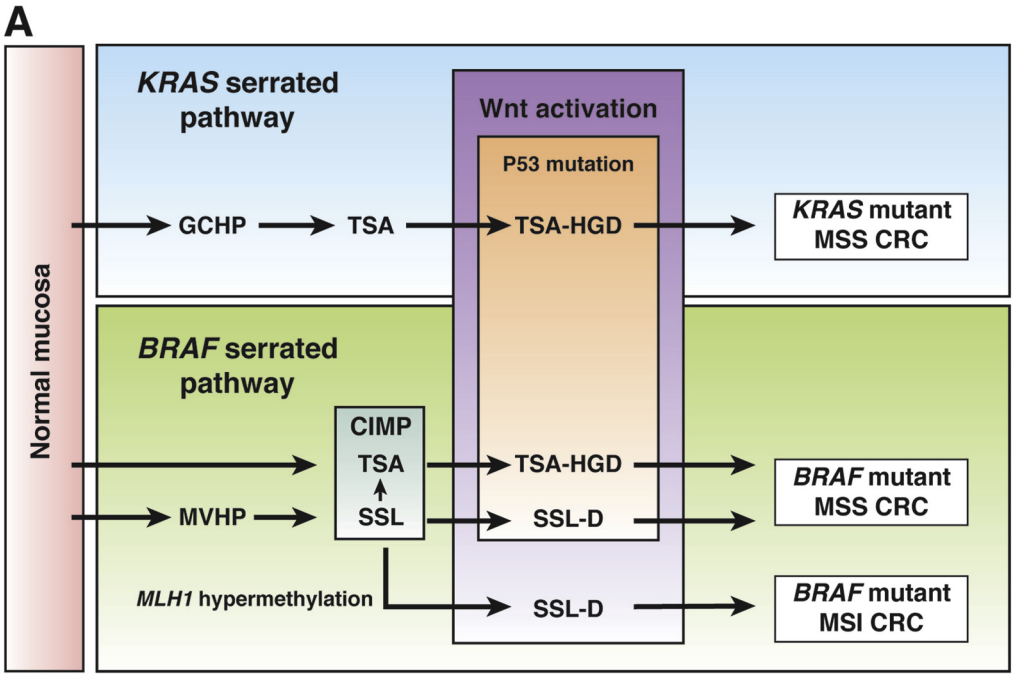
It is also important to recognize that there is significant overlap among the prevalence of serrated polyps and conventional adenomas. In most series, roughly half of patients with SSLs also had synchronous conventional adenomas (Figure 3*B*). TSAs are less common than SSLs—TSAs are found in 0.1%–0.7% of average-risk patients undergoing colonoscopy.[8,54,62,73,74] Because TSAs tend to be larger and easier to recognize than SSLs, they are less susceptible to endoscopic underdetection. However, TSAs can be challenging to identify and might be mistaken for villous adenomas by pathologists, which could lead to underestimation of TSA prevalence.

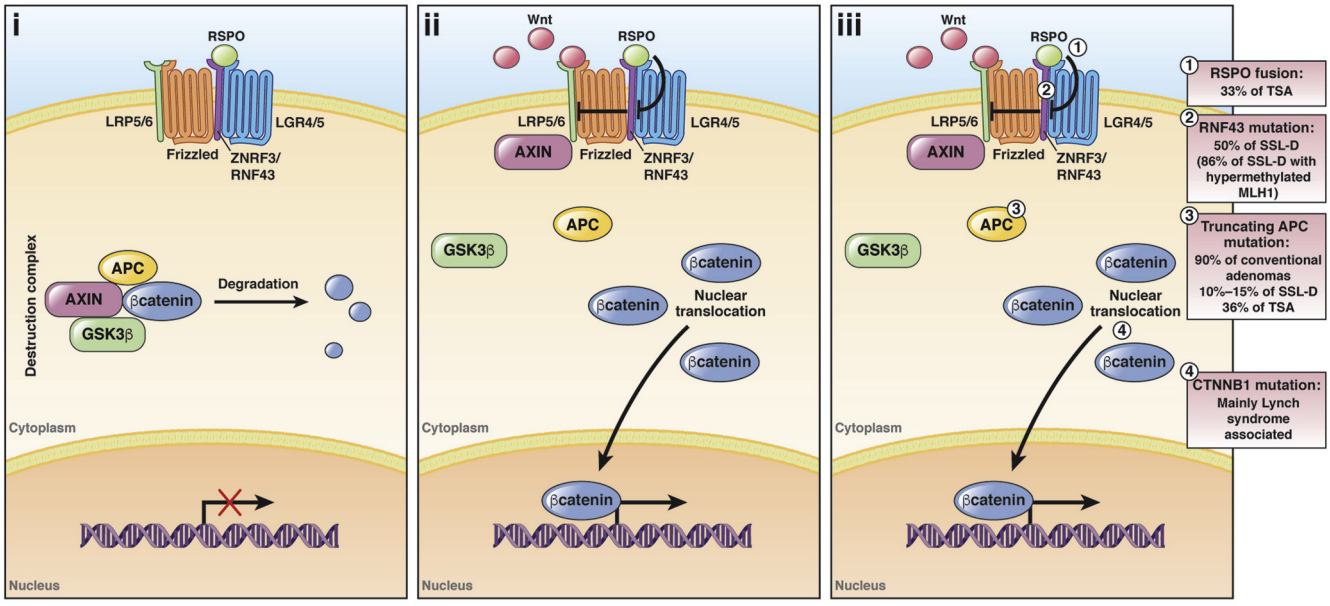
Prevalence Based on Autopsy Data

Although endoscopic population-based studies have provided a good estimate of the prevalence of serrated polyps, they are limited by endoscopic equipment, patient factors, colonoscopy quality, and inter-observer variation. Autopsy studies are informative with respect to the epidemiology of serrated polyps, and provide useful data regarding worldwide variation in the prevalence of serrated polyps. We searched the literature for autopsy series reporting data on serrated polyps of the colorectum. Given the variation in the periods of study, it was not possible to distinguish different polyp types, but the data give a clear indication of the variations based on geography and age. Of 8440 patients included in 16 studies, 1147 (13.6%) had 1 or more serrated polyps (Supplementary Table 3).[83–96] There was a large geographic variation in the prevalence of serrated polyps, with high prevalence in the United Kingdom[90,91] New Zealand,[95] and the United States,[94] and very low prevalence in Singapore and Japan (Figure 4*A*).[84,85,93] There were also large within-country differences related to urbanization (in Norway and Columbia).[83,86,88,89] Most studies included different age categories, making them difficult to compare, but in general the prevalence of serrated polyps increased with patient age (Figure 4*B*).

Nonmodifiable Risk Factors

Contemporary studies have identified a number of risk factors for SSLs in particular. In contrast to conventional adenomas, older age and male sex are not strong risk factors for


A
Normal mucosa
KRAS serrated pathway
GCHP
TSA
Wnt activation
P53 mutation
TSA-HGD
KRAS mutant MSS CRC
BRAF serrated pathway
CIMP
TSA
SSL
MVHP
TSA-HGD
SSL-D
BRAF mutant MSS CRC
MLH1 hypermethylation
SSL-D
BRAF mutant MSI CRC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GSK3β
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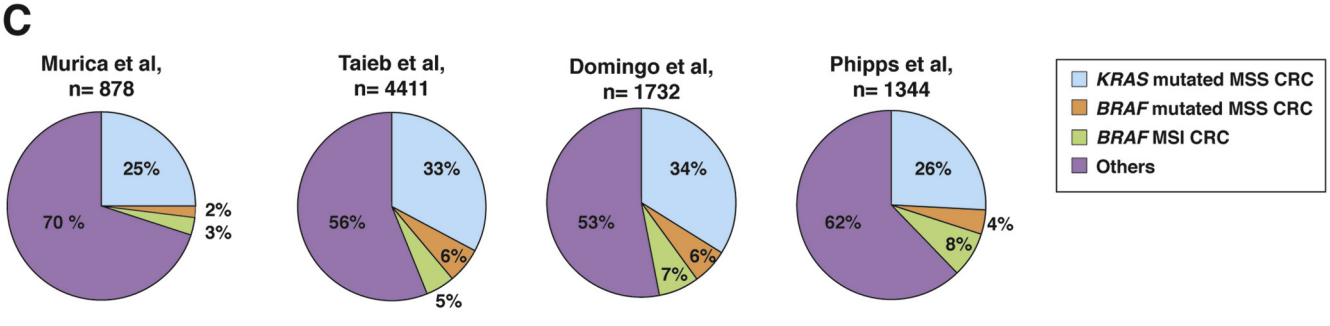
Nucleus
ii
Wnt
RSPO
LRP5/6
LGR4/5
AXIN
Frizzled
ZNRF3/ RNF43
APC
GSK3β
βcatenin
Nuclear translocation
βcatenin
Cytoplasm
βcatenin
Nucleus
iii
Wnt
RSPO
1
2
LRP5/6
LGR4/5
AXIN
Frizzled
ZNRF3/ RNF43
APC
3
GSK3β
βcatenin
Nuclear translocation
4
βcatenin
Cytoplasm
βcatenin
Nucleus
1 RSPO fusion: 33% of TSA
2 RNF43 mutation: 50% of SSL-D (86% of SSL-D with hypermethylated MLH1)
3 Truncating APC mutation: 90% of conventional adenomas 10%–15% of SSL-D 36% of TSA
4 CTNNB1 mutation: Mainly Lynch syndrome associated


C
Murica et al, n= 878
25%
2%
3%
70 %
Taieb et al, n= 4411
33%
6%
5%
56%
Domingo et al, n= 1732
34%
6%
7%
53%
Phipps et al, n= 1344
26%
4%
8%
62%
KRAS mutated MSS CRC
BRAF mutated MSS CRC
BRAF MSI CRC
Others

