# Prevalence and Clinical Features of Sessile Serrated Polyps: A Systematic Review

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r = reference category; * = statistical difference (highlighted); TSA=traditional serrated adenoma; **wide range across studies, 3.7-42.9%.
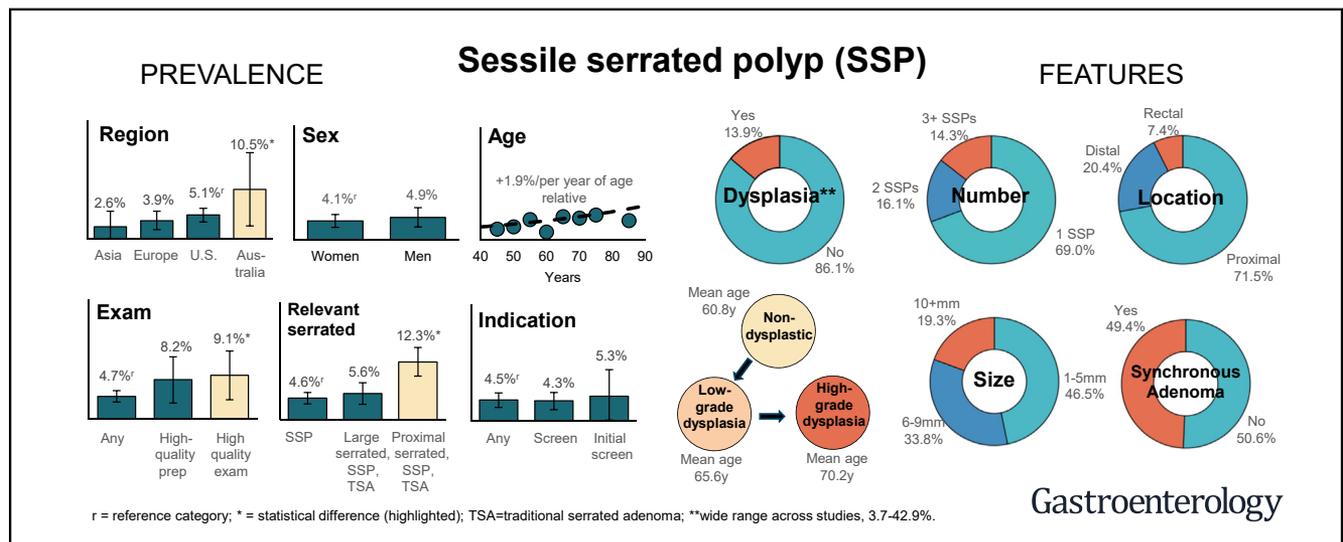
BACKGROUND & AIMS: Sessile serrated polyps (SSPs) could account for a substantial proportion of colorectal cancers. We aimed to increase clarity on SSP prevalence and clinical features. **METHODS:** We performed a systematic review of MEDLINE, Web of Science, Embase, and Cochrane databases for original studies published in English since 2000. We included studies of different populations (United States general or similar), interventions (colonoscopy, autopsy), comparisons (world regions, alternative polyp definitions, adenoma), outcomes (prevalence, clinical features), and study designs (cross-sectional). Random-effects regression was used for meta-analysis where possible. **RESULTS:** We identified 74 relevant colonoscopy studies. SSP prevalence varied by world region, from 2.6% in Asia (95% confidence interval [CI], 0–5.9) to 10.5% in Australia (95% CI, 2.8–18.2). Prevalence values did not differ significantly between the United States and Europe ($P = .51$); the pooled prevalence was 4.6% (95% CI, 3.4–5.8), and SSPs accounted for 9.4% of polyps with malignant potential (95% CI, 6.6–12.3). The mean prevalence was higher when assessed through high-performance examinations (9.1%; 95% CI, 4.0–14.2; $P = .04$) and with an alternative definition of clinically relevant serrated polyps (12.3%; 95% CI, 9.3–15.4; $P < .001$). Increases in prevalence with age were not statistically significant, and prevalence did not differ significantly by sex. Compared with adenomas, a higher proportion of SSPs were solitary (69.0%; 95% CI, 45.9–92.1; $P = .08$), with diameters of 10 mm or more (19.3%; 95% CI, 12.4–26.2; $P = .13$) and were proximal (71.5%; 95% CI, 63.5–79.5; $P = .008$). The mean ages for detection of SSP without dysplasia, with any or low-grade dysplasia, and with high-grade dysplasia were 60.8 years, 65.6 years, and 70.2 years, respectively. The range for proportions of SSPs with dysplasia was 3.7%–42.9% across studies, possibly reflecting different study populations. **CONCLUSIONS:** In a systematic review, we found that SSPs are relatively uncommon compared with adenoma. More research is needed on appropriate diagnostic criteria, variations in detection, and long-term risk.

Keywords: Colon Cancer; Neoplasm; PICOS; US.

C olorectal cancer (CRC) is a leading cause of cancer deaths.[1] The disease develops primarily from precancerous lesions called *adenomas*.[2] In a series of seminal papers from the 1970s and 1980s,[3,4] this process was first characterized as relatively slow, with many adenomas

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BACKGROUND & CONTEXT

Sessile serrated polyps (SSPs) might account for 30% of colorectal cancers, but there is uncertainty about SSP prevalence and clinical features.

NEW FINDINGS

In a systematic review, we found the reported prevalence of SSPs to be less than 5%, on average, with limited variation by age and sex. However, prevalence varies with study location, diagnostic criteria, and examination quality. SSPs are solitary, large, and proximal relatively often; the proportion that have dysplasia, based on cytologic analysis, varied widely across studies, possibly reflecting population differences.

LIMITATIONS

Cancer risk could not be assessed.

IMPACT

Standardized diagnostic criteria, training, and quality verification for endoscopists and pathologists should be considered to ensure adequate SSP detection, diagnosis and removal. Additional research is needed to determine differences in prevalence with age and among different locations, and long-term risk.

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resulting in relatively few cancers. Because adenomas are detectable and removable at endoscopy, CRC is highly amenable to screening, as was first shown in the National Polyp Study in 1993.[5]

More recently, it has been suggested that CRC may also arise from an alternative pathway with serrated polyp precursors.[6,7] Because serrated polyps were generally considered innocuous until the World Health Organization (WHO) included them in its manual for tumor classification of the digestive system,[8] relatively little is known about their epidemiology and risk.[9] The serrated polyp family includes sessile serrated polyps (SSPs), also known as sessile serrated adenomas or lesions; traditional serrated adenomas, and hyperplastic polyps. Hyperplastic polyps are the most common, and, especially, small distal hyperplastic polyps are not believed to harbor risk of malignancy. Traditional serrated adenomas are the most rare and can lead to CRC. SSPs appear to be substantially less common than adenomas,[10] but their associated molecular features may be overrepresented among CRC cases,[11,12] suggesting potentially higher risk of CRC compared to adenomas.

In this study, we sought to increase clarity on the prevalence and clinical features of SSPs by systematically reviewing the relevant literature from the last 2 decades. Review outcomes included prevalence by age, sex, and clinical definition; the multiplicity, size, and localization; and the proportion with cytologic dysplasia, the pathologic bridge to cancer.

Methods

General Study Design

The review was planned and designed in consultation with Stanford and Erasmus University librarians and consisted of 6 steps: (1) defining the scope, (2) literature search, (3) literature review and selection, (4) quality appraisal, (5) data abstraction, and (6) statistical analysis. Two different investigators performed steps 3–5 independently, with disagreements resolved through consensus.

Scope of the Review

We addressed several research questions under 5 main headers (Supplementary Table 1): the (1) prevalence and (2) clinical features of SSPs. Specific research questions under the first header included the prevalence by (1a) calendar year; (1b) world region; (1c) clinical definition; (1d) age/sex; (1e) indication for the prevalence assessment (eg, CRC screening vs follow-up of occult blood in stool); and (1f) quality of the examination (with *high quality* defined as examination with enhanced endoscopes or by providers from the upper quartile [minimum] of SSP detection rate). In addition, (1g) the fraction of SSPs among all potentially precancerous polyps (including adenomas, SSPs, or traditional serrated adenomas) was also assessed to gain insight into the relative proportions of polyps vs CRCs with characteristics of the serrated pathway.[13] Specific research questions under the second header included (2a) polyp number, (2b) size, (2c) anatomic location, (2d) coexistence with adenoma, and (2e) presence and (2f) age at detection of cytologic dysplasia.

Most research questions focused entirely on SSPs according to strict histopathologic criteria.[8] Because what is considered a *clinically relevant* serrated polyp and pathologists' attention to the difference between sessile serrated and hyperplastic polyps have all evolved over time, under research question 1c, we also considered various more liberal definitions for clinically relevant serrated polyps as encountered in the literature, including large and/or proximal hyperplastic polyps in addition to the more strict histologic definition. Under research question 1c only, we also considered inclusion of traditional serrated adenomas. Reported definitions were grouped into 3 different categories: (1) older terminology used before the 2010 WHO classification of tumors,[8] consisting of large hyperplastic polyps (≥10 mm in diameter), proximal hyperplastic polyps (located proximal of the splenic flexure), and serrated adenomas (including but not distinguishing SSPs and traditional serrated adenoma); (2) strict terminology similar to the histopathologic criteria from the 2010 WHO classification manual, consisting of only SSPs and traditional serrated adenomas; and (3) more recently introduced composite definitions, including clinically relevant histology, size, and location. The latter category combined SSP and traditional serrated adenomas, with either any large hyperplastic polyps (with large distal polyps excluded for some studies) or any proximal hyperplastic polyps (with large distal polyps included for some studies).

Literature Search

Ovid MEDLINE, Web of Science, Embase, and the Cochrane database were searched from January 1, 2000, through April 19, 2018, for original studies on serrated polyps written in English. General search terms were used to minimize the risk of missed information (Supplementary Table 2).

Literature Review and Selection

Covidence systematic review software was used to manage references, discard duplicates, review literature, and compare reviewer decisions. Selection of studies by each reviewer was based on scanning titles and abstracts, followed by potential full-text review. Studies were selected according to predefined criteria for Population, Intervention, Comparison, Outcome, and Study Design (PICOS) (Supplementary Table 1). The target population was the US general population, with data from other world regions included for research question 1a and 1b and for other research questions if not statistically significantly different from the United States under 1b. The intervention was colonoscopy or autopsy with pathologic assessment of findings. The comparators depended on the research question and included prevalence data from other world regions and CRC incidence data[14] for research question 1b, alternative definitions for clinically relevant serrated lesions for research question 1c, and adenoma data from 11 autopsy studies (identified elsewhere[15] and not systematically reviewed here)[16–26] for research questions 1d and 2a–c. The outcome of interest was the percentage of the population with SSPs or the percentage of SSPs with the feature of interest, relying on study criteria for the diagnosis of SSPs. The study design was cross sectional.

Quality Appraisal

There is no standard instrument for quality appraisal of prevalence studies. Therefore, we modified a validated tool designed for the appraisal of studies measuring the prevalence of lower back pain,[27] answering only the 8 of the 10 questions deemed pertinent to our study design (Supplementary Table 3). Assessment criteria concerned study characteristics such as the method of sampling, the case definition, and the study instrument. The overall risk of bias was qualified as low, moderate, or high depending on the level of confidence in the study estimates.

Data Abstraction

Data were stored in a spreadsheet template designed to enable easy cross-reviewer comparison. We collected all relevant outcome data, as well as all study characteristics relevant to outcome interpretation or subanalyses. For each outcome, both the numerator and denominator were recorded (eg, the numbers of patients with polyps and the total study participants). Age- and sex-specific data were ascertained to the extent available.

Statistical Analysis

Random-effects regression was used to meta-analyze outcome data where possible, and t tests (Wald) were used to examine the differences in outcomes against comparators defined in Supplementary Table 1—first for prevalence by world region, then for other outcomes, including all world regions with prevalence not statistically different from the United States at a standard 5% significance level. Q and I^2 statistics were calculated to measure outcome heterogeneity across studies. Bar charts were used with forest plots to visualize meta-analysis results. Linear models and t tests (Wald) were used to examine overall and region-specific trends in prevalence by calendar year. Log-linear models were fitted for overall and study-specific trends by age.

All analyses were performed using R statistical software, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Selection

The literature search returned 4462 references through April 19, 2018 (Supplementary Figure 1). After duplicate removal, 2123 studies were selected for review. During abstract review, 1669 irrelevant studies were removed. During full-text review, an additional 380 studies were excluded. In total, 74 studies on serrated polyps were included, of which 69 reported on prevalence[28–96] and 21 reported on clinical features.[28,37,39,47,50,52,55–57,65,67,70,86,88,91,92,97–101] Of the excluded studies, some were relevant but discarded because of overlap with larger studies from the same source population.[102–107] For the same reason, specific outcomes for some of the included studies were excluded.

Study Characteristics and Quality Appraisal

All included studies used colonoscopy in combination with pathology review as the instrument for serrated polyp detection. No autopsy studies were identified. Study setting ranged from community hospital to academic medical center from 4 different world regions: the United States (n = 36), Europe (n = 23), Asia (n = 11), and Australia (n = 4). Although inclusion criteria varied, studies often included examinations for screening or symptoms and excluded patients with a history of polypectomy, CRC, colectomy, familial risk syndromes, inflammatory bowel disease, or a recent colon examination. Generally, the study examinations were performed between 2005 and 2015, diagnostic criteria were based on the WHO classification manual or various earlier sources, mean patient age was approximately 60 years, and the average percentages of female patients was approximately 50%–60%. For details, see Supplementary Table 4.

Because study enrollment was nonrandom (based on selection for colonoscopy instead of random sampling of the general population) and outcome assessment is operator-dependent (colonoscopy and pathology),[49] the risk of bias for the included studies was judged to be moderate to high (Supplementary Table 5).

Prevalence of Sessile Serrated Polyps by Study Publication Year and Size

Few reports on the prevalence of SSPs were published before 2010, but the number of reports increased dramatically after the serrated polyp was first included in the 2010 WHO manual for tumor classification (Supplementary Figure 2).[8] The range for reported prevalence of SSPs at colonoscopy across all studies was very broad (0.0; 95% confidence interval [CI], 0.0–0.1 in Cao et al[40] and up to 20.0%; 95% CI; 17.3–23.2 in Bettington et al[36]). Despite an increasing awareness of SSPs, there was no significant

upward trend in reported prevalence over time across all studies (+0.1% per year; 95% CI −0.2 to 0.4; P = .49). However, trends varied by world region and did increase among US studies specifically (+0.3% per year; 95% CI, 0.0–0.7; P = .03) (Supplementary Figure 2).