SSLs. Although patients younger than 50 years have a lower risk of SSLs than patients older than 50 years, risk does not appear to increase substantially with age beyond 50 years.[48,54,97] With regard to sex distribution, men and women appear to have a roughly equivalent risk of SSL,[73,98–100] although some studies reported a higher risk in men,[76,101] whereas others reported a higher risk in women.[69,71]

White race is a consistent risk factor for SSLs in US and European studies of average-risk patients, whereas black, Asian, and American Indian/Alaskan Native populations have a lower prevalence.[80,99,100,102,103] In a large US study with data from 1.6 million screening colonoscopies, white men and women were found to have a 2- to 3-fold increase in risk of SSLs compared to black or Asian individuals (Supplementary Figure 1*B*).[99] Patients with a family history of CRC or a personal history of premalignant serrated polyps also have an increased risk of SSLs.[45,104,105]

Modifiable Risk Factors

There is strong evidence that smoking and serrated polyps (and SSLs in particular) are linked. A pooled analysis of data from more than 130,000 participants from the Nurses' Health Study and Health Professionals Follow-up Study reported that users of tobacco had a 2.5-fold increase in risk of serrated polyps.[106] Other studies reported similar results,[97,100,103,104,107–110] and a meta-analysis associated smoking with a more than 3-fold increase in risk of SSLs.[111] Interestingly, smoking appears to be more strongly associated with distal serrated polyps, which seems counterintuitive, given that SSLs are predominantly found in the proximal colon; the clinical significance of this phenomenon is uncertain.[112,113]

Multiple studies have also found an association between alcohol intake and SSLs. Higher intakes of alcohol are modestly associated with an increased risk of SSLs, with risk or odds ratios on the order of 1.1–1.8 compared with nondrinkers.[100,111]

There is also some evidence to support a weak association between obesity and serrated polyps and SSLs specifically. In the Nurses' Health Study and Health Professionals Follow-up Study, He et al[106] reported that patients in the highest categories of body mass index had a roughly 30% increase in risk of serrated polyps compared to normal-weight individuals. Other studies reported stronger associations between obesity and SSLs. However, the evidence is somewhat conflicting, and some studies report null associations.[100] Furthermore, a meta-analysis did not find a significant association between high body mass index and SSLs (summary odds ratio, 1.31; 95% confidence interval, 0.89–1.92).[111] Therefore, if obesity does increase the risk of SSLs, the effect is likely modest.

There is also consistent evidence associating intake of aspirin and non-steroidal anti-inflammatory drugs with reduced risk of SSLs. In a post-hoc analysis of data from an aspirin polyp chemoprevention trial, Wallace et al[113] reported that aspirin reduced the risk of proximal serrated polyps by roughly 40%. A recent meta-analysis also found an inverse association between non-steroidal anti-inflammatory drug use and SSL occurrence, with a pooled risk ratio of 0.62.

In addition to these risk factors, individual studies have reported associations between premalignant serrated polyps and diabetes,[107] high socioeconomic status,[100] and supplementary folate[113] and calcium intake.[114] However, given limited evidence, these findings are considered inconclusive.

Clinical Implications

Clinical Features and Endoscopic Appearance

HPs are small, round, pale polyps that are predominantly located in the distal rectosigmoid colon. HPs are typically flat or minimally elevated, may flatten further with insufflation. HPs typically have absent or thin, lacy overlying capillaries, and a papillary or stellate pit pattern. Use of narrow band imaging and the Narrow Band Imaging International Colorectal Endoscopic classification criteria can reliably differentiate HP from conventional adenomas.[115] SSLs are typically larger than HPs, with an average size of 5–7 mm (Supplementary Figure 1*A*), but are also pale and have either a flat or sessile morphology.[54,55] Distinguishing features of SSLs include a cloud-like surface, an overlying mucus cap, a rim of debris or stool around the lesion, and obscuration of the underlying mucosal vasculature.[116,117] Like HPs, SSLs are International Colorectal Endoscopic type 1 lesions, but additional NBI criteria, such as a cloud-like surface, irregular shape, and dark spots inside crypts, can help distinguish them from HPs.[118] TSAs are typically larger lesions (average size 15 mm), found in the distal colorectum, that resemble pedunculated or semi-pedunculated conventional adenomas.[11] TSAs can have an erythematous, pine-cone appearance due to villous structure (Figure 1*A*).[119]

Detection by Screening Tests

Serrated polyps, and SSLs in particular, are more difficult to detect than conventional adenomas. With respect to non-colonoscopy screening tests, detection is generally either null or very poor.[120] Sigmoidoscopy does not examine the proximal colon, where most SSLs reside. Kahi et al[121] found that distal neoplasia is not a marker of proximal serrated polyps. Fecal occult blood tests and fecal immunochemical tests detect serrated polyps poorly because even large serrated polyps rarely bleed.[122] Computed tomography

Figure 2. The serrated pathway. (*A*) Changes in different types of serrated polyps. (*B*) The role of WNT activation in development of serrated polyps and conventional adenomas showing (*i*) normal cell, with inactivated WNT; (*ii*) cell with activated WNT and proliferation due to transcription of MYC and cyclin D1, regulated by R-spondins and ZNRF3–RNF43; and (*iii*) different forms of WNT activation in colorectal carcinogenesis. (*C*) Frequencies of molecular subtypes relevant in the serrated pathway: evidence from large-scale molecular studies. *Blue*, KRAS-mutated with MSS tumor; *orange*, BRAF-mutated with MSS tumor; *green*, BRAF-mutated with MSI tumor; *purple*, others.

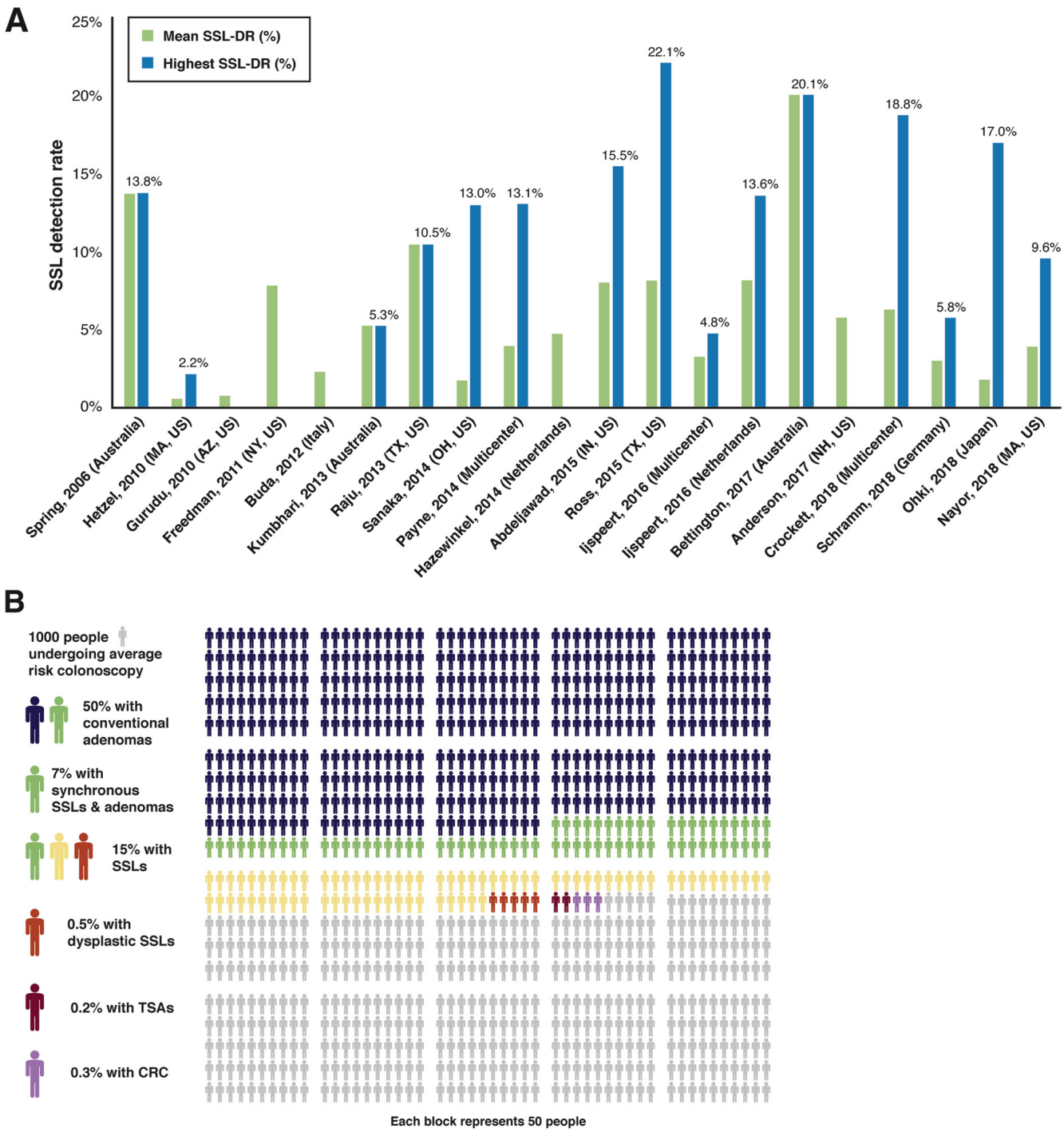


Figure 3. Epidemiology. (*A*) Rates of endoscopic detection of SSLs in studies of average-risk patients, with comparison of the average detection rate (*green*) and the highest SSL detection rate per center or endoscopist (*blue*) (see also Supplementary Table 2). (*B*) *Pictogram* demonstrating the estimated true prevalence of conventional adenomas, SSLs, TSAs, and colorectal cancer in an average-risk screening population.

colonography does not detect serrated polyps or other flat lesions well, due to its dependence on morphology.[123] Recently developed stool DNA tests seem promising but detect only a fraction of large SSLs.[122,124] For these reasons, colonoscopy (though also imperfect) offers the best chance to optimize detection of premalignant serrated polyps.