Prevalence of Sessile Serrated Polyps by World Region

The prevalence of SSPs at colonoscopy in the United States was 5.1% (95% CI, 3.6–6.5) (Supplementary Figures 3 and 4). Prevalence was higher in Australia (10.5%; 95% CI, 2.8–18.2; P = .03) but not statistically different in Asia (2.6%; 95% CI, 0–5.9; P = .14) and Europe (3.9%; 95% CI, 2.0–5.9; P = .51) compared with the United States (Supplementary Figures 3 and 4). Excluding 1 extreme statistical outlier,[42] the mean prevalence for Asia was statistically different from the United States (0.9%; 95% CI, 0.5–1.3; P = .004). The pattern in polyp prevalence across regions was qualitatively similar to the reported CRC incidence pattern,[14] although relative prevalence differences appear larger (Supplementary Figure 3).

The mean overall prevalence of SSPs at colonoscopy across all US and European studies was 4.6% (95% CI, 3.4–5.8) (Figure 1).

The mean fraction of all potentially precancerous polyps with sessile serrated histology in US and European studies was 9.4% (95% CI, 6.6–12.3) (Figure 2).

Even within US and European studies there was substantial heterogeneity in estimates, with study-specific prevalences ranging from as low as 0.4% (95% CI, 0.0–0.8)[64] to as high as 13.8% (95% CI, 9.0–18.6; Q = 1716; P < .001) (Figure 1)[68] and with the fraction of polyps with sessile serrated histology ranging from 3.9% (95% CI, 3.3–4.6)[37] to 25.4% (95% CI, 19.5–31.3; Q = 2430, P < .001) (Figure 2).[68]

Prevalence According to Definition for Clinically Relevant Serrated Polyps

Under older terminology, the prevalence of clinically relevant serrated polyps in US and European studies varied from 1.8% (95% CI, 1.3–2.2) for large hyperplastic polyps to 3.3% (95% CI, 1.6–5.0) for serrated adenomas, to 8.5% (95% CI, 6.7–10.4) for proximal serrated polyps (Figure 3 and Supplementary Figure 5). The last was significantly higher than the prevalence with the strict SSP definition (4.6%; 95% CI, 3.4–5.8; P < .001).

Under strict terminology, the prevalence of SSPs and traditional serrated adenomas combined (4.4%; 95% CI, 2.9–5.9) was somewhat lower than the prevalence of only SSPs (Figure 3), but this difference was not significant (P = .93) and was due to study selection, because not all studies reported on both histologies. The prevalence of SSPs alone in the studies reporting on both SSPs and traditional serrated adenoma was 4.1% (95% CI, 2.6–5.5), suggesting a net prevalence for traditional serrated adenomas of approximately 0.3%.

Under more liberal definitions for clinically relevant histology, size, and location, the prevalence estimates were higher than under the strict SSP definition, ranging from 5.6% (95% CI, 3.3–7.9; P = .44) for definitions based primarily on histology and large size to 12.3% (95% CI, 9.3–15.4; P < .001) for definitions based primarily on histology and proximal location (Figure 3).

Prevalence of Sessile Serrated Polyps According to Examination Indication and Quality

The prevalence of SSPs in US and European studies was not related to examination indication, that is, whether the colonoscopy detecting the polyps was performed for screening in asymptomatic adults vs for screening or other indications (4.3%; 95% CI, 2.4–6.1 vs 4.5%; 95% CI, 2.9–6.0; P = .89) (Figure 4 and Supplementary Figure 6). Although prevalence at a patient's initial screening examination was higher (5.3%; 95% CI, 0–11.0; P = .73), this estimate was based on only 3818 examinations from 2 studies with wide confidence intervals (Figure 4).

Prevalence was higher when patients were examined by high polyp detectors or with enhanced endoscopes (9.1%; 95% CI, 4.0–14.2 for these high-performance examinations vs 4.7%; 95% CI, 3.5–5.9 for unselected examinations; P = .04) (Figure 4 and Supplementary Figure 6). Prevalence was also higher for examinations with good to excellent bowel preparation (8.2%; 95% CI, 3.3–13.0), although the difference vs all examinations was not significant (P = .10) (Figure 4).

Prevalence of Sessile Serrated Polyps by Age and Sex

Few US and European studies reported on the prevalence of SSPs by age and sex. The age pattern for SSPs contrasted with that for adenomatous polyps (Figure 5). SSP prevalence increased with age, but the relative increase was smaller than that for adenoma and did not reach statistical significance (relatively, +1.9% per age year; 95% CI, −0.1–3.9 for 2 studies providing a denominator; P = .06 vs +2.7%; 95% CI, 2.0–3.3 for adenomas; P < .001). Across studies, the relative age increases declined over time (Supplementary Figure 7 and Supplementary Tables 6 and 7).

The ratio for the reported prevalence of SSPs in men vs women of 1.20 (4.9%; 95% CI, 2.8–7.0 for men vs 4.1%; 95% CI, 2.7–5.5 for women; P = .54) (Supplementary Figures 8 and 9) was comparable to the ratio of 1.19 for adenomas (39.9%; 95% CI, 31.3–48.6 for men vs 33.4%, 95% CI, 25.9–40.8 for women; P = .35) (Supplementary Table 8).

Number, Size, and Location of Sessile Serrated Polyps

The number, size, and localization of sessile serrated vs adenomatous polyps in US and European studies is presented in Figure 6.

Compared with adenomatous polyps, SSPs were characterized by a relatively lower multiplicity, with 69.0%
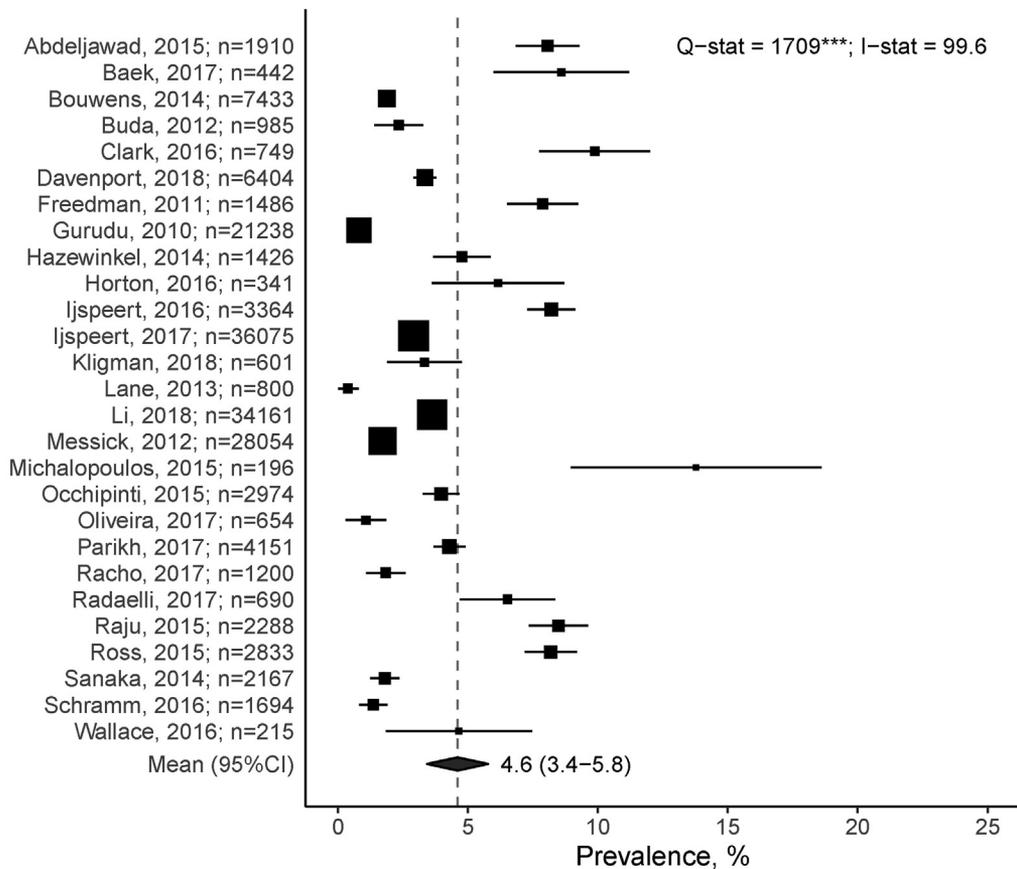
Figure 1. The prevalence of SSPs across included studies from the US and European. Squares indicate means, square size represents population size, whiskers show 95% CIs, and the polygon indicates the pooled mean, random-effects metaregression. ***Significant heterogeneity ($P < .001$).

(95% CI, 45.9–2.1%; $P = .08$) (Supplementary Figure 10) of patients with SSPs vs 43.3% (95% CI, 38.0–48.6) (Supplementary Table 9) of patients with adenomas having only 1 polyp and 14.3% (95% CI, 0–31.3; $P = .07$) vs 34.0% (95% CI, 28.0–40.0) of those having 3 or more, respectively.

SSPs were somewhat larger on average than adenomas, with 19.3% (95% CI, 12.4–26.2; $P = .13$) (Supplementary Figure 11) vs 13.2% (95% CI, 10.4–16.1) (Supplementary Table 10) having a diameter of more than 10 mm.

Compared with adenomas, more SSPs were located proximal to the splenic flexure: 71.5% (95% CI, 63.5–79.5;
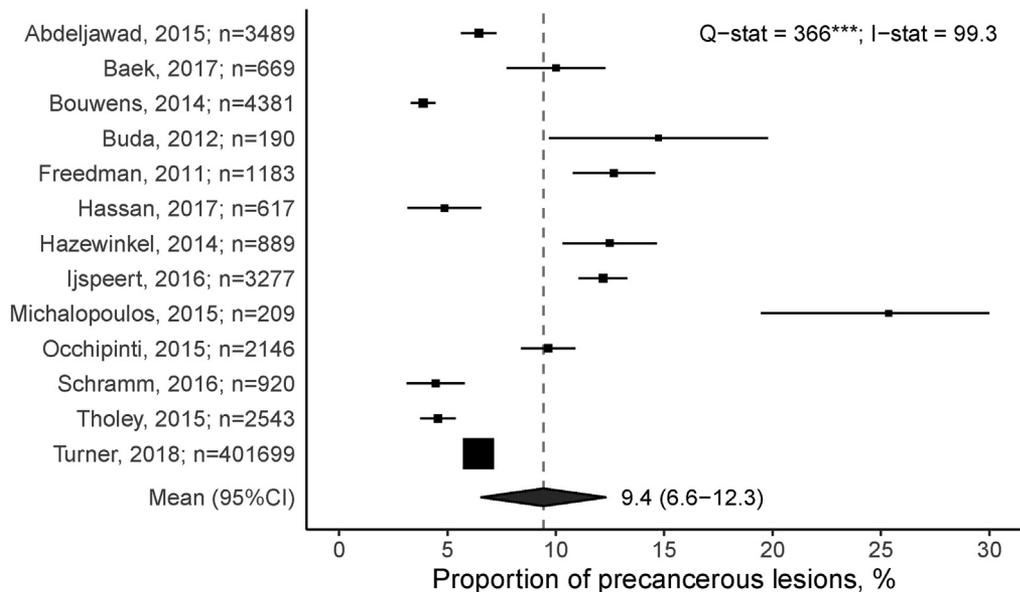

Figure 2. The fraction of polyps with sessile serrated histology across included. US and European studies. Squares indicate means, square size represents population size, whiskers show 95% CIs, and the polygon indicates the pooled mean, random-effects metaregression. Precancerous lesions include conventional adenoma, SSPs, and traditional serrated adenoma.***Significant heterogeneity ($P < .001$).
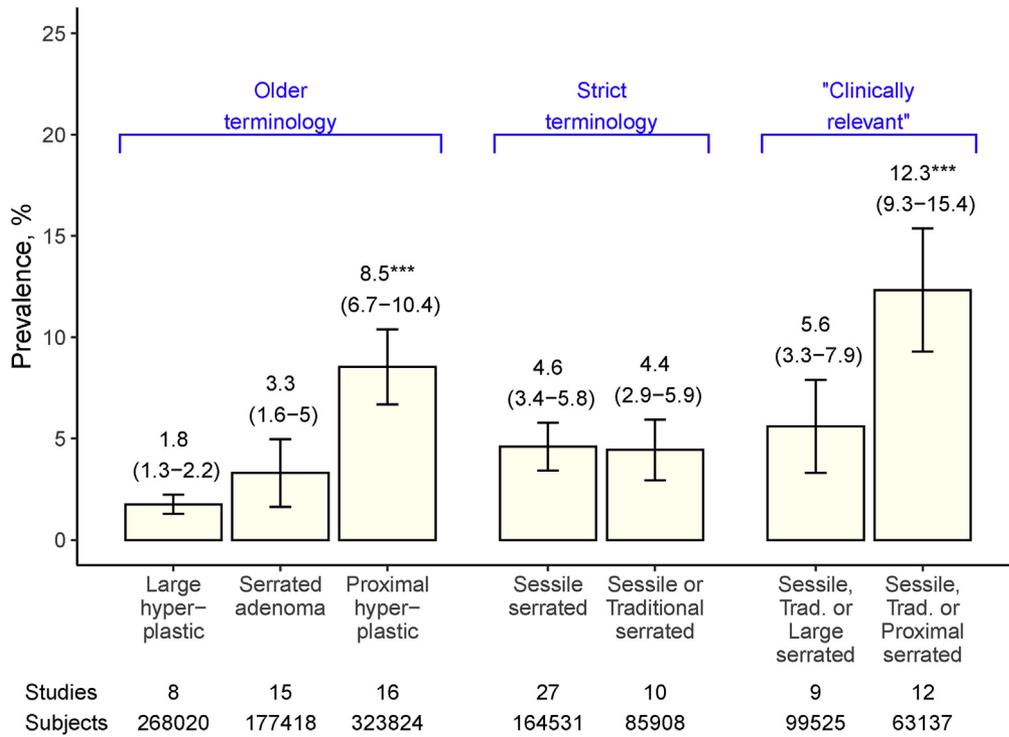
Figure 3. The prevalence of serrated polyps according to clinical definition in US and European studies. Whiskers show 95% CIs. The clinically relevant grouping includes definitions combining sessile serrated, traditional serrated, and hyperplastic polyps by size (>5 or >10 mm) and/or location (proximal). See Supplementary Figure 5 for corresponding forest plots and more detail on polyp definitions. ***Significant difference vs SSP prevalence (P < .001).

$P = .008$) (Supplementary Figure 12) vs 59.3% (95% CI, 54.3–64.2) (Supplementary Table 11). The proportion of polyps located in the rectum was similar ($P = .77$) and less than 10% for both types of polyps.