Endoscopic Detection

A number of studies from different settings have demonstrated that endoscopic detection of proximal serrated polyps, and SSLs in particular, varies. There is as much as 18-fold variation among endoscopists in detection of clinically relevant serrated polyps (Figure 3*A*,

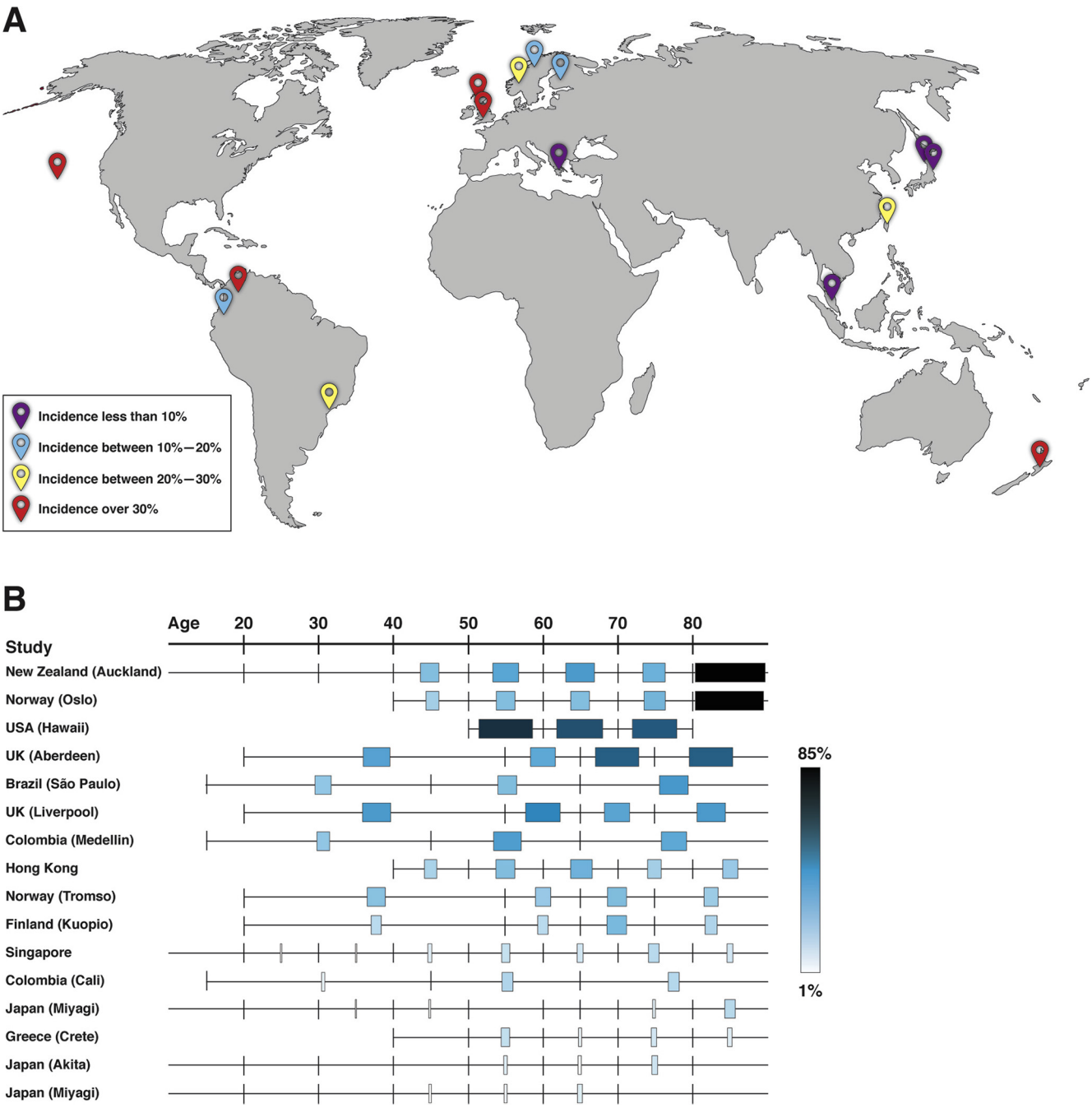


Figure 4. (*A*) Worldwide differences in incidence of serrated polyps in patients 45–69 years old, based on autopsy studies (see also Supplementary Table 3). (*B*) Age-related incidence of serrated polyps; results are given as a percentage of included patients per age group. Data retrieved from autopsy studies; definitions of the different age groups vary with study.

Supplementary Table 2).[54,74,76,98,125] Factors associated with improved detection include better bowel preparation,[126] longer withdrawal time (optimal 9 minutes or more),[127] and careful examination of the right colon in particular (repeat anterograde examination or retroflexion in the cecum).[128] In addition, endoscopic tools may be helpful to improve endoscopic visualization, particularly for operators with suboptimal detection, including use of a transparent cap, endocuff, or other mucosa exposure devices.[129–131] Chromoendoscopy also appears to be beneficial, but may add procedure time and complexity.[132] The benefit of image-enhanced endoscopic techniques, such as narrow-band imaging and linked color imaging, may be associated with marginal improvements in SSL detection as well, but the benefits are uncertain.[133–135]

Resection

Most SSLs can be removed with either standard cold snare (for smaller lesions) or endoscopic mucosal resection

Table 1. Guidelines for Post-Polypectomy Surveillance of Serrated Polyps

		Guideline recommended surveillance intervals						
Polyp findings	Definition	International Serrated Consensus Panel, *y*	US Multi-Society Task Force, *y*	British Society of Gastroenterology, *y*	European Union Guidelines, *y*	European Society of Gastrointestinal Endoscopy, *y*	Korean Multi-Society Task Force, *y*	Cancer Council of Australia, *y*
Low-risk HP	Small (<10 mm) rectosigmoid HPs	10	10	No surveillance	Routine screening	Routine screening	NR	10
	1–3 small (<6 mm) proximal HPs	10	NR	No surveillance	NR	Routine screening	NR	NR
Intermediate-risk serrated polyp	Large (≥10 mm) HP	5	NR	No surveillance	NR	3	3[a]	NR
	>3 proximal HP	5	NR	No surveillance	NR	Routine screening	NR	NR
	1–2 SSL, <10 mm in size	5	5	No surveillance	NR	Routine screening	NR	5
High-risk serrated polyp	Large (≥10 mm) SSL	3	3	3	NR	3	3	3
	≥3 SSL	3	3–5	No surveillance	NR	Routine screening	NR	3
	SSL with dysplasia	1–3	3	3	NR	3 years	NR	5[b]
	TSA	3–5[c]	3	3	1–10[d]	3[e]	3–5[a]	3–5
SPS	WHO criteria (see text)	1	1	1–2	NR	NR[f]	NR	NR

NR, no recommendation.
[a]Korean guidelines recommend 3-y surveillance for any serrated polyp ≥10 mm (HP, SSP, or TSA). Small (<10 mm) TSA would fall into low-risk category (5-y surveillance).
[b]Australian guidelines recommend managing SSPs and TSAs identical to conventional adenomas, with 3- to 5-y surveillance based on number and size. Only high-grade dysplasia (rare in SSPs) considered high risk.
[c]Consensus panel recommends 3-y interval for large or multiple (≥3) TSAs
[d]European Union guidelines recommend managing TSAs identical to conventional adenomas, which could result in interval from 1-10 years based on size and multiplicity
[e]European Society of Gastrointestinal Endoscopy guidelines recommend 3 year surveillance for any serrated polyp ≥10 mm (HP, SSP, or TSA). Guideline is ambiguous as to management of small TSAs.
[f]European Society of Gastrointestinal Endoscopy guidelines do recognize SPS and recommend referral to genetic counseling for SPS, but do not recommend a specific surveillance interval for these patients.

(for larger lesions) procedures.[136] In recent years, there has been an interest in alternative resection methods, such as underwater endoscopic mucosal resection and piecemeal cold-snare polypectomy, though additional research is needed to establish the efficacy and safety of these techniques.[137,138]

There is some evidence that SSLs, and particularly large SSLs, may be prone to incomplete resection. This stands to reason, given that SSLs are often subtle lesions, and the margin between polyp and normal tissue can be difficult to appreciate. One study reported that nearly 33% of SSLs (and roughly 50% of large SSLs) removed by hot-snare polypectomy left residual polyp tissue behind after resection attempts.[139] This study also found substantial variability among endoscopists in the SSL resection rate. However, at experienced centers, even large (>2 cm) SSLs can be resected completely with a low rate of residual neoplasia, when careful endoscopic mucosal resection technique is used.[140] Importantly, use of dye-tinted submucosal injectate can help delineate lesion borders and ensure adequate resection (Figure 5). Taken together, results of these studies indicate that, in practice, SSL resection is imperfect and that endoscopist skill and experience, as well as choice of technique, are required to ensure that SSLs (particularly larger SSLs) are completely removed. There is a need for quality improvement efforts in endoscopy programs to focus on polyp resection practices in addition to polyp detection.

Risk of Synchronous and Metachronous Neoplasia

There is consistent epidemiologic evidence that individuals with SSLs and TSAs have increased risks of synchronous and metachronous advanced neoplasia (typically defined as an advanced adenoma or CRC) compared to persons without polyps. A meta-analysis found that patients with SSLs have a 2- to 4-fold increased risk of synchronous advanced neoplasia,[141–145] and roughly 30% of these patients have multiple SSLs.[144]

SSLs and large HPs are also associated with an increased risk of metachronous polyps and CRC.[141,146–148] Patients with baseline SSLs appear to have a risk of future polyps that is similar or greater than the risk in patients with conventional adenomas.[16,141,146] Retrospective studies reported that patients with SSLs have a significantly increased long-term risk of future CRC compared to patients without SSLs.[147,148] In a large population-based case–control study in Denmark, Erichsen et al[147] found that patients with antecedent SSLs had a 3-fold increased risk of CRC compared to patients without polyps. Furthermore, CRC risks were even greater for women with SSLs, and patients with proximal SSLs, SSL-Ds, or TSAs. In a secondary analysis of data from the Norwegian Colorectal Cancer Prevention flexible sigmoidoscopy trial, Holme et al[148] reported that participants with large (≥10 mm) serrated polyps found during screening had a 4-fold increase in long-term risk of CRC compared to subjects without polyps. Several studies

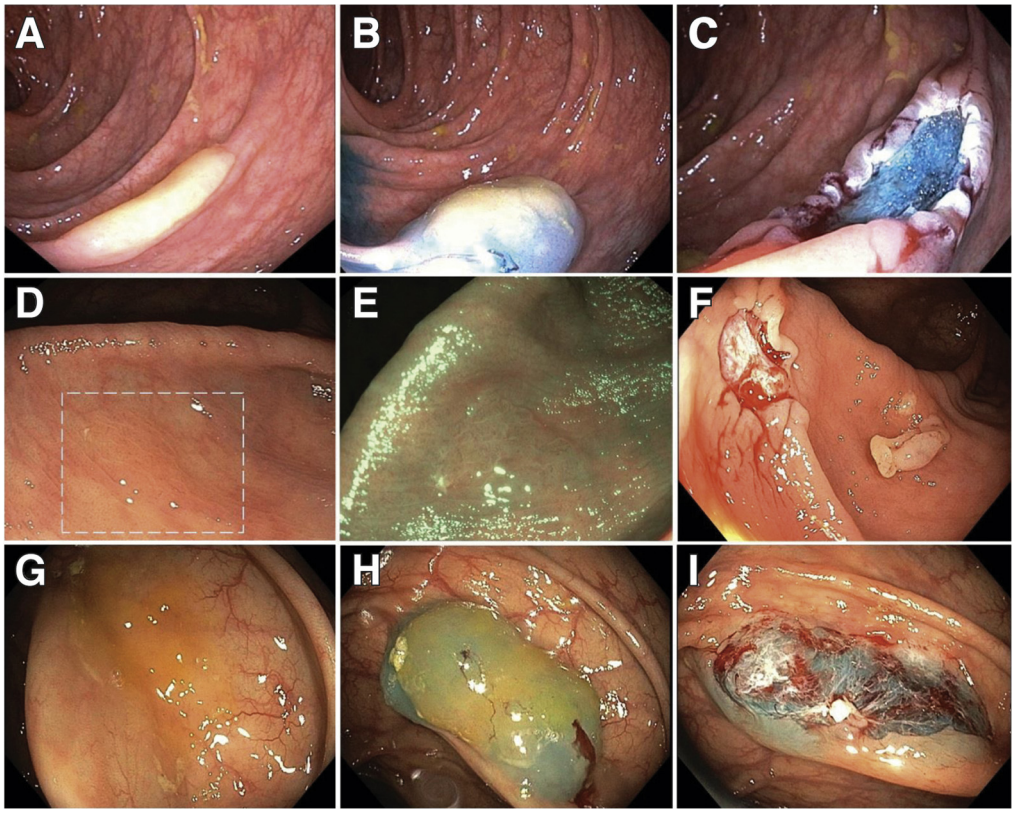


Figure 5. Endoscopic images of 3 different SSLs before and after resection. *First row* shows a 15-mm minimally elevated lesion (*A*) in the ascending colon, removed with traditional endoscopic mucosal resection. Submucosal injection of methylene blue–tinted saline (*B*) helps delineate lesion borders before en bloc hot-snare resection (*C*). *Second row* depicts a smaller 6-mm flat SSL in the cecum viewed with white light (*D*) and narrow-band imaging (*E*) before cold-snare resection (*F*). *Third row* depicts a larger, 3-cm flat SSL in the ascending colon (*G*). Submucosal injection of methylene blue and colloid solution performed (*H*) before piecemeal cold-snare polypectomy (*I*).

reported that patients with SSLs or large serrated polyps with synchronous conventional adenomas are at higher risk of metachronous advanced neoplasia (advanced adenomas) than patients with isolated SSLs.[141,149] It is also important to remember that studies examining short-term outcomes have found that patients with SSLs or other clinically significant serrated polyps are at risk for recurrent serrated polyps compared with other lesion types.[146,149]

Given the increased risk of future CRC associated with SSLs and evidence that the serrated pathway accounts for 20%–25% of all sporadic CRC, it is puzzling that the intermediary lesion, the SSL-D is not found more frequently than it is. SSL-Ds are found in only around 0.5% of average-risk patients.[8] This paradox of low SSL-D prevalence is likely attributable to a combination of factors. The endoscopic miss rate for SSLs varies, so many SSL-D may be missed during screening. Development of dysplasia often coincides with inactivation of *MLH1*, MSI, and presumed rapid growth of the lesion, so the window of detection of SSL-D might be relatively short (compared to conventional adenomas, which are thought to have more gradual growth).[150] SSLs that have extensive cytologic dysplasia may be difficult for pathologists to differentiate from conventional adenomas, leading to misdiagnosis.[151] Furthermore, SSL-Ds often have a fried egg morphology: the dysplastic portion is polypoid and surrounded by a ring of nondysplastic SSL tissue that is more flat. Endoscopists may resect the protuberant portion only, which might be read as a conventional adenoma rather than an SSL-D.[152]

Surveillance Guidelines

Multiple societies and organizations have issued surveillance guidelines for patients who have serrated polyps removed during screening or surveillance colonoscopy. The most widely used surveillance guidelines from the US are from the Multi-Society Task Force,[153] though British,[154,155] European,[156,157] Japanese,[158] Korean,[159] and Australian[160] guidelines with disparate recommendations have also been published. In addition, an international consensus panel on serrated neoplasia published surveillance recommendations in 2012 (Table 1).[161] In general, US guidelines and those of the international consensus panel are more aggressive with respect to surveillance for SSLs and other potentially precancerous serrated lesions, recommending surveillance intervals that are similar to those of conventional adenomas. Because of issues regarding pathologist interpretation of serrated lesions (and the difficulty distinguishing HP from SSLs in particular), some groups recommend managing patients with proximal HPs (especially 1 cm or more proximal HPs) similar to those with SSLs.[161] Annual colonoscopy is generally recommended for patients with confirmed SPS, though longer intervals (eg, 24 months) may be adequate in patients once endoscopic control is achieved.[52]

Future Directions

There are many controversies over serrated neoplasias—studies are needed to inform evidence-based practice recommendations. Researchers have debated the nomenclature, and worldwide differences in terms (SSA, SSP, SSA/P, and SSL), pathology reports, and publications, has caused confusion for patients and providers alike. This lack of synchronization is problematic. Although no single term will satisfy all experts, we support the acceptance of a standard terminology as recommended by the WHO, and specifically the use of *sessile serrated lesion* vs other terms. The term *sessile serrated lesion* was introduced years ago in Europe for standardized reporting in population screening and has been implemented successfully. However, debate on this issue is likely to continue after the publication and dissemination of the upcoming WHO update, and incongruous nomenclature may persist. Therefore, clinicians should be aware of the multiple historical terms used to describe the SSL entity.

Identification of SSLs based on pathology features, and in particular the differentiation of HPs from SSLs, can be challenging in some specimens due to small size, tangential sectioning, and/or poor orientation. Adoption of the 1 crypt rule is expected to improve inter-observer variation in detection of SSLs, but variations in diagnoses among centers and among pathologists are likely to persist.[162] Use of additional immunohistochemical or molecular markers could aid in detection and determination of risk.[163]

There is also controversy over surveillance guidelines for serrated-class lesions. This could be because the risk of metachronous neoplasia associated with serrated lesions is not entirely clear. We also lack sufficient data to inform surveillance decisions for certain situations, such as patients with 1 or 2 small SSLs, or patients with proximal and/or large HPs. Although it seems reasonable to follow surveillance guidelines that mirror those for conventional adenomas, some experts believe this approach is too aggressive. Additional longitudinal studies will help clarify these areas of uncertainty.

The past decade has seen tremendous advances in the understanding of serrated colorectal neoplasia. Recently updated WHO criteria outline the proper diagnosis, classification, and nomenclature of HPs, TSAs, and SSLs. Molecular changes associated with serrated neoplasia include mutations in the mitogen-activated protein kinase and WNT pathways, as well as epigenetic modifications, leading to either MSS or MSI cancers. SSLs are the most prevalent premalignant serrated polyp subtype, and are found in as many as 15% of average risk patients undergoing colonoscopy by high-detecting endoscopists. Efforts are needed, worldwide, to optimize detection, resection, and accurate classification of serrated polyps and lesions, and to determine the most appropriate surveillance practices for the patients who have them.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.06.041.