Sessile Serrated Polyps and Synchronous Adenoma

Among 2 studies reporting coexistence of adenomas and SSPs, 49.4% (95% CI, 45.4–53.9) of patients with SSPs had

adenomas (Supplementary Figure 13), notably more than the average prevalence of adenoma in autopsy studies (Supplementary Figure 8).

Presence and Age at Detection of Cytologic Dysplasia in Sessile Serrated Polyps

The proportion of SSPs with reported cytologic dysplasia ranged from 3.7% to 42.9% across 4 US and 4 European studies (Figure 7), with an overall mean of 13.9% (95% CI,

Figure 4. SSP prevalence according to examination indication and quality level in US and European studies. Whiskers show 95% CIs. *Significant difference vs prevalence in unselected examinations (P < .05). Good–excellent bowel preparation was determined by the Aronchick scale, 7–9 Boston Bowel Preparation Score, or split dose; high-quality examinations indicates enhanced endoscopes or a provider from the upper quartile of SSP detection. See Supplementary Figure 6 for forest plots and definitions.

A

Sessile serrated polyps

B

Adenomatous polyps
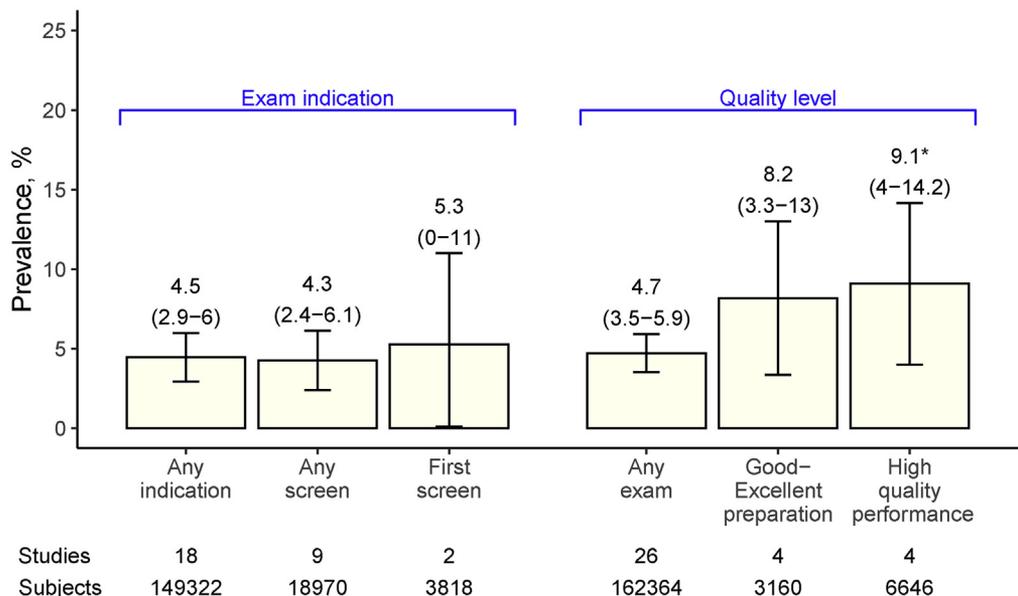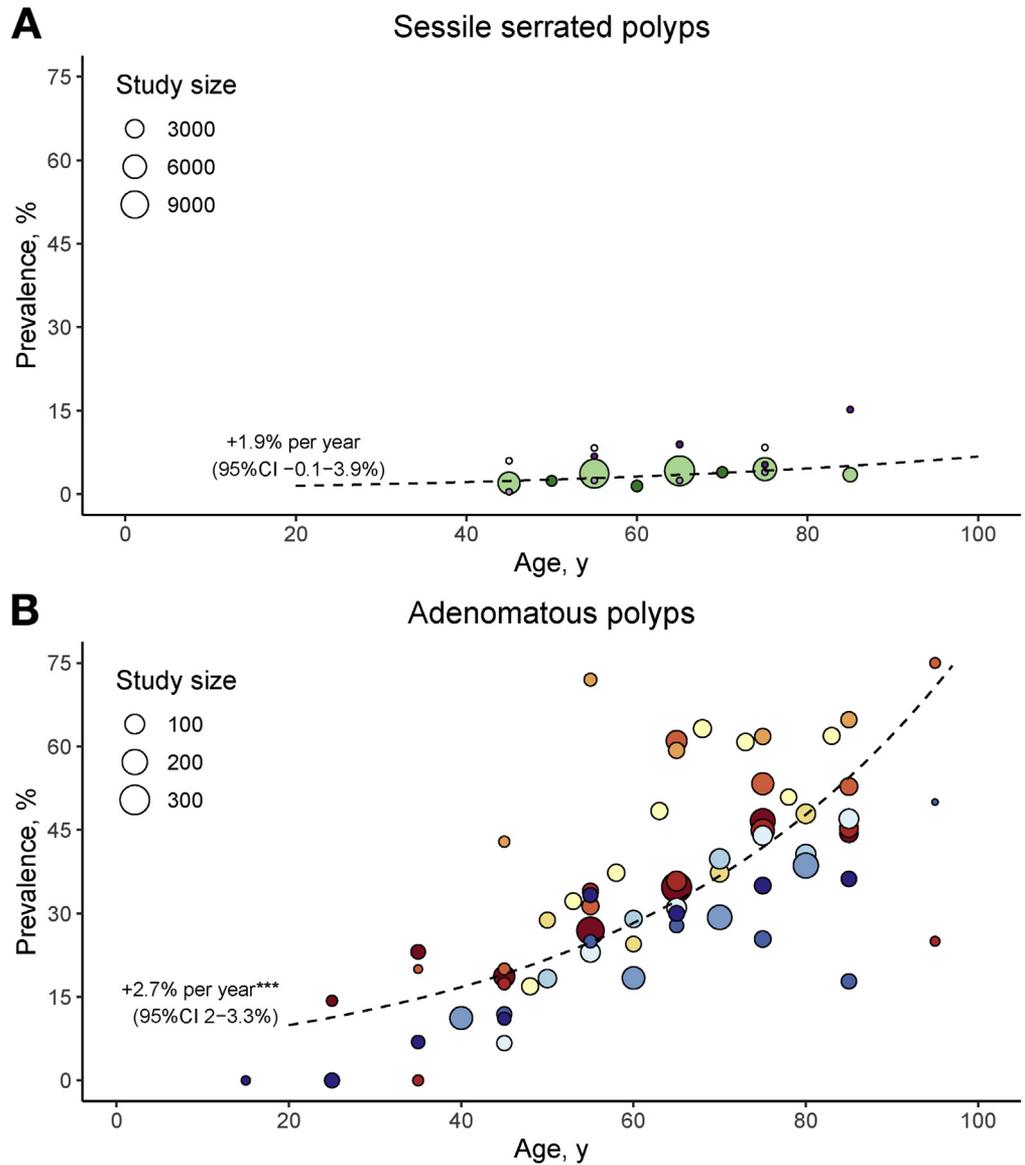
Figure 5. The prevalence of (*A*) sessile serrated vs (*B*) adenomatous polyps by age. Dots represent study observations by age, colors indicate the different US and European studies (Supplementary Tables 6 and 7), size shows patient denominator, and the dashed line is fitted log-linear trend for ages 40–100 years, measuring relative increase by age-year. Some studies in *A* provided no patient denominator and were excluded from trends and represented with small constant numbers. ***Significant trend (*P* < .001).

4.8–23.0). Although both US and European studies consisted of a mix of studies including examinations for screening or other indications (Supplementary Table 4), the proportion of SSPs with cytologic dysplasia differed between US and European studies (7.8%; 95% CI, 2.9–12.6 vs 20.6%, 95% CI, 3.6–37.5; *P* = .15) (Supplementary Figure 3), possibly due to relatively more nonscreening examinations in Europe (Supplementary Table 12). Excluding 1 extreme statistical outlier,[37] the proportion of SSPs with dysplasia decreased to 9.7% (95% CI, 4.5–14.9).

SSPs with dysplasia tended to be reported at higher ages than SSPs without dysplasia (Supplementary Figure 14 and Supplementary Table 13). Among 4 US and European studies reporting age at diagnosis, SSPs without dysplasia were detected at an average age of 60.8 years, SSPs with low-grade or any dysplasia at an average age of 65.6 years, and SSPs with high-grade dysplasia at an average age of 70.2 years.

Discussion

We performed a systematic review including meta-analysis of studies published since 2000 on the prevalence and clinical features of SSPs to provide perspective into the potential importance of these lesions. The overall prevalence of SSPs in colonoscopy studies varied around the world. In studies from the United States and Europe, based on strict histologic definitions, the prevalence was 4.6% (95% CI, 3.4–5.8), and SSPs accounted for 9.4% (95% CI, 6.6–12.3) of potentially precancerous lesions. Prevalence estimates were as high as 9.1% when based on high-quality colonoscopy examinations and 12.3% when also counting potentially clinically relevant hyperplastic polyps. Compared with adenomas, SSPs more often presented solitary, with large size and in the proximal colon. SSPs with dysplasia and high-grade dysplasia were reported at approximately 5 and 10 years older average ages, respectively, than nondysplastic SSPs.
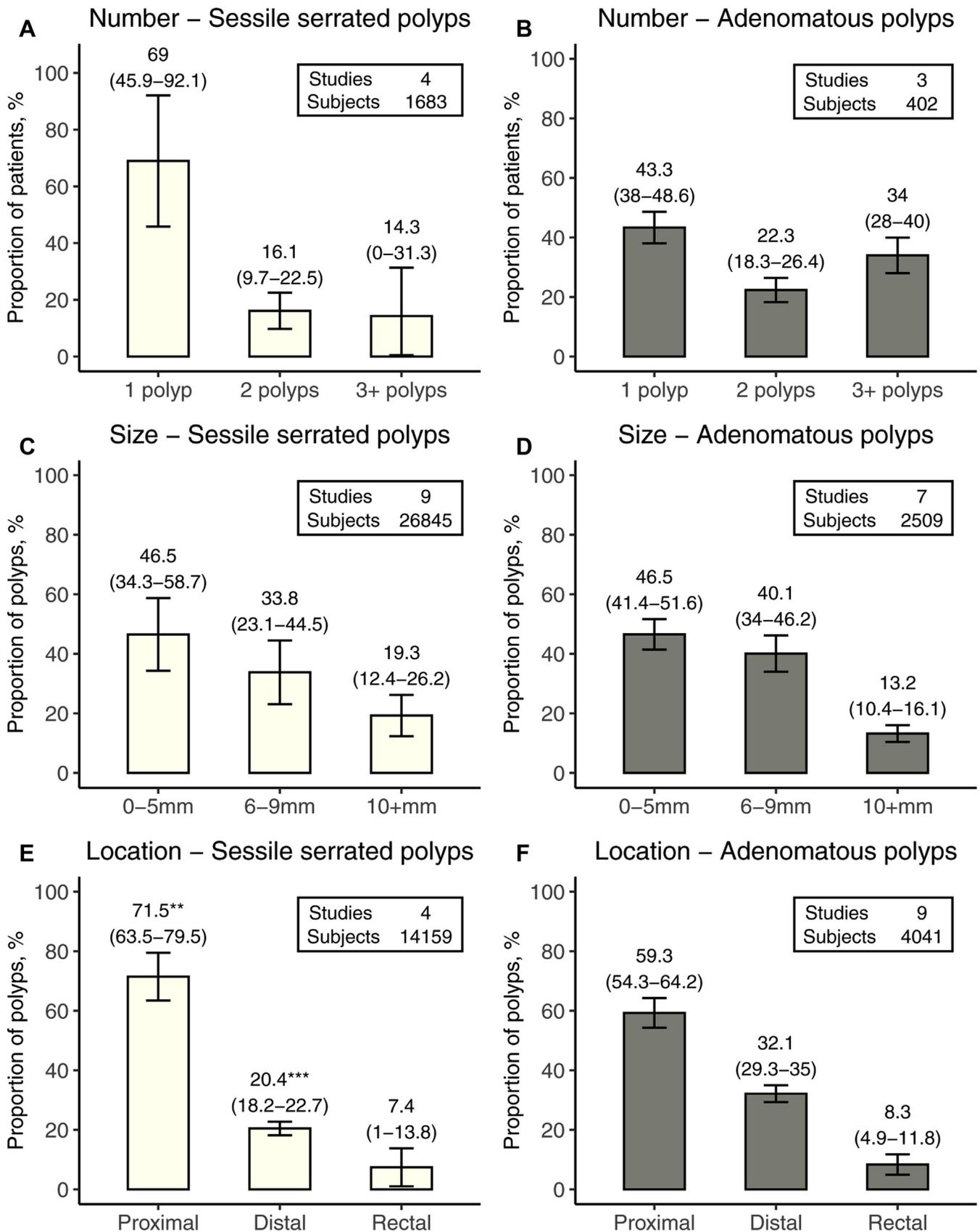
Figure 6. The (*A*, *B*) number, (*C*, *D*) size, and (*E*, *F*) localization of (*A*, *C*, *E*) sessile serrated vs (*A*, *B*, *F*) adenomatous polyps. US and European studies. See Supplementary Figures 10–12 for forest plots and Supplementary Tables 9–11 for adenoma data. Whiskers show 95% CIs. Significant differences for SSP vs adenoma: **$P < .01$; ***$P < .001$. Sizes were small (0–5 mm), medium (6–9 mm), or large (10+ mm); location was proximal (cecum, ascending colon, hepatic flexure, transverse colon), distal (splenic flexure, descending colon, sigmoid colon), or rectal.
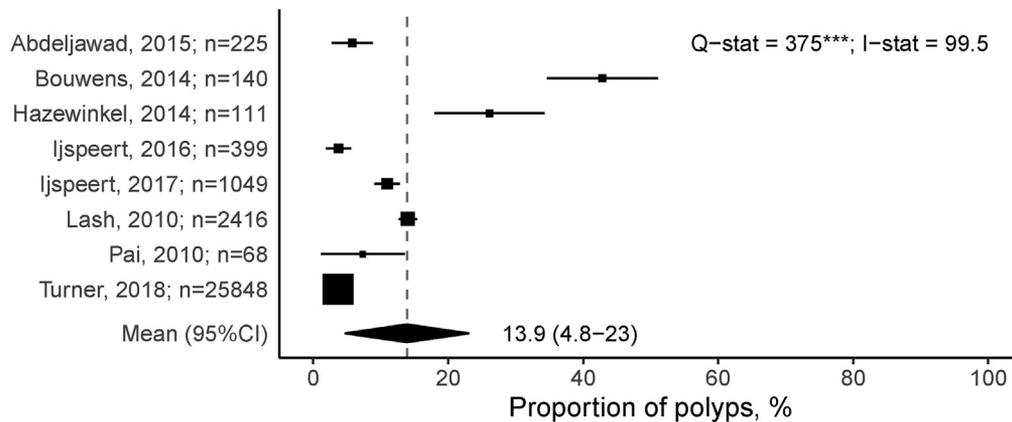
Figure 7. The proportion of SSPs with cytological dysplasia across studies. US and European studies, including nonscreening indications. Squares indicate means, square size represents population size, whiskers show 95% CIs, and the polygon indicates the pooled mean, random-effects metaregression. US, 7.8% (95% CI, 2.9–12.6) vs European studies, 20.6% (95% CI, 3.6–37.5) (*P* = .15). For some studies, the relative prevalence of dysplastic vs all SSPs was used as an approximation (Supplementary Table 12). Excluding 1 outlier,[37] the proportion decreased to 9.7% (95% CI, 4.5–14.9); Europe: 13.1% (95% CI, 0.6–25.5).***Significant heterogeneity (*P* < .001).

There is no consensus in the literature on which serrated polyps are clinically relevant, and this has consequences for the estimates of prevalence and risk. Histologically, SSPs and hyperplastic polyps may be difficult to distinguish,[49,53] creating the potential for misclassification under strict histologic definitions that consider SSPs and traditional serrated adenomas as the only clinically relevant serrated polyps.[8] More liberal definitions have been proposed to address this, but studies differ on whether these should include large,[33,57,89] proximal,[59,81] or both large and proximal hyperplastic polyps.[32,78,97] We report separate results based on older terminology, strict definitions, and more liberal definitions to shed light on what can be a confusing subject.

We found no significant association between SSP detection and calendar year when all studies were pooled. However, lower SSP rates in Asia, including in large recent studies, affected the pooled estimates. Among US studies, there was a significant upward trend (+0.3% point/year), consistent with reports from specific settings.[53,65] Differences in prevalence between Asia and the United States may be due to practice variation or more fundamental causes. The lower reported SSP rates in Asia are consistent with CRC incidence data (Supplementary Figure 3*B*) and race-specific data from the United States.[65] Further research on these differences could help elucidate SSP etiology.

SSP prevalence increased with age, but the increases did not quite meet the traditional criteria for statistical significance, unlike increases for adenoma. The relationship between SSP prevalence and age may have evolved over time by period or cohort effects (Supplementary Figure 7), such as more prior colonoscopies with polypectomy in older patients or an increased risk of SSPs in younger adults. An increased risk in younger persons would synchronize with documented young-onset CRC increases,[108] although those increases were mostly confined to the rectum, where SSPs are uncommon.

Prevalence was not associated with symptomatic indications. This is consistent with previous studies[65,109] and suggests SSPs may cause fewer symptoms than adenomas.

There was substantial heterogeneity in SSP prevalence across studies, which may be partly due to study biases. Studies included in this review were judged to have moderate to high risk of bias due to patient selection, detection bias, and possible misclassification. No studies ascertained unselected samples from the general population. In the United States, undergoing a colonoscopy is associated with socioeconomic indicators, such as health literacy and insurance status.[110] Patients with a previous screening history were usually included, which could be associated with lower SSP prevalence either due to polypectomy earlier in life or selection of healthy individuals if patients with a polypectomy earlier in life were excluded (Figure 5). Although colonoscopy is the criterion standard for colon examination, it may have missed a substantial proportion of serrated polyps (Figure 4),[111] particularly in earlier years (Supplementary Figure 2). Thus, the true prevalence of serrated polyps should be considered higher than what is reported in colonoscopy studies, because it must be corrected by the miss rate. Finally, it may be difficult for pathologists to distinguish sessile serrated from hyperplastic polyps. Both the endoscopic detection and pathology assessment of SSPs require training and verification of quality to ensure adequate diagnosis.

Dysplasia occurred in 3.7%–42.9% of SSPs across studies in our review. This wide range must be interpreted with caution (Supplementary Table 12). It may reflect small sample sizes, population differences in risk behavior (eg, smoking), or the presence of symptoms signaling dysplastic but not nondysplastic SSPs. Further research should determine the true prevalence of dysplastic SSPs in unselected populations and the effect of risk factors including smoking.

Strengths of this study include the systematic character, the sensitive search strategy, and the broad scope encompassing many relevant questions regarding SSP

epidemiology. The study also has limitations. First, we did not attempt to reclassify hyperplastic polyps from the era before awareness of SSPs.[112] Although this might reduce the risk of detection bias and contamination, it is not feasible to perform histopathology reassessment of all specimens in these older studies. Few of the reviewed autopsy studies provided detailed information on hyperplastic polyps. Second, although our review addressed several questions related to SSP risk, such as regarding the size and presence of dysplasia, we could not directly assess the risk of malignancy. Our literature search suggests that very few studies with longitudinal patient follow-up exist. A large trial following patients after SSP removal is recruiting, but results are not expected for >10 years,[113] and there is no plan to observe SSPs unresected. Observational data suggest no higher postpolypectomy risk for SSPs vs adenomas, whereas features such as large size and dysplasia, which we estimated to each occur in up to 10%–15% of SSPs, may increase risk.[114–116]

In conclusion, although SSP prevalence may be underestimated by colonoscopy studies with inherent miss rates, SSPs appear to be relatively uncommon compared with adenomas. More standardized diagnostic criteria for clinically relevant serrated polyps, training, and quality verification for endoscopists and pathologists are needed to ensure SSP detection and removal. Additional research is needed to increase clarity on actual prevalence by age, variation across settings, and long-term risk with and without removal.

Supplementary Material

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Conflicts of interest
This author discloses the following: Uri Ladabaum has acted as an advisor to UniversalDx and Lean and as a consultant to Covidence, Motus GI, Quorum, and Clinical Genomics. The remaining authors disclose no conflicts.

Supplementary References

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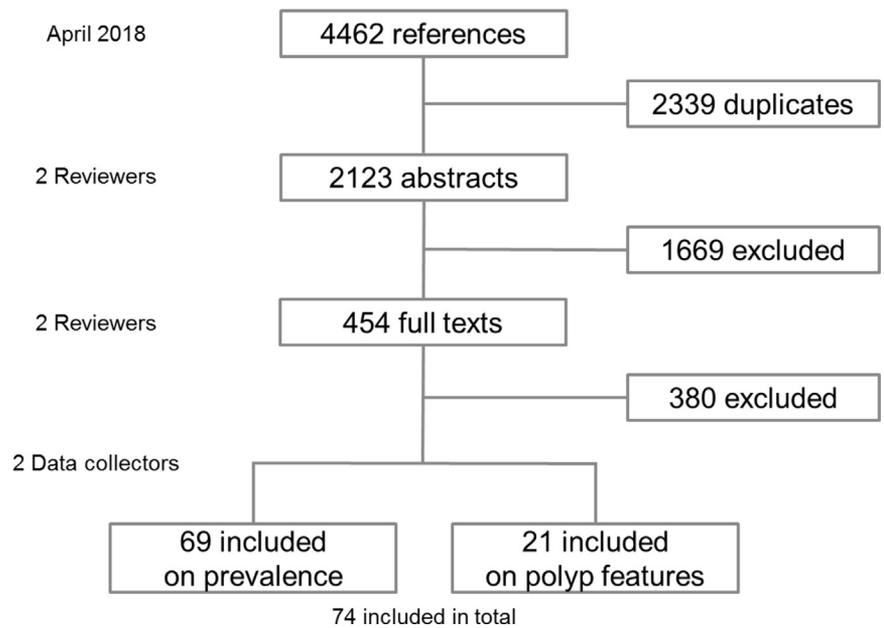
Supplementary Figure 1. The review process.
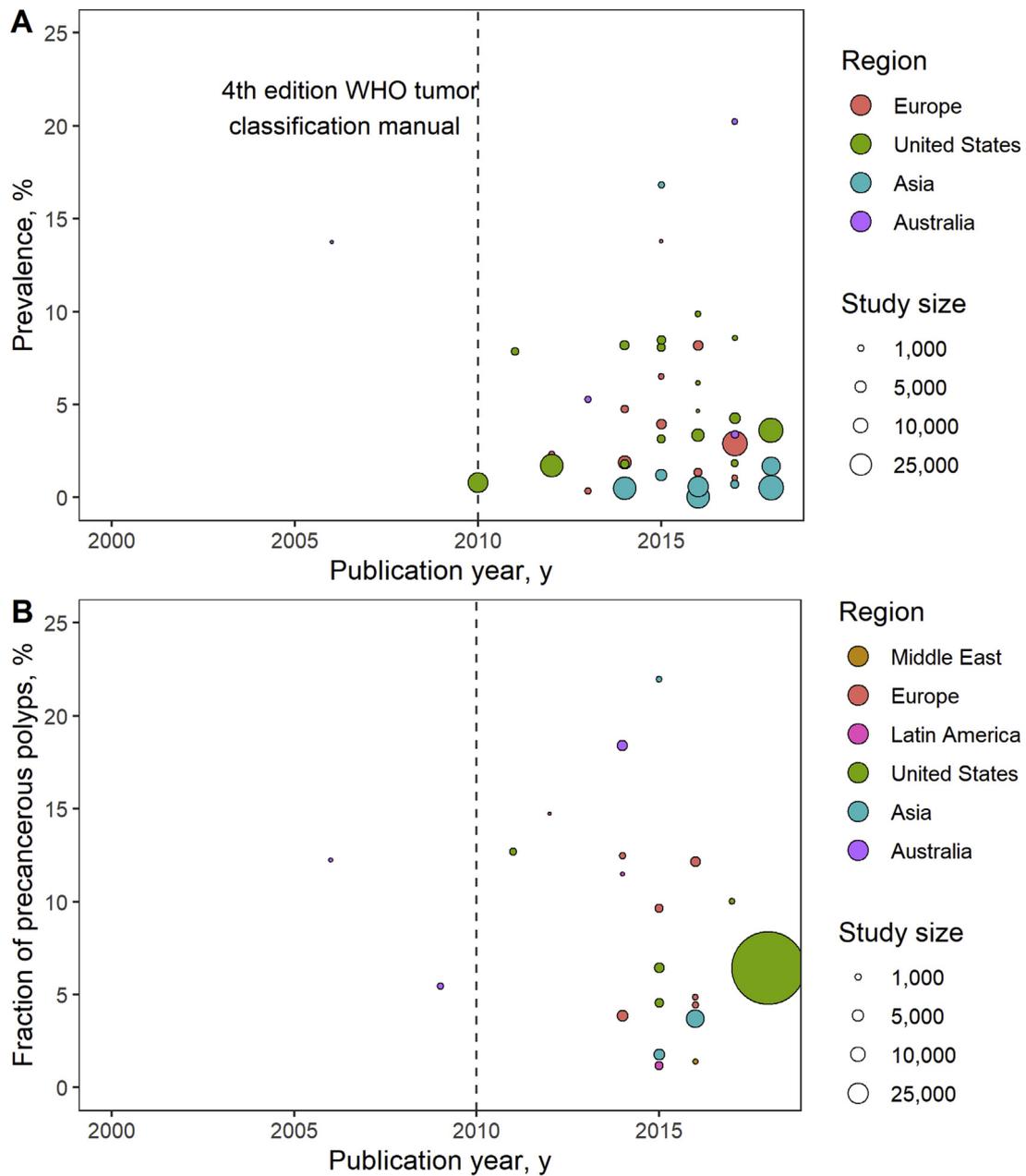
Supplementary Figure 2. Studies reporting SSP prevalence by year of publication. Dots indicate different studies, and size represents the population size. There was no significant overall trend over time in reported prevalence in (*A*) (excluding the 2006 outlier, +0.1% p/y; 95% CI, –0.2 to 0.4; *P* = .49) or (*B*) (–0.3% p/y; 95% CI, –1.1 to 0.5; *P* = .46). (*A*) Prevalence trends differed by region: Europe, +0.1%/y (95% CI, –0.9 to 1.0; *P* = .87), +0.3%/y (95% CI, 0.0–0.7; *P* = .03); Asia, +0.1%/y (95% CI, –0.7 to 0.9%; *P* = .83); and Australia, +0.8%/y (95% CI, –43.9 to 45.6; >2006, *P* = .85).
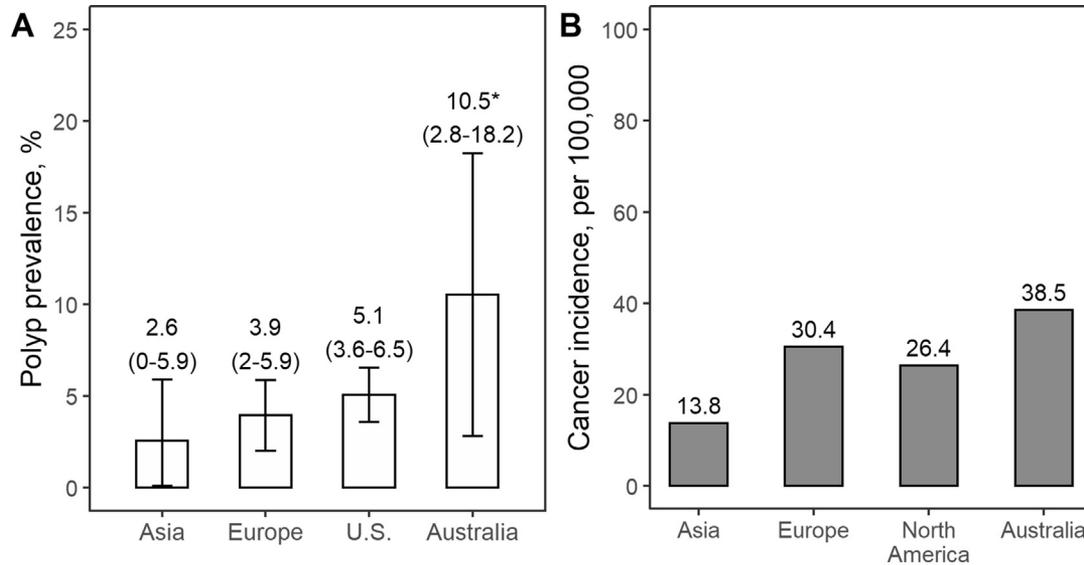
Supplementary Figure 3. SSP (*A*) prevalence and (*B*) cancer incidence by world region. Bars in *A* represent pooled mean estimates across studies from random-effects meta-regression (see Supplementary Figure 4 for corresponding forest plots), whiskers represent 95% CIs, and *asterisks* mark statistically significant differences compared to studies from the United States at a 5% significance threshold. Excluding 1 statistical outlier,[S1] the mean prevalence for Asia was 0.9% (95% CI, 0.4–1.3), also significantly different from the US prevalence (*P* = .004). Incidence data were taken from Ferlay et al.[S2] No incidence data specific to the United States were available from this publication, so North American data excluding Central America are presented instead.
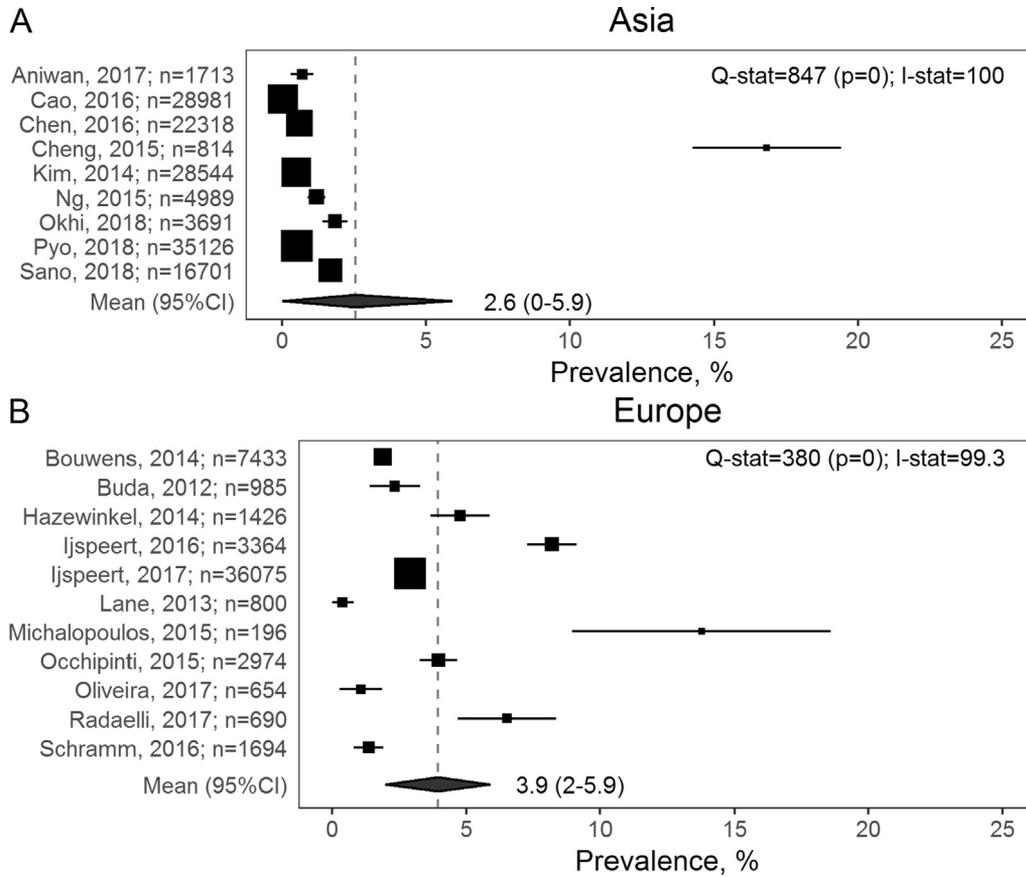
Supplementary Figure 4. Forest plots of SSP prevalence by world region: (*A*) Asia, (*B*) Europe, (*C*) the United States, and (*D*) Australia. Dots represent study means, symbol size represents population size, whiskers represent 95% CIs, and the polygon represents the pooled mean estimated from random-effects metaregression. In *A*, For Cao, 2016 (Cao et al[40]), the number of SSPs was used as a proxy for the prevalence numerator. The total prevalence of serrated polyps including hyperplastic polyps in that study was 0.5%. Excluding 1 extreme statistical outlier,[S1] the mean prevalence for Asia was 0.9% (95% CI, 0.5–1.3).