References

1. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol 1990; 14:524–537.
2. Goldman H, Ming S, Hickock DF. Nature and significance of hyperplastic polyps of the human colon. Arch Pathol 1970;89:349–354.
3. World Health Organisation. Classification of Tumours of the Digestive Tract. Lyon: IARC Press, 2019.
4. Hu K, Shen S, Zhang L. Herniation of crypts in hyperplastic polyp and sessile serrated adenoma: a prospective study. Am J Cancer Res 2018;8:144–153.
5. Pai RK, Mojtahed A, Rouse RV, et al. Histologic and molecular analyses of colonic perineurial-like proliferations in serrated polyps: perineurial-like stromal proliferations are seen in sessile serrated adenomas. Am J Surg Pathol 2011;35:1373–1380.
6. Erlenbach-Wunsch K, Bihl M, Hartmann A, et al. Serrated epithelial colorectal polyps (hyperplastic polyps, sessile serrated adenomas) with perineurial stroma: clinicopathological and molecular analysis of a new series. Ann Diagn Pathol 2018;35:48–52.
7. Yang JF, Tang SJ, Lash RH, et al. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. Arch Pathol Lab Med 2015; 139:388–393.
8. Abdeljawad K, Vemulapalli KC, Kahi CJ, et al. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. Gastrointest Endosc 2015;81:517–524.
9. Liu C, Walker NI, Leggett BA, et al. Sessile serrated adenomas with dysplasia: morphological patterns and correlations with MLH1 immunohistochemistry. Mod Pathol 2017;30:1728–1738.
10. Cenaj O, Gibson J, Odze RD. Clinicopathologic and outcome study of sessile serrated adenomas/polyps with serrated versus intestinal dysplasia. Mod Pathol 2018;31:633–642.
11. Bettington ML, Walker NI, Rosty C, et al. A clinicopathological and molecular analysis of 200 traditional serrated adenomas. Mod Pathol 2015; 28:414–427.
12. Davis H, Irshad S, Bansal M, et al. Aberrant epithelial GREM1 expression initiates colonic tumorigenesis from cells outside the stem cell niche. Nat Med 2015;21:62–70.
13. Ensari A, Bilezikci B, Carneiro F, et al. Serrated polyps of the colon: how reproducible is their classification? Virchows Arch 2012;461:495–504.
14. Rau TT, Agaimy A, Gehoff A, et al. Defined morphological criteria allow reliable diagnosis of colorectal serrated polyps and predict polyp genetics. Virchows Arch 2014; 464:663–672.
15. Wong NA, Hunt LP, Novelli MR, et al. Observer agreement in the diagnosis of serrated polyps of the large bowel. Histopathology 2009;55:63–66.
16. Lu FI, van Niekerk de W, Owen D, et al. Longitudinal outcome study of sessile serrated adenomas of the colorectum: an increased risk for subsequent right-sided colorectal carcinoma. Am J Surg Pathol 2010;34:927–934.
17. Schramm C, Kaiser M, Drebber U, et al. Factors associated with reclassification of hyperplastic polyps after pathological reassessment from screening and surveillance colonoscopies. Int J Colorectal Dis 2016;31:319–325.
18. Singh H, Bay D, Ip S, et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. Gastrointest Endosc 2012;76:1003–1008.
19. Lin YC, Chiu HM, Lee YC, et al. Hyperplastic polyps identified during screening endoscopy: reevaluated by histological examinations and genetic alterations. J Formos Med Assoc 2014;113:417–421.
20. Tinmouth J, Henry P, Hsieh E, et al. Sessile serrated polyps at screening colonoscopy: have they been under diagnosed? Am J Gastroenterol 2014;109:1698–1704.
21. Kim SW, Cha JM, Lee JI, et al. A significant number of sessile serrated adenomas might not be accurately diagnosed in daily practice. Gut Liver 2010;4:498–502.
22. Bettington M, Walker N, Rosty C, et al. Critical appraisal of the diagnosis of the sessile serrated adenoma. Am J Surg Pathol 2014;38:158–166.
23. Snover DC, Ahnen D, Burt R, Odze RD. Serrated Polyps of the Colon and Rectum and Serrated Polyposis, WHO Classification of Tumours of the Digestive System. 4th ed. Lyon, France: IARC Press, 2010.
24. Kolb JM, Morales SJ, Rouse NA, et al. Does better specimen orientation and a simplified grading system promote more reliable histologic interpretation of serrated colon polyps in the community practice setting? Results of a nationwide study. J Clin Gastroenterol 2016; 50:233–238.
25. Morales SJ, Bodian CA, Kornacki S, et al. A simple tissue-handling technique performed in the endoscopy suite improves histologic section quality and diagnostic accuracy for serrated polyps. Endoscopy 2013;45:897–905.
26. IJspeert JEG, Madani A, Overbeek LI, et al. Implementation of an e-learning module improves consistency in the histopathological diagnosis of sessile serrated lesions within a nationwide population screening programme. Histopathology 2017;70:929–937.
27. Garcia-Solano J, Perez-Guillermo M, Conesa-Zamora P, et al. Clinicopathologic study of 85 colorectal serrated adenocarcinomas: further insights into the full recognition of a new subset of colorectal carcinoma. Hum Pathol 2010;41:1359–168.
28. O'Brien MJ, Yang S, Clebanoff JL, et al. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and K-ras mutation to location and histologic subtype. Am J Surg Pathol 2004; 28:423–434.
29. Bond CE, Liu C, Kawamata F, et al. Oncogenic BRAF mutation induces DNA methylation changes in a murine model for human serrated colorectal neoplasia. Epigenetics 2018;13:40–48.
30. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF

mutation in colorectal cancer. Nat Genet 2006;38:787–793.
31. Fennell LJ, Jamieson S, McKeone D, et al. MLH1-93 G/a polymorphism is associated with MLH1 promoter methylation and protein loss in dysplastic sessile serrated adenomas with BRAF(V600E) mutation. BMC Cancer 2018;18:35.
32. Bettington M, Walker N, Rosty C, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut 2017;66:97–106.
33. Borowsky J, Dumenil T, Bettington M, et al. The role of APC in WNT pathway activation in serrated neoplasia. Mod Pathol 2018;31:495–504.
34. Hashimoto T, Yamashita S, Yoshida H, et al. WNT pathway gene mutations are associated with the presence of dysplasia in colorectal sessile serrated adenoma/polyps. Am J Surg Pathol 2017;41:1188–1197.
35. Yan HHN, Lai JCW, Ho SL, et al. RNF43 germline and somatic mutation in serrated neoplasia pathway and its association with BRAF mutation. Gut 2017;66:1645–1656.
36. Koo BK, Spit M, Jordens I, et al. Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors. Nature 2012;488:665–669.
37. Sekine S, Ogawa R, Hashimoto T, et al. Comprehensive characterization of RSPO fusions in colorectal traditional serrated adenomas. Histopathology 2017;71:601–609.
38. de Lau W, Peng WC, Gros P, et al. The R-spondin/Lgr5/Rnf43 module: regulator of Wnt signal strength. Genes Dev 2014;28:305–316.
39. Phipps AI, Limburg PJ, Baron JA, et al. Association between molecular subtypes of colorectal cancer and patient survival. Gastroenterology 2015;148:77–87 e2.
40. Domingo E, Camps C, Kaisaki PJ, et al. Mutation burden and other molecular markers of prognosis in colorectal cancer treated with curative intent: results from the QUASAR 2 clinical trial and an Australian community-based series. Lancet Gastroenterol Hepatol 2018;3:635–643.
41. Taieb J, Le Malicot K, Shi Q, et al. Prognostic value of BRAF and KRAS mutations in MSI and MSS stage III colon cancer. j Natl Cancer Inst 2017;109.
42. Murcia O, Juarez M, Rodriguez-Soler M, et al. Colorectal cancer molecular classification using BRAF, KRAS, microsatellite instability and CIMP status: prognostic implications and response to chemotherapy. PLoS One 2018;13:e0203051.
43. Kim JH, Bae JM, Cho NY, et al. Distinct features between MLH1-methylated and unmethylated colorectal carcinomas with the CpG island methylator phenotype: implications in the serrated neoplasia pathway. Oncotarget 2016;7:14095–14111.
44. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21:1350–1356.
45. Spring KJ, Zhao ZZ, Karamatic R, et al. High prevalence of sessile serrated adenomas with BRAF mutations: a prospective study of patients undergoing colonoscopy. Gastroenterology 2006;131:1400–1407.
46. Kakar S, Deng G, Cun L, et al. CpG island methylation is frequently present in tubulovillous and villous adenomas and correlates with size, site, and villous component. Hum Pathol 2008;39:30–36.
47. Gala MK, Mizukami Y, Le LP, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology 2014;146:520–529.
48. IJspeert JEG, Bevan R, Senore C, et al. Detection rate of serrated polyps and serrated polyposis syndrome in colorectal cancer screening cohorts: a European overview. Gut 2017;66:1225–1232.
49. Edelstein DL, Axilbund JE, Hylind LM, et al. Serrated polyposis: rapid and relentless development of colorectal neoplasia. Gut 2013;62:404–408.
50. Carballal S, Rodriguez-Alcalde D, Moreira L, et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. Gut 2016;65:1829–1837.
51. IJspeert JEG, Rana SA, Atkinson NS, et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. Gut 2017;66:278–284.
52. MacPhail ME, Thygesen SB, Patel N, et al. Endoscopic control of polyp burden and expansion of surveillance intervals in serrated polyposis syndrome. Gastrointest Endosc 2019;90:96–100.
53. Hazewinkel Y, Tytgat KM, van Eeden S, et al. Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. Gastroenterology 2014;147:88–95.
54. IJspeert JEG, de Wit K, van der Vlugt M, et al. Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists. Endoscopy 2016;48:740–746.
55. Turner KO, Genta RM, Sonnenberg A. Lesions of all types exist in colon polyps of all sizes. Am J Gastroenterol 2018;113:303–306.
56. Anderson JC, Lisovsky M, Greene MA, et al. Factors associated with classification of hyperplastic polyps as sessile serrated adenomas/polyps on morphologic review. J Clin Gastroenterol 2018;52:524–529.
57. Min YW, Lee JH, Lee SH, et al. Prevalence of proximal colon serrated polyps in a population at average risk undergoing screening colonoscopy: a multicenter study. Clin Res Hepatol Gastroenterol 2012;36:604–608.
58. Ohki D, Tsuji Y, Shinozaki T, et al. Sessile serrated adenoma detection rate is correlated with adenoma detection rate. World J Gastrointest Oncol 2018;10:82–90.
59. Oono Y, Fu K, Nakamura H, et al. Progression of a sessile serrated adenoma to an early invasive cancer within 8 months. Dig Dis Sci 2009;54:906–909.
60. Chen S, Sun K, Chao K, et al. Detection rate and proximal shift tendency of adenomas and serrated polyps: a retrospective study of 62,560 colonoscopies. Int J Colorectal Dis 2018;33:131–139.
61. Liu TY, Jin DC, Khan S, et al. Clinicopathological features of advanced colorectal serrated lesions: a single-center study in China. J Dig Dis 2018;19:235–241.