C

United States

D

Australia
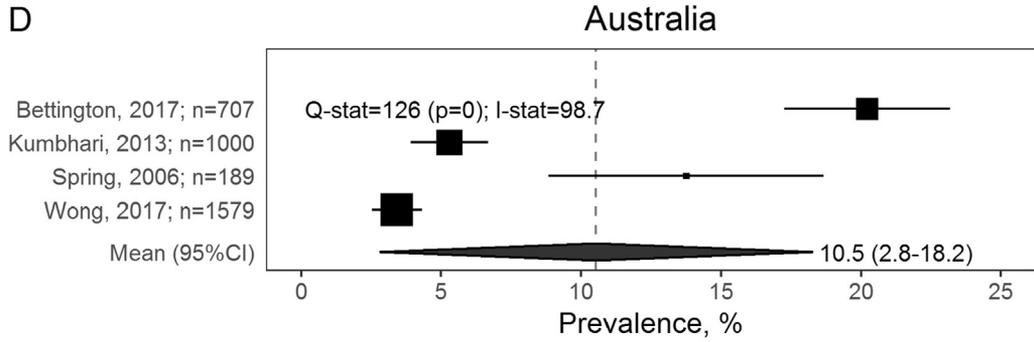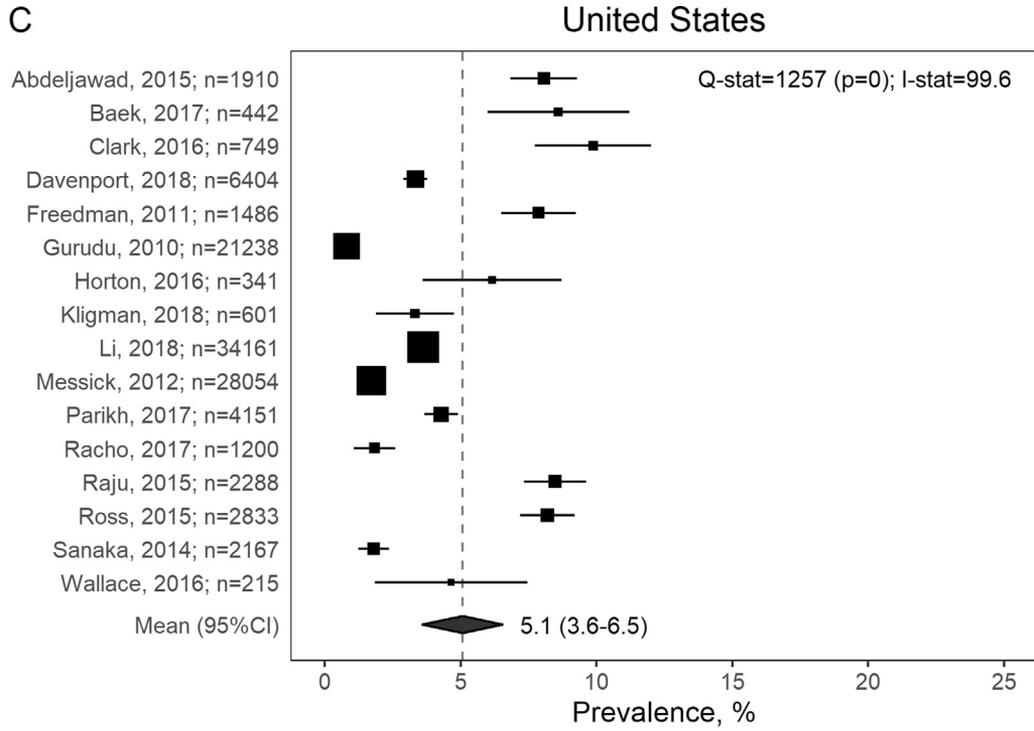
Supplementary Figure 4. (*continued*).

A   Large hyperplastic polyps

Alvarez, 2013; n=5059
Hazewinkel, 2014; n=1426
Ijspeert, 2017; n=242024
Kahi, 2015; n=1910
Lieberman, 2008; n=13992
Occhipinti, 2015; n=2974
Rzouq, 2015; n=420
Wallace, 2016; n=215
Mean (95%CI)

Q-stat=32 (p=0); I-stat=94.1

1.8 (1.3-2.2)

Prevalence, %

B   Serrated adenoma

Adike, 2018; n=1991
Alvarez, 2013; n=5059
Fantry, 2016; n=657
Glazer, 2008; n=17226
Gourevitch, 2018; n=85526
Hassan, 2017; n=658
Hetzel, 2010; n=7192
Imler, 2015; n=42569
Lieberman, 2008; n=13992
Pezzoli, 2007; n=562
Pohl, 2011; n=1008
Raju, 2013; n=343
Rodriguez, 2016; n=155
Rodriguez, 2016; n=60
Rzouq, 2015; n=420
Mean (95%CI)

Q-stat=6218 (p=0); I-stat=99.9

3.3 (1.6-5)

Prevalence, %

C   Proximal serrated polyps

Alvarez, 2013; n=5059
Anderson, 2017b; n=45996
Bouwens, 2014; n=7433
Bretagne, 2016; n=2979
DeWijkerslooth, 2013; n=1354
Hassan, 2017; n=658
Hazewinkel, 2014; n=1426
Ijspeert, 2017; n=242024
Kahi, 2012; n=6681
Kahi, 2015; n=1910
Occhipinti, 2015; n=2974
Parikh, 2017; n=4151
Raju, 2013; n=343
Rzouq, 2015; n=420
Wallace, 2016; n=215
Yen, 2013; n=201
Mean (95%CI)

Q-stat=1838 (p=0); I-stat=99.4

8.5 (6.7-10.4)

Prevalence, %

←

Supplementary Figure 5. Forest plots of SSP prevalence by clinical definition: (*A*) large hyperplastic polyps, (*B*) serrated adenomas, (*C*) proximal serrated polyps, (*D*) SSPs, (*E*) SSPs or traditional serrated adenomas, (*F*) clinically relevant size or histology, and (*G*) clinically relevant location or histology. Dots represent study means, symbol size represents population size, whiskers represent 95% CIs, and the polygon represents the pooled mean estimated from random-effects meta-regression. Large indicates >10-mm diameter. Proximal means left of the splenic flexure. In *C*, Kahi, 2012 (Kahi et al[59]) partly overlaps with the 2015[60] study but used wider selection criteria, justifying independent inclusion here. In *D*, the prevalence of SSPs in studies reporting both SSPs and traditional serrated polyps was 4.1% (95% CI, 2.6–5.5). Outcomes in *F* and *G* were composite definitions consisting of clinically relevant histology (sessile serrated or traditional serrated), size (large), and location (proximal). In *F*, Anderson, 2017b (Anderson et al[33]) reported the combined prevalence of SSPs, traditional serrated adenoma, distal hyperplastic polyps >10 mm, and proximal hyperplastic polyps >5 mm in diameter. Payne, 2014 (Payne et al[74]) combined prevalence of SSPs or proximal hyperplastic polyps >10 mm. Riverso, 2017 (Riverso et al[82]) combined SSPs, traditional serrated adenoma, and proximal hyperplastic polyps > 10 mm. Schreiner, 2010 (Schreiner et al[89]) combined SSPs, traditional serrated adenoma, or hyperplastic polyps >10 mm. For other studies, this outcome was derived by adding up the prevalence of SSPs, traditional serrated adenoma, and large hyperplastic polyps. In *G*, Anderson, 2013 (Anderson et al[31]) and Raju, 2013 (Raju et al[81]) combined prevalence of SSPs, traditional serrated adenomas, and proximal hyperplastic polyps. Anderson, 2017a (Anderson et al[32]) and Rzouq, 2015 (Rzouq et al[96]) combined SSPs, traditional serrated adenoma, proximal hyperplastic polyps, and distal hyperplastic polyps >10 mm. Racho, 2017 (Racho et al[78]) combined SSPs, traditional serrated adenoma, proximal hyperplastic polyps, and distal hyperplastic polyps >5 mm. For other studies, this outcome was derived by adding up prevalence of SSPs, traditional serrated adenoma, proximal, and >10-mm hyperplastic polyps.

D

Sessile serrated polyps

E

Sessile serrated polyps or
traditional serrated adenoma
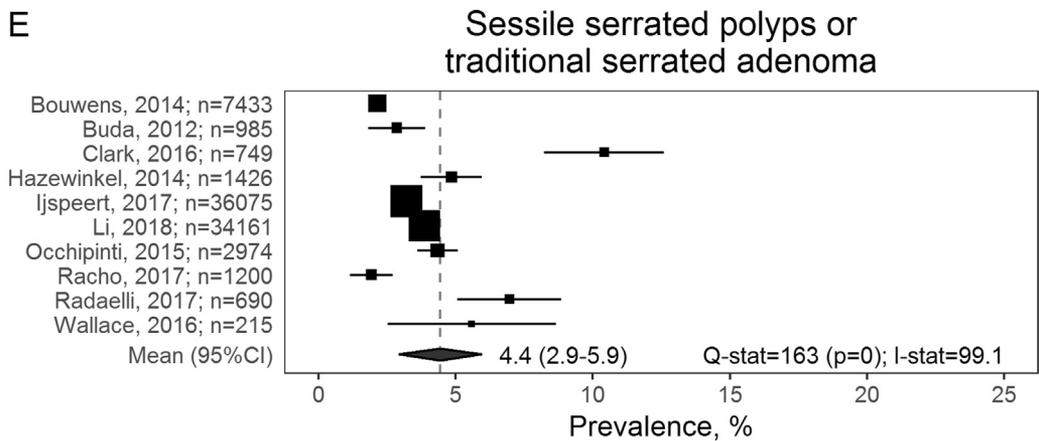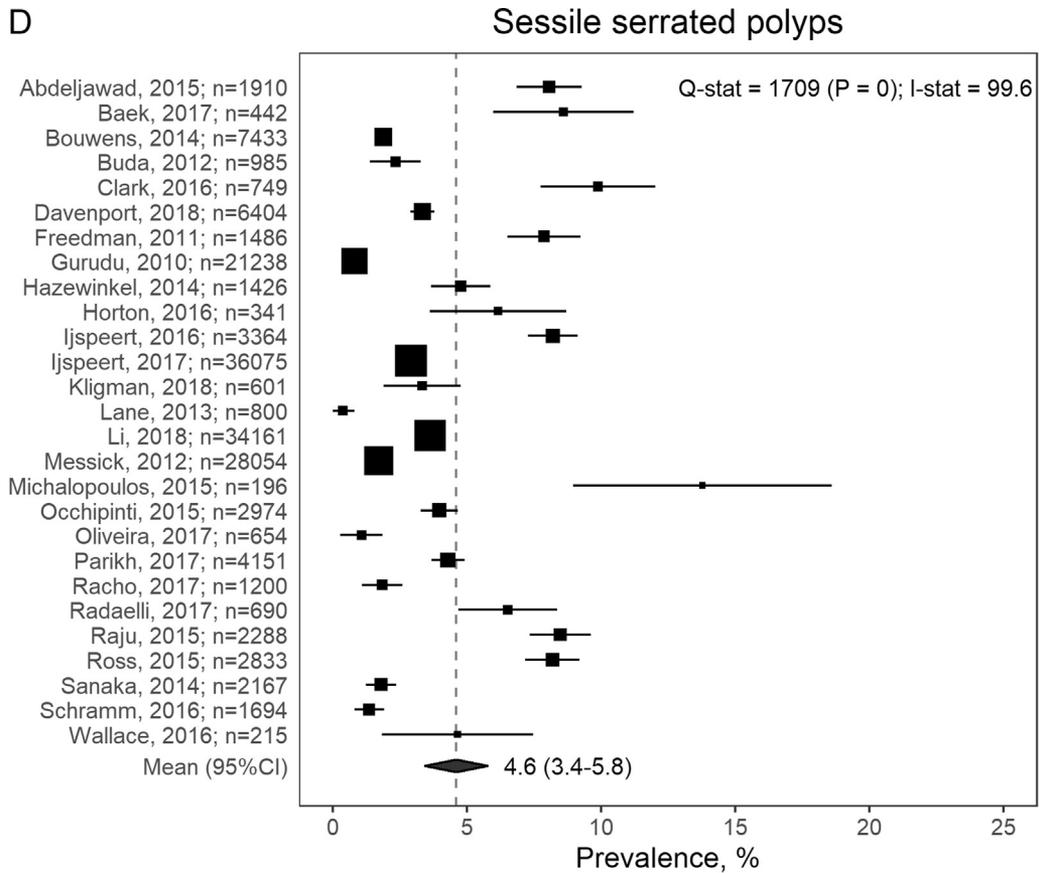
Supplementary Figure 5. (*continued*).