62. Bettington M, Walker N, Rahman T, et al. High prevalence of sessile serrated adenomas in contemporary outpatient colonoscopy practice. Intern Med J 2017; 47:318–323.
63. Castillo O, Barreda C, Recavarren S, et al. [Clinical and endoscopic features of a selected population with serrated colorectal adenomas in a private clinic in Lima - Peru]. Rev Gastroenterol Peru 2013;33:209–216.
64. Pereyra L, Gomez EJ, Gonzalez R, et al. Finding sessile serrated adenomas: is it possible to identify them during conventional colonoscopy? Dig Dis Sci 2014;59:3021–3026.
65. Oleynikova NA, Kharlova OA, Malkov PG, et al. [Coexpression of CD44 and Ki-67 in colon`s neoplast]. Arkh Patol 2018;80:27–36.
66. Kefeli A, Basyigit S, Yeniova AO, et al. General properties of colon polyps in central Anatolia. Euroasian J Hepatogastroenterol 2014;4:7–10.
67. Kumar A, Kim M, Lukin DJ. *Helicobacter pylori* is associated with increased risk of serrated colonic polyps: analysis of serrated polyp risk factors. Indian J Gastroenterol 2018;37:235–242.
68. Alatise OI, Arigbabu AO, Agbakwuru AE, et al. Polyp prevalence at colonoscopy among Nigerians: a prospective observational study. Niger J Clin Pract 2014; 17:756–762.
69. Carr NJ, Mahajan H, Tan KL, et al. Serrated and non-serrated polyps of the colorectum: their prevalence in an unselected case series and correlation of BRAF mutation analysis with the diagnosis of sessile serrated adenoma. J Clin Pathol 2009;62:516–518.
70. Higuchi T, Sugihara K, Jass JR. Demographic and pathological characteristics of serrated polyps of colorectum. Histopathology 2005;47:32–40.
71. Lash RH, Genta RM, Schuler CM. Sessile serrated adenomas: prevalence of dysplasia and carcinoma in 2139 patients. J Clin Pathol 2010;63:681–686.
72. Hurlstone DP, Cross SS, Slater R, et al. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376–380.
73. Schramm C, Janhsen K, Hofer JH, et al. Detection of clinically relevant serrated polyps during screening colonoscopy: results from seven cooperating centers within the German colorectal screening program. Endoscopy 2018;50:993–1000.
74. Crockett SD, Gourevitch RA, Morris M, et al. Endoscopist factors that influence serrated polyp detection: a multicenter study. Endoscopy 2018;50:984–992.
75. Kumbhari V, Behary J, Hui JM. Prevalence of adenomas and sessile serrated adenomas in Chinese compared with Caucasians. J Gastroenterol Hepatol 2013;28:608–612.
76. Sanaka MR, Gohel T, Podugu A, et al. Adenoma and sessile serrated polyp detection rates: variation by patient sex and colonic segment but not specialty of the endoscopist. Dis Colon Rectum 2014;57:1113–1119.
77. Payne SR, Church TR, Wandell M, et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol 2014; 12:1119–1126.
78. Ross WA, Thirumurthi S, Lynch PM, et al. Detection rates of premalignant polyps during screening colonoscopy: time to revise quality standards? Gastrointest Endosc 2015;81:567–574.
79. Anderson JC, Butterly LF, Weiss JE, et al. Providing data for serrated polyp detection rate benchmarks: an analysis of the New Hampshire Colonoscopy Registry. Gastrointest Endosc 2017;85:1188–1194.
80. Parikh MP, Muthukuru S, Jobanputra Y, et al. Proximal sessile serrated adenomas are more prevalent in Caucasians, and gastroenterologists are better than non-gastroenterologists at their detection. Gastroenterol Res Pract 2017;2017:6710931.
81. Nayor J, Borges LF, Goryachev S, et al. Natural language processing accurately calculates adenoma and sessile serrated polyp detection rates. Dig Dis Sci 2018; 63:1794–1800.
82. Buda A, De Bona M, Dotti I, et al. Prevalence of different subtypes of serrated polyps and risk of synchronous advanced colorectal neoplasia in average-risk population undergoing first-time colonoscopy. Clin Transl Gastroenterol 2012;3:e6.
83. Correa P, Duque E, Cuello C, et al. Polyps of the colon and rectum in Cali, Colombia. Int J Cancer 1972; 9:86–96.
84. Sato E. Adenomatous polyps of large intestine in autopsy and surgical material. Gan 1974;65:295–306.
85. Sato E, Ouchi A, Sasano N, et al. Polyps and diverticulosis of large bowel in autopsy population of Akita prefecture, compared with Miyagi. High risk for colorectal cancer in Japan. Cancer 1976;37:1316–1321.
86. Eide TJ, Stalsberg H. Polyps of the large intestine in Northern Norway. Cancer 1978;42:2839–2848.
87. Marigo C, Correa P, Haenszel W. Cancer and "cancer related" colorectal lesions in Sao Paulo, Brazil. Int J Cancer 1978;22:645–654.
88. Restrepo C, Correa P, Duque E, et al. Polyps in a low-risk colonic cancer population in Colombia, South America. Dis Colon Rectum 1981;24:29–36.
89. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer 1982; 49:819–825.
90. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23:835–842.
91. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer 1985;36:179–186.
92. Coode PE, Chan KW, Chan YT. Polyps and diverticula of the large intestine: a necropsy survey in Hong Kong. Gut 1985;26:1045–1058.
93. Lee YS. Adenomas, metaplastic polyps and other lesions of the large bowel: an autopsy survey. Ann Acad Med Singapore 1987;16:412–420.
94. Stemmermann GN, Heilbrun LK, Nomura A, et al. Adenomatous polyps and atherosclerosis: an autopsy

study of Japanese men in Hawaii. Int J Cancer 1986; 38:789–794.
95. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut 1992; 33:1508–1514.
96. Paspatis GA, Papanikolaou N, Zois E, et al. Prevalence of polyps and diverticulosis of the large bowel in the Cretan population. An autopsy study. Int J Colorectal Dis 2001;16:257–261.
97. Haque TR, Bradshaw PT, Crockett SD. Risk factors for serrated polyps of the colorectum. Dig Dis Sci 2014; 59:2874–2889.
98. Hetzel JT, Huang CS, Coukos JA, et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol 2010; 105:2656–2664.
99. Peery AF, Crockett SD, Murphy CC, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019; 156:254–272.e11.
100. Burnett-Hartman AN, Passarelli MN, Adams SV, et al. Differences in epidemiologic risk factors for colorectal adenomas and serrated polyps by lesion severity and anatomical site. Am J Epidemiol 2013;177:625–637.
101. Alvarez C, Andreu M, Castells A, et al. Relationship of colonoscopy-detected serrated polyps with synchronous advanced neoplasia in average-risk individuals. Gastrointest Endosc 2013;78:333–341 e1.
102. Wallace K, Brandt HM, Bearden JD, et al. Race and prevalence of large bowel polyps among the low-income and uninsured in South Carolina. Dig Dis Sci 2016; 61:265–272.
103. Li D, Woolfrey J, Jiang SF, et al. Diagnosis and predictors of sessile serrated adenoma after educational training in a large, community-based, integrated healthcare setting. Gastrointest Endosc 2018;87:755–765 e1.
104. Bouwens MW, Winkens B, Rondagh EJ, et al. Simple clinical risk score identifies patients with serrated polyps in routine practice. Cancer Prev Res (Phila) 2013;6:855–863.
105. Teriaky A, Driman DK, Chande N. Outcomes of a 5-year follow-up of patients with sessile serrated adenomas. Scand J Gastroenterol 2012;47:178–183.
106. He X, Wu K, Ogino S, et al. Association between risk factors for colorectal cancer and risk of serrated polyps and conventional adenomas. Gastroenterology 2018; 155:355–373 e18.
107. Anderson JC, Rangasamy P, Rustagi T, et al. Risk factors for sessile serrated adenomas. J Clin Gastroenterol 2011;45:694–699.
108. Davenport JR, Su T, Zhao Z, et al. Modifiable lifestyle factors associated with risk of sessile serrated polyps, conventional adenomas and hyperplastic polyps. Gut 2018;67:456–465.
109. Anderson JC, Calderwood AH, Christensen BC, et al. Smoking and other risk factors in individuals with synchronous conventional high-risk adenomas and clinically significant serrated polyps. Am J Gastroenterol 2018; 113:1828–1835.
110. Lee JY, Chang HS, Kim TH, et al. Association between cigarette smoking and alcohol consumption and sessile serrated polyps in subjects 30 to 49 years old. Clin Gastroenterol Hepatol 2019;17:1551–1560.e1.
111. Bailie L, Loughrey MB, Coleman HG. Lifestyle risk factors for serrated colorectal polyps: a systematic review and meta-analysis. Gastroenterology 2017;152:92–104.
112. Figueiredo JC, Crockett SD, Snover DC, et al. Smoking-associated risks of conventional adenomas and serrated polyps in the colorectum. Cancer Causes Control 2015; 26:377–386.
113. Wallace K, Grau MV, Ahnen D, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prev 2009;18:2310–2317.
114. Crockett SD, Barry EL, Mott LA, et al. Calcium and vitamin D supplementation and increased risk of serrated polyps: results from a randomised clinical trial. Gut 2018 Mar 1. pii: gutjnl-2017-315242. https://doi.org/10.1136/gutjnl-2017-315242. [Epub ahead of print].
115. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012;143:599–607 e1.
116. Tadepalli US, Feihel D, Miller KM, et al. A morphologic analysis of sessile serrated polyps observed during routine colonoscopy (with video). Gastrointest Endosc 2011;74:1360–1368.
117. Hazewinkel Y, Lopez-Ceron M, East JE, et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. Gastrointest Endosc 2013;77:916–924.
118. IJspeert JEG, Bastiaansen BA, van Leerdam ME, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Gut 2016;65:963–970.
119. Hasegawa S, Mitsuyama K, Kawano H, et al. Endoscopic discrimination of sessile serrated adenomas from other serrated lesions. Oncol Lett 2011;2:785–789.
120. Crockett SD. Sessile serrated polyps and colorectal cancer. JAMA 2017;317:975–976.
121. Kahi CJ, Vemulapalli KC, Snover DC, et al. Findings in the distal colorectum are not associated with proximal advanced serrated lesions. Clin Gastroenterol Hepatol 2015;13:345–351.
122. Imperiale TF, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;371:187–188.
123. IJspeert JEG, Tutein Nolthenius CJ, Kuipers EJ, et al. CT-colonography vs. colonoscopy for detection of high-risk sessile serrated polyps. Am J Gastroenterol 2016; 111:516–522.
124. Lidgard GP, Domanico MJ, Bruinsma JJ, et al. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. Clin Gastroenterol Hepatol 2013;11:1313–1318.
125. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps

during screening colonoscopy. Clin Gastroenterol Hepatol 2011;9:42–46.
126. Clark BT, Laine L. High-quality bowel preparation is required for detection of sessile serrated polyps. Clin Gastroenterol Hepatol 2016;14:1155–1162.
127. Butterly L, Robinson CM, Anderson JC, et al. Serrated and adenomatous polyp detection increases with longer withdrawal time: results from the New Hampshire Colonoscopy Registry. Am J Gastroenterol 2014;109:417–426.
128. Hewett DG, Rex DK. Miss rate of right-sided colon examination during colonoscopy defined by retroflexion: an observational study. Gastrointest Endosc 2011; 74:246–252.
129. Baek MD, Jackson CS, Lunn J, et al. Endocuff assisted colonoscopy significantly increases sessile serrated adenoma detection in veterans. J Gastrointest Oncol 2017;8:636–642.
130. Desai M, Sanchez-Yague A, Choudhary A, et al. Impact of cap-assisted colonoscopy on detection of proximal colon adenomas: systematic review and meta-analysis. Gastrointest Endosc 2017; 86:274–281 e3.
131. Ngu WS, Bevan R, Tsiamoulos ZP, et al. Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. Gut 2019;68:280–288.
132. Pohl J, Schneider A, Vogell H, et al. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomised two-centre trial. Gut 2011;60:485–490.
133. Rex DK, Clodfelter R, Rahmani F, et al. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. Gastrointest Endosc 2016;83:166–171.
134. Yoshida N, Inada Y, Yasuda R, et al. Additional thirty seconds observation with linked color imaging improves detection of missed polyps in the right-sided colon. Gastroenterol Res Pract 2018;2018:5059834.
135. Parikh ND, Chaptini L, Njei B, et al. Diagnosis of sessile serrated adenomas/polyps with image-enhanced endoscopy: a systematic review and meta-analysis. Endoscopy 2016;48:731–739.
136. Fan C, Younis A, Bookhout CE, et al. Management of serrated polyps of the colon. Curr Treat Options Gastroenterol 2018;16:182–202.
137. Tate DJ, Awadie H, Bahin FF, et al. Wide-field piecemeal cold snare polypectomy of large sessile serrated polyps without a submucosal injection is safe. Endoscopy 2018; 50:248–252.
138. Binmoeller KF, Hamerski CM, Shah JN, et al. Attempted underwater en bloc resection for large (2-4 cm) colorectal laterally spreading tumors (with video). Gastrointest Endosc 2015;81:713–718.
139. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology 2013;144:74–80 e1.
140. Pellise M, Burgess NG, Tutticci N, et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. Gut 2017;66:644–653.
141. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. Gastroenterology 2010;139:1497–1502.
142. Hiraoka S, Kato J, Fujiki S, et al. The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology 2010;139:1503–1510; 1510 e1–e3.
143. Li D, Jin C, McCulloch C, et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. Am J Gastroenterol 2009;104:695–702.
144. Vu HT, Lopez R, Bennett A, et al. Individuals with sessile serrated polyps express an aggressive colorectal phenotype. Diseases of the colon and rectum 2011; 54:1216–1223.
145. Gao Q, Tsoi KK, Hirai HW, et al. Serrated polyps and the risk of synchronous colorectal advanced neoplasia: a systematic review and meta-analysis. Am J Gastroenterol 2015;110:501–509; quiz 510.
146. Macaron C, Vu HT, Lopez R, et al. Risk of metachronous polyps in individuals with serrated polyps. Dis Colon Rectum 2015;58:762–768.
147. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016; 150:870–878.
148. Holme O, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. Gut 2015;64:929–936.
149. Anderson JC, Butterly LF, Robinson CM, et al. Risk of metachronous high-risk adenomas and large serrated polyps in individuals with serrated polyps on index colonoscopy: data from the New Hampshire Colonoscopy Registry. Gastroenterology 2018;154:117–127 e2.
150. Haque T, Greene KG, Crockett SD. Serrated neoplasia of the colon: what do we really know? Curr Gastroenterol Rep 2014;16:380.
151. Snover DC. Sessile serrated adenoma/polyp of the large intestine: a potentially aggressive lesion in need of a new screening strategy. Dis Colon Rectum 2011;54:1205–1206.
152. Burgess NG, Tutticci NJ, Pellise M, et al. Sessile serrated adenomas/polyps with cytologic dysplasia: a triple threat for interval cancer. Gastrointest Endosc 2014;80:307–310.
153. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844–857.
154. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010; 59:666–689.
155. East JE, Atkin WS, Bateman AC, et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017;66:1181–1196.
156. Atkin W, Valori R, Kuipers EJ, et al. Colonoscopic surveillance after adenoma removal. In: Segnan N, Patnick J, von Karsa L, eds. *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis*. 1st ed. Lyon, France: IARC Press, 2010.

157. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842–851.
158. Tanaka S, Saitoh Y, Matsuda T, et al. Evidence-based clinical practice guidelines for management of colorectal polyps. J Gastroenterol 2015;50:252–260.
159. Yang DH, Hong SN, Kim YH, et al. Korean guidelines for postpolypectomy colonoscopy surveillance. Clin Endosc 2012;45:44–61.
160. Cancer Council Australia Colonoscopy Surveillance Working Party. Clinical Practice Guidelines for Surveillance Colonoscopy–in adenoma Follow-Up; Following Curative Resection of Colorectal Cancer; and for Cancer Surveillance in Inflammatory Bowel Disease. Sydney, Australia: Cancer Council Australia, December 2011.
161. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315–1329; quiz 1314, 1330.
162. Gourevitch RA, Rose S, Crockett SD, et al. Variation in pathologist classification of colorectal adenomas and serrated polyps. Am J Gastroenterol 2018;113:431–439.
163. Gonzalo DH, Lai KK, Shadrach B, et al. Gene expression profiling of serrated polyps identifies annexin A10 as a marker of a sessile serrated adenoma/polyp. J Pathol 2013;230:420–429.
164. Gurudu SR, Heigh RI, De Petris G, et al. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. World J Gastroenterol 2010;16:3402–3405.
165. Freedman JS, Harari DY, Bamji ND, et al. The detection of premalignant colon polyps during colonoscopy is stable throughout the workday. Gastrointest Endosc 2011;73:1197–1206.
166. Raju GS, Vadyala V, Slack R, et al. Adenoma detection in patients undergoing a comprehensive colonoscopy screening. Cancer Med 2013;2:391–402.

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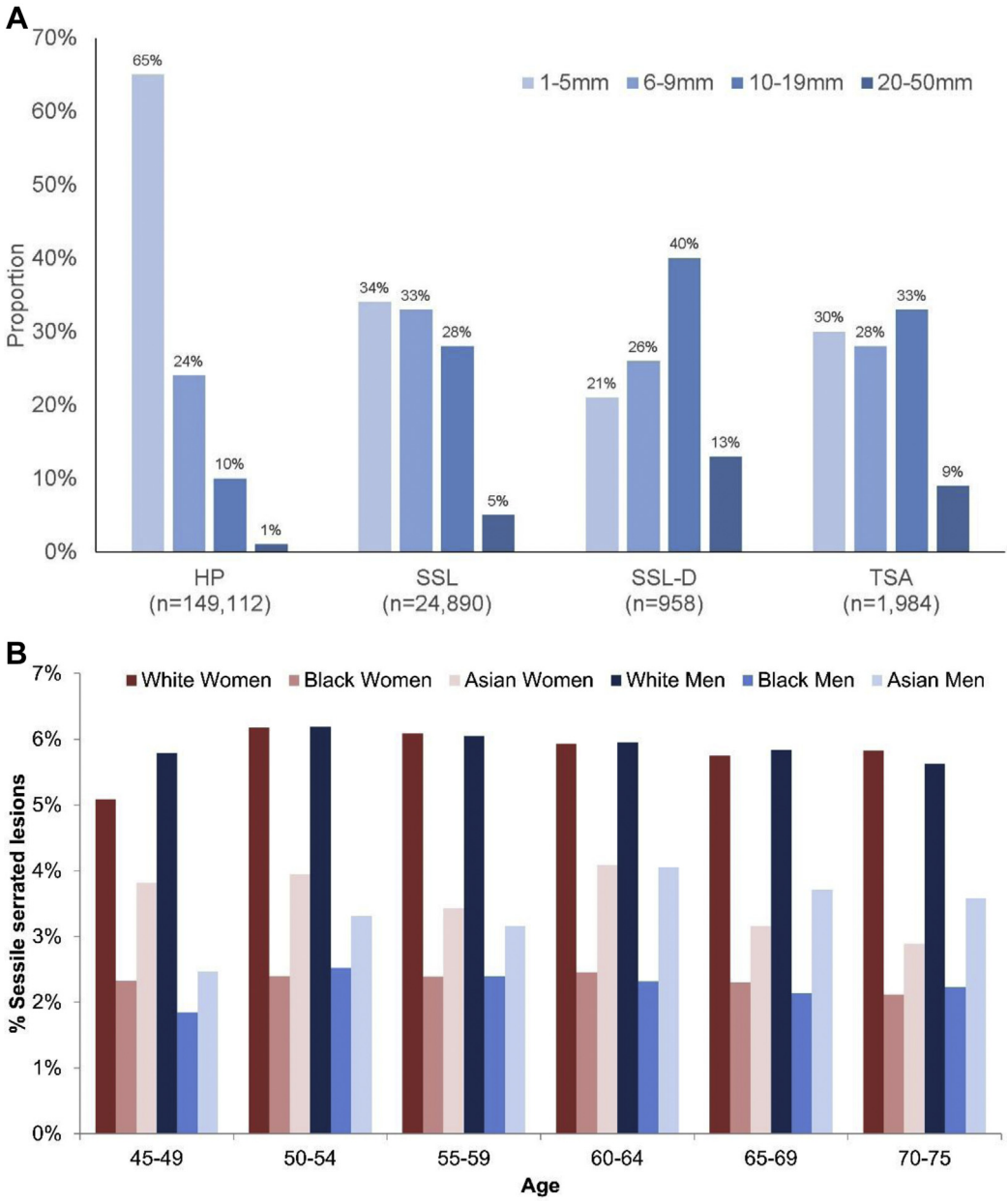
Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. (*A*) Size distribution of different serrated polyp subtypes. Data from Turner et al.[55] (*B*) Prevalence of SSLs by age, sex, and race, using data from US screening colonoscopy data, 2012–2016 (n = 1.6 million procedures). Figure shows the lack of a strong effect of age or sex on risk of SSLs and that nonwhite race is associated with lower risk of SSLs. Modified from Peery et al,[99] with permission.

Supplementary Table 1. Definitions and Changes in the 5th Edition of the WHO Classification

Lesion or condition	Defining features and key changes from prior WHO edition
HPs	Characterized by superficial serrated epithelium and funnel-shaped, evenly spaced crypts with proliferative zones confined to the crypt basis. No characteristics of SSLs. Two subtypes can be recognized: microvesicular HPs and goblet cell–rich HPs, although these have no known clinical implications. The previously recognized mucin-poor variant is no longer considered a separate entity.
SSLs (formerly known as sessile serrated adenomas or sessile serrated polyps)	*Sessile serrated lesion* is the recommended term for this lesion. Other terms are discouraged. Characterized by serrated epithelium and an overall distortion of the crypt architecture, most likely resulting from alterations of the proliferative zone. There are defining features of SSL crypt distortion: horizontal growth along the muscularis mucosa, dilation of the crypt base, serrations extending into the crypt base, and asymmetric proliferation. The unequivocal presence of at least 1 of these features in a single crypt is sufficient for the diagnosis of SSL. Dysplasia can be present in SSL, and loss of MLH1 expression indicates the presence of dysplasia. Normal expression of MLH1 does not exclude dysplasia.
TSAs	Characterized by slit-like serrated and eosinophilic cells with pencillate nuclei. Ectopic crypt formation is usually present but not necessary for this diagnosis. Often found with in association with HPs or SSLs, which are considered precursors to TSAs.
SPS	Defined as meeting 1 of the following 2 criteria: At least 5 SSLs or serrated polyps proximal to the rectum, all being >5 mm in size, with 2 or more at least 10 mm in size. Or, more than 20 SSLs or serrated polyps distributed throughout the large bowel, with at least 5 proximal to the rectum. In the previous WHO edition, first-degree relatives of patients with SPS were considered to have SPS if they presented with at least 1 serrated polyp. However, this criterion has been omitted due to the unknown pattern of genetic inheritance and the lack of genetic markers for serrated polyposis.

Supplementary Table 2. Endoscopic Detection of Sessile Serrated Lesions

First author, year of publication	Location of study	Study period	Total patients (colonoscopies), n	Endoscopists, n	Detection rates, %			
					Conventional adenomas	SSL	SSL-D	Highest SSL-DR[a]
Spring, 2006[45]	Australia	2003	189	1	NR	13.6	NR	13.6
Hetzel, 2010[98]	US (Massachusetts)	2006–2008	7192	20	22.2	0.6	0.2%[b]	2.2
Gurudu, 2010[164]	US (Arizona)	2005–2007	21,238	20	NR	0.8	NR	NR
Freedman, 2011[165]	US (New York)	2009	1486	3	42.5	7.9	NR	NR
Buda, 2012[82]	Italy	2007–2008	985	4	14.8	2.3	NR	NR
Kumbhari, 2013[75]	Australia	2010–2011	1000	1	34.6	5.3	NR	5.3
Raju, 2013[166]	US (Texas)	2009–2011	343	1	60.3	10.5	NR	10.5
Sanaka, 2014[76]	US (Ohio)	2008–2009	2167	65	25.6	1.8	NR	13.0
Payne, 2014[77]	US and Germany (multisite)	2008–2010	7215	32 centers	27.0	4.0[c]	NR	13.1[c]
Hazewinkel, 2014[53]	Netherlands	2014	1426	5	29.4	4.8	1.5%	NR
Abdeljawad, 2015[8]	US (Indiana)	2005–2012	1910	1	47.9	8.1	0.6%	15.5[d]
Ross, 2015[78]	US (Texas)	2010–2013	2833	13	42.0	8.2	NR	22.1
IJspeert, 2016[48]	Europe (multisite)	2009–2015	243,450	NR	29.4–47.8	3.3	0.4%	4.8[e]
IJspeert, 2016[54]	Netherlands	2011–2015	3364	25	38.5[f]	8.2	0.4%	13.6
Bettington, 2017[62]	Australia	2013–2014	707	1	47.9	20.1	0.4%	20.1
Anderson, 2017[79]	US (New Hampshire)	2009–2014	45,996	77	NR	5.8	NR	NR
Parikh, 2017[80]	US (Ohio)	2012–2014	4151	84	26.4	4.3	NR	NR
Crockett, 2018[74]	US (multisite)	2013–2015	104,618	201	33.2	6.3	NR	18.8
Schramm, 2018[73]	Germany	2012–2016	4161	15	29.1	3.0	NR	5.8
Ohki, 2018[58]	Japan	2014	3691	35	28.8	1.8	0.05	17.0[b]
Nayor, 2018[81]	US (Massachusetts)	2010–2015	8032	24	29.3	4.0	NR	9.6

NR, not reported in text; SP, serrated polyp; SSL-DR, sessile serrated lesion detection rate.
[g]Estimated from graph of SSL-DR by endoscopist.
[a]Prevalence of SSLs among colonoscopies performed by endoscopist (or center) with best SSL detection rate.
[b]SSL-D category includes SSL-Ds and TSAs.
[c]"Serrated lesions" included SSLs + large (≥1 cm) HPs.
[d]SSL-DR reported during last year of study (2012).
[e]Highest center rate (The Netherlands). Endoscopist-level data not reported.
[f]Median ADR.

Supplementary Table 3. Incidence of Serrated Polyps in Autopsy Studies

First author, year of publication	Location of study	Study period	Total patients, n	Patients with serrated polyps, n (%)
Correa, 1972[83]	Columbia (Cali)	1967–1969	1499	103 (6.9)
Sato, 1974[84]	Japan (Miyagi)	1968–1971	1000	11 (1.1)
Sato, 1976[85]	Japan (Miyagi)	1970–1973	471	9 (1.9)
Sato, 1976[85]	Japan (Akita)	1970–1973	300	9 (3.0)
Eide, 1978[86]	Norway (Tromso)	1974–1976	280	55 (19.6)
Marigo, 1978[87]	Brazil (Sao Paulo)	1973–1975	832	159 (19.1)
Restrepo, 1981[88]	Colombia (Medellin)	1971–1973	508	102 (20.1)
Vatn, 1982[89]	Norway (Oslo)	1972–1973	445	104 (23.4)
Williams, 1982[90]	UK (Liverpool)	(1 y)	365	126 (34.5)
Clark, 1985[91]	UK (Aberdeen)	1976–1979	200	83 (41.5)
Clark, 1985[91]	Finland (Kuopio)	1976–1979	200	29 (14.5)
Coode, 1985[92]	Hong Kong	NR	200	40 (20.0)
Stemmerman, 1986[94]	USA (Hawai)	1966–1983	288	163 (56.6)
Lee, 1987[93]	Singapore	NR	1014	67 (6.6)
Jass, 1992[95]	New Zealand (Auckland)	(3 y)	336	62 (18.5)
Paspatis, 2001[96]	Greece (Crete)	1997–1999	502	25 (5.0)
Total			8440	1147 (13.6)

NR, not reported.