F

"Clinically-relevant" size or histology

G
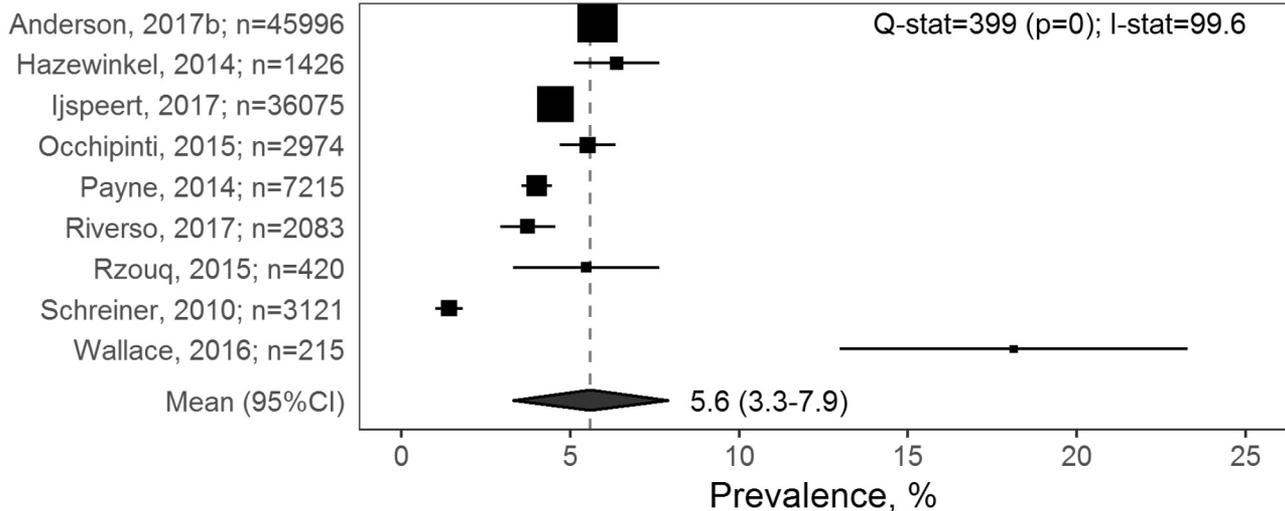
"Clinically-relevant" location or histology

Supplementary Figure 5. (continued).

A

Any exam indication

Baek, 2017; n=442
Bouwens, 2014; n=7433
Clark, 2016; n=749
Davenport, 2018; n=6404
Freedman, 2011; n=1486
Gurudu, 2010; n=21238
Horton, 2016; n=341
Ijspeert, 2016; n=3364
Ijspeert, 2017; n=36075
Li, 2018; n=34161
Messick, 2012; n=28054
Michalopoulos, 2015; n=196
Occhipinti, 2015; n=2974
Oliveira, 2017; n=654
Racho, 2017; n=1200
Radaelli, 2017; n=690
Sanaka, 2014; n=2167
Schramm, 2016; n=1694
Mean (95%CI)

Q-stat=1208 (p=0); I-stat=99.7

4.5 (2.9-6)

Prevalence, %

B

Any screening exam

Abdeljawad, 2015; n=1910
Hazewinkel, 2014; n=1426
Kligman, 2018; n=601
Lane, 2013; n=800
Li, 2018; n=7469
Oliveira, 2017; n=110
Parikh, 2017; n=4151
Raju, 2015; n=2288
Wallace, 2016; n=215
Mean (95%CI)

Q-stat=371 (p=0); I-stat=97.9

4.3 (2.4-6.1)

Prevalence, %

C

First screening exam

Buda, 2012; n=985
Ross, 2015; n=2833
Mean (95%CI)

Q-stat=69 (p=0); I-stat=98.6

5.3 (0-11)

Prevalence, %

◄──

Supplementary Figure 6. Forest plots of SSP prevalence by examination indication and quality level. Dots represent study means, symbol size represents population size, whiskers represent 95% CIs, and the polygon represents the pooled mean estimated from random-effects metaregression. Good-excellent bowel preparation means good-excellent by Aronchick scale, 7–9 Boston Bowel Preparation Score, or preparation according to split-dose regimens. High-quality examination indicates that it was performed with enhanced endoscopes (eg, cap-assisted) or by providers from the upper quartile (minimum) of SSP detection rates. More detail is underneath the panels. In *E*, Clark, 2016 (Clark and Laine[43]) selected examinations with 7–9 Boston Bowel Preparation Score. Horton, 2016 (Horton et al[54]) and Radaelli, 2017 (Radaelli et al[79]) selected examination with split-dose bowel preparation. Sanaka, 2014 (Sanaka et al[86]) selected good-excellent preparation by Aronchick scale. In *F*, data for the highest detectors were extracted from Ijspeert, 2015 (Ijspeert et al[55]) (upper quartile of relevant serrate polyp detection rates); Li, 2017[65] (upper quintile of SSP detection rates); and Racho, 2017 (Racho et al[78]) (highest 4/15 SSP detection rates). From Baek, 2017 (Baek et al[35]), data for endocuff-assisted colonoscopy were extracted.

D   Any exam quality

Abdeljawad, 2015; n=1910
Baek, 2017; n=442
Bouwens, 2014; n=7433
Buda, 2012; n=985
Clark, 2016; n=749
Davenport, 2018; n=6404
Freedman, 2011; n=1486
Gurudu, 2010; n=21238
Hazewinkel, 2014; n=1426
Horton, 2016; n=341
Ijspeert, 2016; n=3364
Ijspeert, 2017; n=36075
Kligman, 2018; n=601
Lane, 2013; n=800
Li, 2018; n=34161
Messick, 2012; n=28054
Michalopoulos, 2015; n=196
Occhipinti, 2015; n=2974
Oliveira, 2017; n=654
Parikh, 2017; n=4151
Racho, 2017; n=1200
Radaelli, 2017; n=690
Raju, 2015; n=2288
Ross, 2015; n=2833
Schramm, 2016; n=1694
Wallace, 2016; n=215
Mean (95%CI)

Q-stat=1708 (p=0); I-stat=99.6

4.7 (3.5-5.9)

Prevalence, %

E   Good-Excellent bowel preparation

Clark, 2016; n=475
Horton, 2016; n=173
Radaelli, 2017; n=345
Sanaka, 2014; n=2167
Mean (95%CI)

Q-stat=79 (p=0); I-stat=93.5

8.2 (3.3-13)

Prevalence, %

F   High performance exam

Baek, 2017; n=225
Ijspeert, 2015; n=669
Li, 2018; n=5358
Racho, 2017; n=394
Mean (95%CI)

Q-stat=46 (p=0);
I-stat=96.7

9.1 (4-14.2)

Prevalence, %

Supplementary Figure 6. (*continued*).
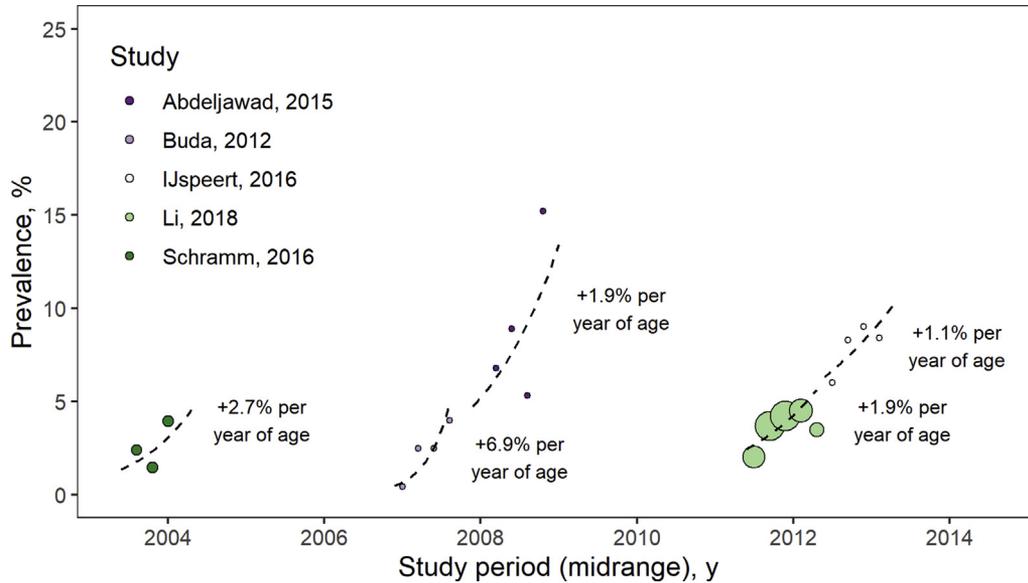
Supplementary Figure 7. Prevalence of SSPs by age and study period. This plot shows the studies reporting prevalence by age in Figure 5 by study period (midrange). Denominators were unknown for Abdeljawad, 2015 (Abdeljawad et al[28]); Buda, 2012 (Buda et al[39]); and Ijspeert, 2016 (Ijspeert et al[56]) and fixed at n = 100 for this figure. Different markers of a similar color represent the age-specific results within each study. Age groups were horizontally spread around the study period's midrange years to show the age pattern (from left to right: youngest to oldest), not to convey differences in timing of observations between individual age groups. Number indicates the relative increase in prevalence by age year.

Supplementary Figure 8. Prevalence of (A) SSPs vs (B) adenomatous polyps by sex. Bars represent pooled mean estimates across studies from random-effects met-aregression (see Supplementary Figure 8 for corresponding forest plots). Whiskers represent 95% CIs.
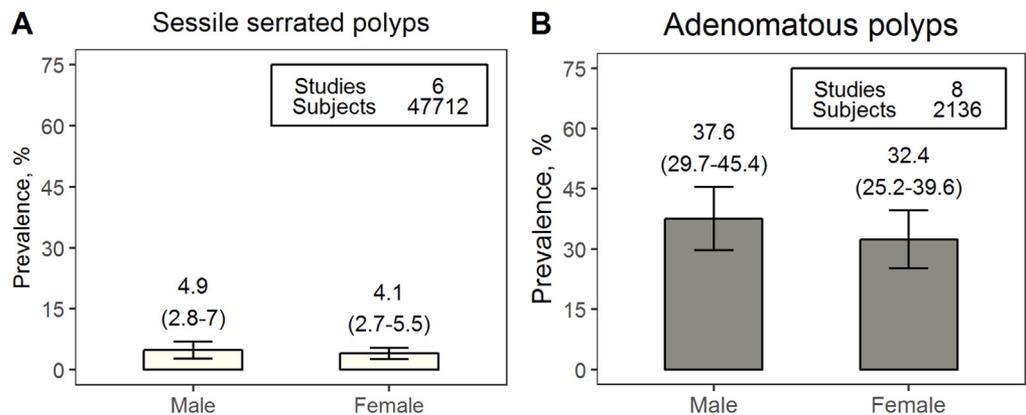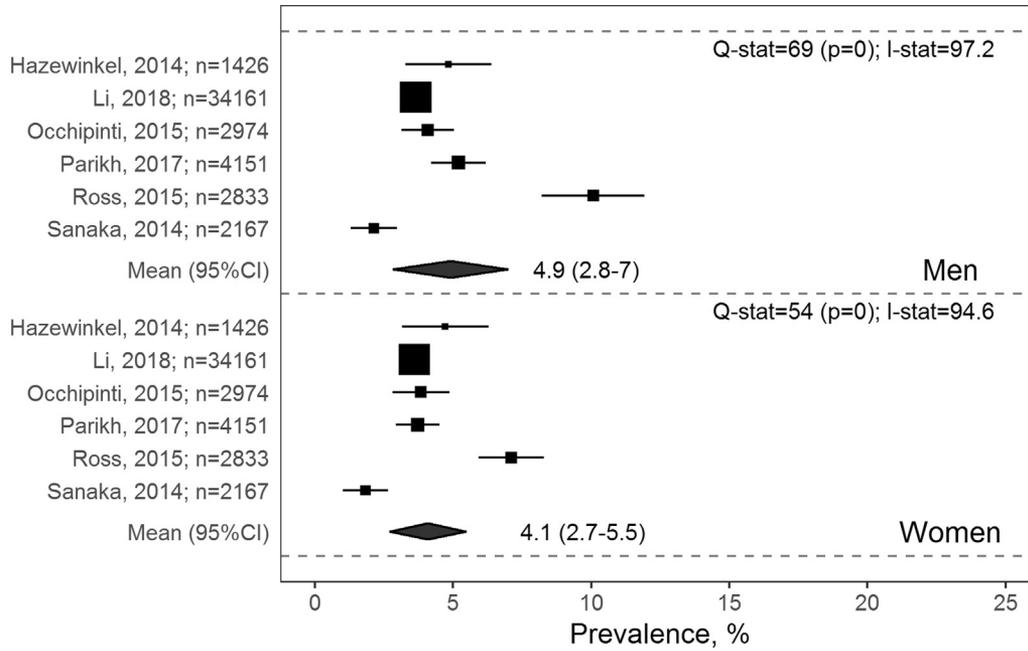
Supplementary Figure 9. Forest plot of SSP prevalence by sex. Dots represent study means, symbol size represents population size, whiskers represent 95% CIs, and the polygon represents the pooled mean estimated from random-effects metaregression.
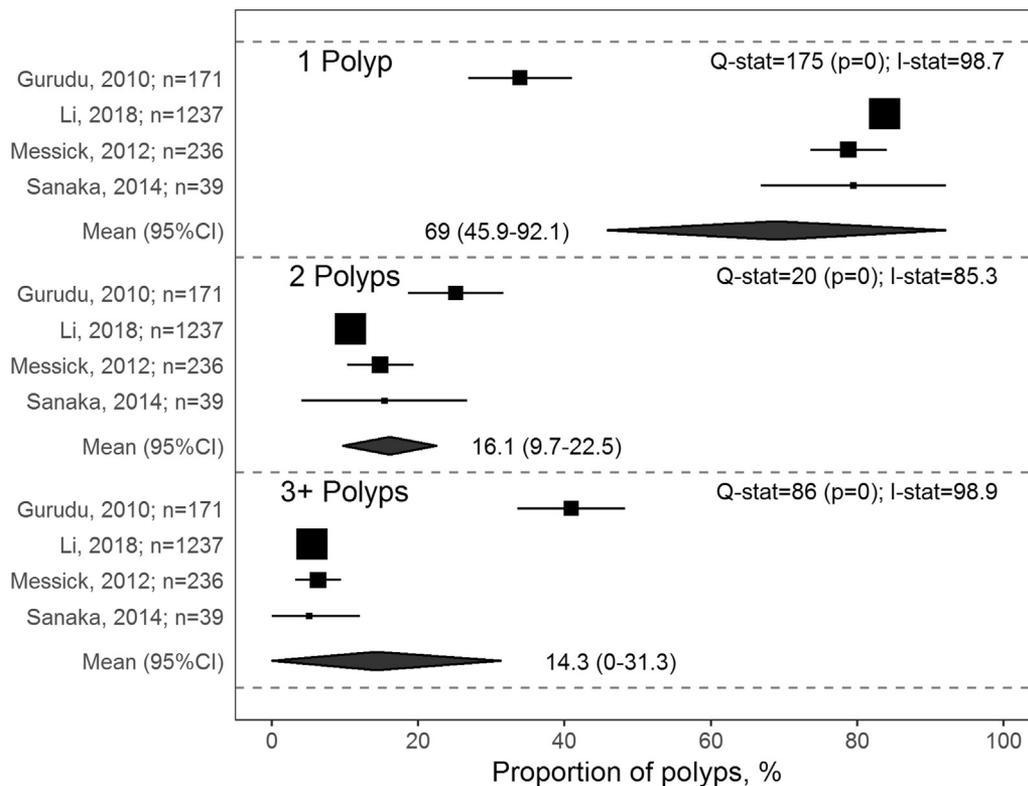
Supplementary Figure 10. Forest plot of the multiplicity distribution of SSPs. Dots represent study means, symbol size represents population size, whiskers represent 95% CIs, and the polygon represents the pooled mean estimated from random-effects metaregression.
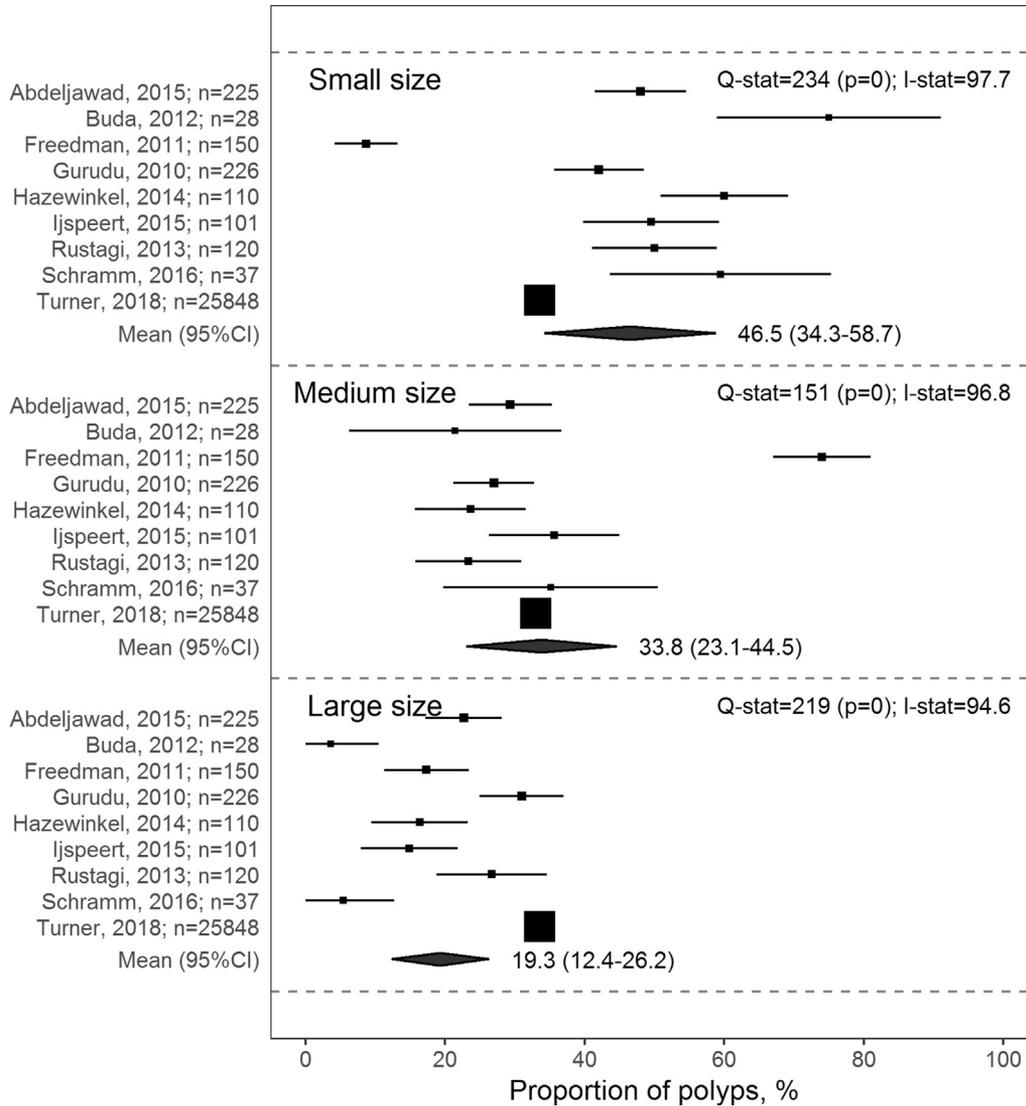
Supplementary Figure 11. Forest plot of the size distribution of SSPs. Dots represent study means, size represents study population size, whiskers represent 95% CIs, and polygons represent pooled mean estimates from random-effects metaregression. Size was divided into small (0–5 mm), medium (6–9 mm), and large (10+ mm).
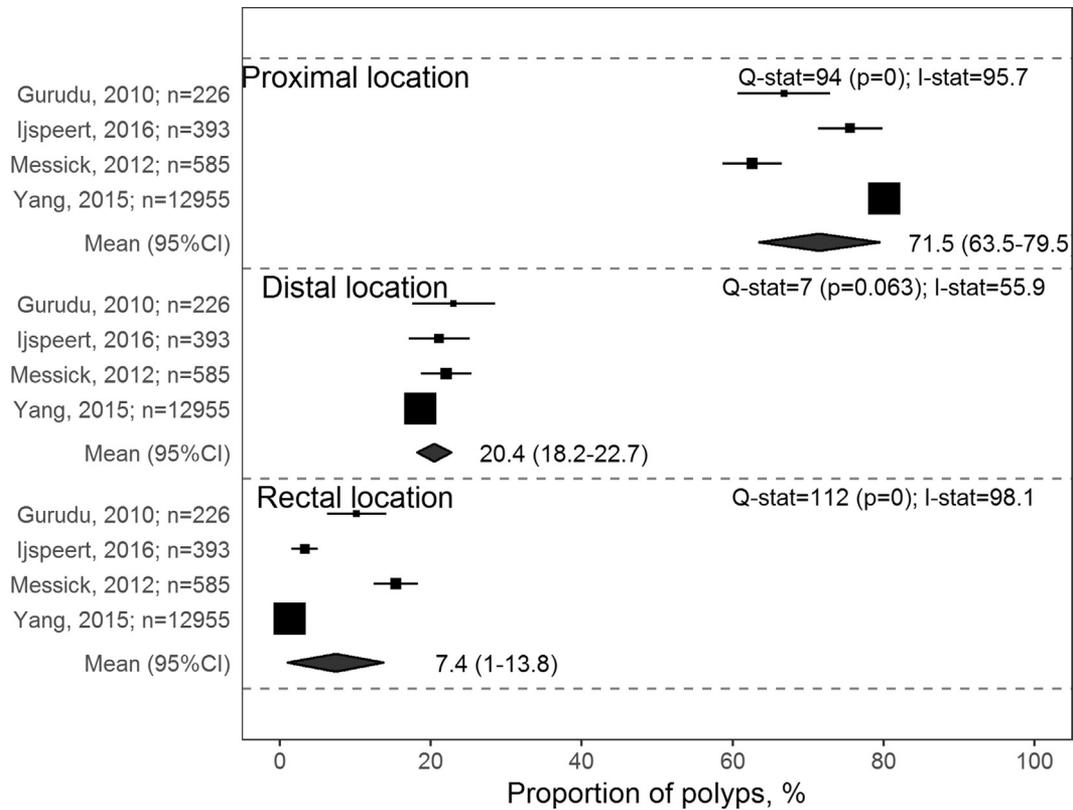
Supplementary Figure 12. Forest plot of the location distribution of SSPs. Dots represent study means, size represents study population size, whiskers represent 95% CIs, and polygons represent pooled mean estimates from random-effects metaregression. Location was divided into proximal (cecum, ascending colon, hepatic flexure, transverse colon), distal (splenic flexure, descending colon, sigmoid colon), and rectal (rectum).
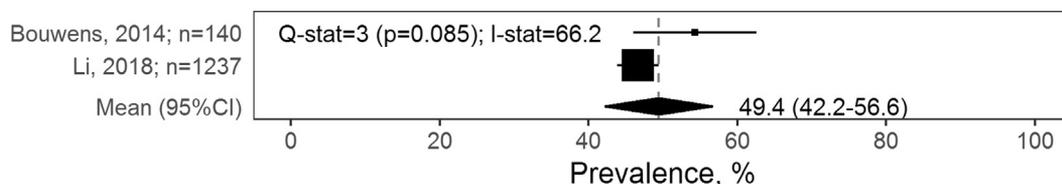
Supplementary Figure 13. Proportion of patients with SSPs with synchronous adenoma. Dots represent study means, size represents study population size, whiskers represent 95% CIs, and polygons represent pooled mean estimates from random-effects metaregression.
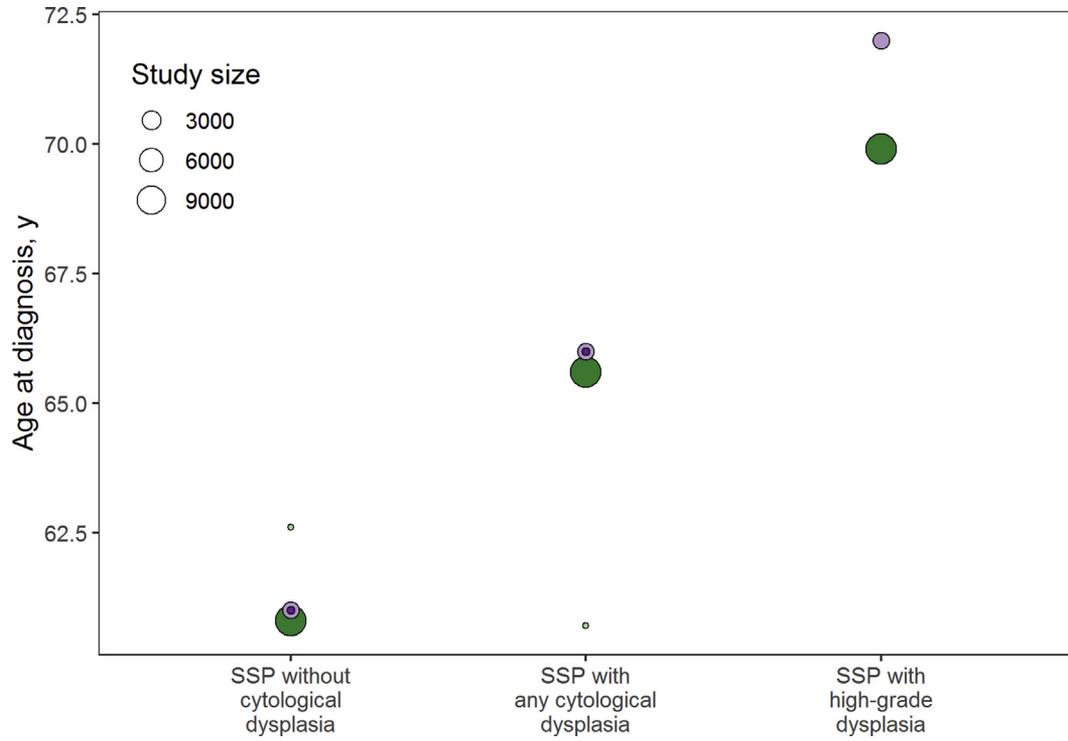
Supplementary Figure 14. Age at detection of SSPs with/without cytologic dysplasia. Dots represent study means, colors represent different studies, and size represents relative population size.

Supplementary Table 1. Study Selection Criteria (PICOS)

Research question	Population	Intervention	Comparison	Outcome	Study design
1. Prevalence	US general population or similar	Autopsy, colonoscopy	—	SSP prevalence[a]	Cross-sectional
a. By calendar year					
b. By world region			vs other world regions, and CRC incidence		
c. By clinical definition[b]			vs alternative clinical definitions (clinically relevant histology, size, or location)		
d. By age, sex[c]			vs adenoma		
e. By examination indication[d]			unselected vs screening examinations		
f. By examination quality[e]			unselected vs high-quality examinations		
g. Among polyps	Patients with adenoma, SSP, or traditional serrated adenoma				
2. Clinical features	SSP patients	Colonoscopy		% of SSPs (/patients)[f]	
a. Number			vs adenoma	1	
				2	
				3+	
b. Size			vs adenoma	1–5 mm	
				6–9 mm	
				10+ mm	
c. Anatomic location			vs adenoma	Proximal	
				Distal	
				Rectal	
d. Coexisting adenoma				With synchronous adenoma	
				Without synchronous adenoma	
e. Presence of dysplasia				Nondysplastic	
				Dysplastic	
f. Age at detection				Age at detection of	
				• Nondysplastic	
				• Low-grade dysplasia	
				• High-grade dysplasia	

PICOS, population, intervention, comparison, outcome, study design.
[a]Among patients and precancerous polyps. Including traditional serrated adenoma, if not distinguished. Following study criteria for diagnosis, considering *SSPs* and serrated *adenoma* as interchangeable terms.
[b]Including studies without reported SSP prevalence.
[c]Autopsy studies.
[d]Unselected examinations vs examinations for screening or initial screening.
[e]Unselected examinations vs examinations with high polyp detectors or enhanced endoscopes.
[f]For 2a and 2d, the denominator is the number of SSP patients.

Supplementary Table 2. Literature Search

Database	Search term	Number of records
Ovid MEDLINE	((serrat* ADJ10 (polyp* OR adeno* OR neoplas* OR carcinom* OR cancer* OR lesion* OR precursor* OR pathway*)).ab,ti.) NOT (abstract* OR book* OR chapter* OR comment* OR congres* OR dissertation abstract* OR editorial* OR letter* OR news*).pt. AND english.la. NOT (exp animals/ NOT humans/)	1343
Embase	('serrated polyp'/de OR (serrat* NEAR/10 (polyp* OR adenom* OR neoplas* OR lesion* OR precursor* OR pathway*)):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [English]/lim NOT ([animals]/lim NOT [humans]/lim)	1353
Web of Science	TS=("serrated polyp"/de OR (serrat* NEAR/10 (polyp* OR adeno* OR neoplas* OR carcinom* OR cancer* OR lesion* OR precursor* OR pathway*))) AND LA=(english) NOT DT=(Book OR Book Chapter OR Editorial Material OR Letter OR Meeting Abstract OR News Item OR Note)	1654
Cochrane Library	((serrat* NEAR/10 (polyp* OR adeno* OR neoplas* OR carcinom* OR cancer* OR lesion* OR precursor* OR pathway*)):ab,ti)	112

Supplementary Table 3. Quality Appraisal Tool

Risk of bias item	Criteria for answers (circle one option)	Additional notes and examples
External validity		
1. Was the study's target population **a close representation** of the national population in relation to relevant variables, e.g. age, sex, occupation?	• **Yes (LOW RISK):** The study's target population was a close representation of the national population. • **No (HIGH RISK):** The study's target population was clearly NOT representative of the national population.	The **target population** refers to the group of people or entities to which the results of the study will be generalised. Examples: • The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: **Yes (LOW RISK).** • The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: **No (HIGH RISK).** • The study was undertaken in one village only and it is clear this was not representative of the national population. The answer is: **No (HIGH RISK).**
2. Was the sampling frame a **true or close representation** of the target population?	• **Yes (LOW RISK):** The sampling frame was a **true or close** representation of the target population. • **No (HIGH RISK):** The sampling frame was NOT a **true or close** representation of the target population.	The **sampling frame** is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population. The answer is: **Yes (LOW RISK).** • The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: **Yes (LOW RISK).** • The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: **No (HIGH RISK).**
3. Was some form of **random selection** used to select the sample, OR, was a census undertaken?	• **Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • **No (HIGH RISK):** A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimise study bias. Examples: • The sample was selected using simple random sampling. The answer is: **Yes (LOW RISK).** • The target population was the village and every person in the village was sampled. The answer is: **Yes (LOW RISK).** • The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: **No (HIGH RISK).**

Risk of bias item	Criteria for answers (circle one option)	Additional notes and examples
4. Was the likelihood of non-response bias minimal?	• **Yes (LOW RISK):** The response rate for the study was $\geq$75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • **No (HIGH RISK)**: The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	Examples: • The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socioeconomic status. The answer is: **Yes (LOW RISK).** • The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: **No (HIGH RISK).** • The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. The answer is: **No (HIGH RISK).**
Internal validity		
5. Were data collected **directly from the subjects** (as opposed to a proxy)?	• **Yes (LOW RISK):** All data were collected directly from the subjects. • **No (HIGH RISK)**: In some instances, data were collected from a proxy.	A proxy is a representative of the subject. Examples: • All eligible subjects in the household were interviewed separately. The answer is: **Yes (LOW RISK).** • A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: **No (HIGH RISK).**
6. Was an acceptable case definition used in the study?	• **Yes (LOW RISK):** An acceptable case definition was used. • **No (HIGH RISK)**: An acceptable case definition was NOT used.	• For a study on low back pain, the following case definition was used: "Low back pain is defined as activity-limiting pain lasting more than one day in the area on the posterior aspect of the body from the bottom of the 12th rib to the lower gluteal folds." The answer is: **Yes (LOW RISK).** • For a study on back pain, there was no description of the specific anatomical location "back" referred to. The answer is: **No (HIGH RISK).** • For a study on osteoarthritis, the following case definition was used: "Symptomatic osteoarthritis of the hip or knee, radiologically confirmed as Kellgren-Lawrence grade 2-4". The answer is: **LOW RISK**.
7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have **reliability and validity (if necessary)**?	• **Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-retest, piloting, validation in a previous study, etc. • **No (HIGH RISK)**: The study instrument had NOT been shown to have reliability or validity (if this was necessary).	• The authors used the COPCORD questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: **Yes (LOW RISK).** • The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: **No (HIGH RISK)**.

Risk of bias item	Criteria for answers (circle one option)	Additional notes and examples
8. Was the **same mode of data collection** used for all subjects?	• **Yes (LOW RISK):** The same mode of data collection was used for all subjects. • **No (HIGH RISK):** The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: • All eligible subjects had a face-to-face interview. The answer is: **Yes (LOW RISK).** • Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: **No (HIGH RISK).**
9. Was the **length of the shortest prevalence period** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence, one-week prevalence, one-year prevalence). • **No (HIGH RISK)**: The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence)	The prevalence period is the period that the subject is asked about e.g. "Have you experienced low back pain over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. low back pain). Examples: • Subjects were asked about pain over the past week. The answer is: **Yes (LOW RISK).** • Subjects were only asked about pain over the past three years. The answer is: **No (HIGH RISK).**
10. Were the **numerator(s) and denominator(s)** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). • **No (HIGH RISK):** The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: **Yes (LOW RISK).** • In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: **No (HIGH RISK).**

11. Summary item on the overall risk of study bias
• **LOW RISK OF BIAS:** Further research is very unlikely to change our confidence in the estimate.
• **MODERATE RISK OF BIAS:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.
• **HIGH RISK OF BIAS:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

NOTE. This questionnaire is reprinted from Hoy et al.[27] Questions 5 and 9 were not used.
COPCORD, Community Oriented Program in the Rheumatic Diseases.

Supplementary Table 4. Study Characteristics
<See Supplementary Table 2.xlsx>

Supplementary Table 5. Quality Appraisal
<See Supplementary Table 3.xlsx>

Supplementary Table 6. SSP Prevalence by Age Across Studies

Study	Region	N	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
With denominator												
Li et al,[65] 2018	United States	34,161	102/5102	→	387/10470	→	475/11314	→	265/5890	→	48/1385	→
Schramm et al,[88] 2016	Europe	1694	—	11/460	→	9/610	→	21/532	→	—	—	—
Other studies												
Abdeljawad et al,[28] 2015	United States	1910	—		6.8%	→	8.9%	→	5.3%	→	15.2%	→
Buda et al,[39] 2012	Europe	985	OR:1	→	OR:5.8	→	OR:5.8	→	OR:9.3	→	—	—
Ijspeert et al,[56] 2016	Europe	3364	6.0%	→	8.3%	→	9.0%	→	8.4%	→	—	—

NOTE. Arrows convey that no specific number was reported for a particular cell and that numbers printed to the left apply.
OR, odds ratio.

Supplementary Table 7. Adenoma Prevalence by Age Across Autopsy Studies

Study	N	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Arminski, 1961[16,a]	1000	2/14	→	9/39	→	23/123	→	66/245	→	107/309	→	88/189	→	36/81	→
Blatt,[17] 1961	448	—	—	0/13	→	4/23	→	18/53	→	38/106	→	71/158	→	41/95	→
Bombi,[18] 1988	212	5/42	→	→	→	→	→	7/28	→	10/36	→	15/59	→	9/47	→
Chapman,[19] 1963	443	0/2	→	1/5	→	4/20	→	20/64	→	72/118	→	73/137	→	56/95	→
Clark et al,[20] 1985	680	—	—	—	—	—	17/152	→	27/147	→	54/184	→	76/197	→	→
Eide and Stalsberg,[21] 1978	280	—	—	—	—	—	15/52	→	12/49	→	31/83	→	46/96	→	→
Jass et al,[22] 1992	297	0/42	→	2/29	→	3/27	→	14/42	→	15/50	→	21/60	→	17/47	→
Rickert et al,[23] 1979	518	—	—	—	—	11/65	→	19/59	25/67	31/64	48/76	42/69	28/55	39/63	→
Stemmerman and Yatani,[24] 1973	202	—	—	—	—	6/14	→	1/25	→	32/54	→	34/55	→	35/54	→
Vatn and Stalsberg,[25] 1982	445	—	—	—	—	3/45	→	23/100	→	31/100	→	44/100	→	47/100	→
Williams et al,[26] 1982	365	—	—	—	—	—	15/82	→	20/69	→	43/108	→	43/106	→	→

NOTE. Arrows convey that no specific number was reported for a particular cell and that numbers printed to the left apply. For studies not specifying the lower age range, this was assumed to have a similar width as the other age ranges.
RR, relative risk.
[a]Rectal adenoma were not included in Arminski, 1961, suggesting true prevalence of adenomas in the colon and rectum may be higher.

Supplementary Table 8. Adenoma Prevalence by Sex Across Autopsy Studies

Study	Male patients, n	Male patients with 1+ polyps, n	Female patients, n	Female patients with 1+ polyps, n
Arminski, 1961[16]	575	198	425	134
Blatt,[17] 1961	248	99	198	73
Clark et al,[20] 1985	370	103	310	71
Eide and Stalsberg,[21] 1978	171	68	109	36
Jass et al,[22] 1992	185	47	118	25
Rickert et al,[23] 1979	307	162	211	81
Stemmermann and Yatani,[24] 1973	125	80	77	45
Williams et al,[26] 1982	198	73	167	48

Supplementary Table 9. Adenoma Multiplicity Distribution Across Autopsy Studies

Study	Patients, n	Patients with 1 polyp, n	Patients with 2 polyps, n	Patients with 3+ polyps, n
Blatt,[17] 1961	173	72	41	60
Stemmerman and Yatani,[24] 1973	125	50	26	49
Eide and Stalsberg,[21] 1978	104	52	23	29

Supplementary Table 10. Adenoma Size Distribution Across Autopsy Studies

Study	Total polyps, n	Small polyps (0–5 mm), n	Medium polyps, (6–9 mm), n	Large polyps, (10+ mm), n
Arminski, 1961[16]	647	379	169	99
Blatt,[17] 1961	465	232	158	75
Bombi,[18] 1988	89	41	42	6
Eide and Stalsberg,[21] 1978	280	123	133	24
Jass et al,[22] 1992	149	58	64	27
Rickert et al,[23] 1979	629	275	257	97
Williams et al,[26] 1982	242	103	108	31

Supplementary Table 11. Adenoma Location Distribution Across Autopsy Studies

Study	Total polyps, n	Proximal polyps, n	Distal polyps, n	Rectal polyps, n
Arminski, 1961[16]	797	368	279	150
Blatt,[17] 1961	465	285	145	35
Bombi,[18] 1988	89	50	32	7
Chapman,[19] 1963	552	349	188	15
Clarke,[20] 1985	680	380	245	54
Eide and Stalsberg,[21] 1978	280	153	102	25
Rickert et al,[23] 1979	629	424	158	47
Stemmerman and Yatani,[24] 1973	328	216	91	21
Williams et al,[26] 1982	242	139	71	32

Supplementary Table 12. Characteristics of Studies Reporting Dysplasia in SSPs

Study	Region	Colonoscopy indication	Screen examinations, %	Other examinations, %	Polyps or patients[a]	N	Dysplasia, %	Large, %
Abdeljawad et al,[28] 2015	North America	Screening	100	0	Patients	225	5.8	22.7
Bouwens et al,[37] 2014	Europe	Screening, symptoms, or surveillance	0–6.9	93.1–100	Polyps	140	42.9	—
Hazewinkel et al,[52] 2014	Europe	Screening (trial)	100	0	Polyps	111	26.1	23.5[b]
Ijspeert et al,[56] 2016	Europe	Any except screening	0	100	Polyps	399	3.8	21.4
Ijspeert et al,[57] 2017	Europe	Screening, or FT+ patients	34	66	Patients	1049	11.0	30.0
Lash et al,[98] 2010	North America	Any	Unknown	Unknown	Patients	2139	15.1	—
Pai et al,[99] 2010	North America	Screening	100	0	Polyps	68	7.4	—
Turner et al,[92] 2018	North America	Any	Unknown	Unknown	Polyps	25,848	3.7	33.6

FT+, positive fecal test result.
[a]Proportion of polyps or patients.
[b]Proportion of patients with SSPs who have large SSPs.

Supplementary Table 13. Age at Detection of SSPs Across Studies

Study	Region	Patients, N	Age at Diagnosis of SSPs With no Dysplasia, y	Age at Diagnosis of SSPs With Any Dysplasia, y	Age at Diagnosis of SSPs With High-Grade Dysplasia, y
Bouwens et al,[37] 2014	Europe	140	61	66	—
Lash et al,[98] 2010	United States	2139	61	66	72
Pai et al,[99] 2010	United States	68	62.6	60.7	
Yang et al,[101] 2015[a]	United States	11,201	60.8	65.6	69.9
Average[b]		13,548	60.8	65.6	70.2

[a]Not included in Figure 7 of the article, the meta-analysis of prevalence of cytologic dysplasia in SSPs, because of overlap with Turner et al.[92]
[b]Average across studies weighted by study size.