SYSTEMATIC REVIEW AND META-ANALYSIS

Risk factors for metachronous colorectal cancer or advanced lesions after endoscopic resection of serrated polyps: a systematic review and meta-analysis

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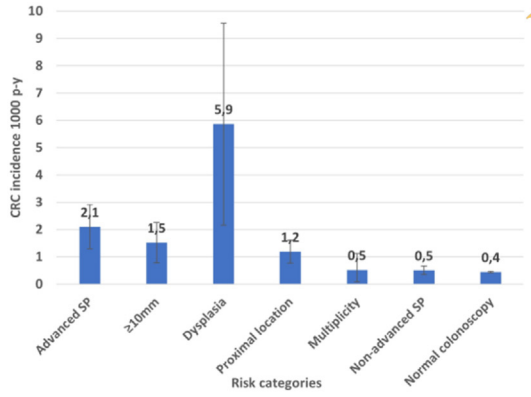
GRAPHICAL ABSTRACT



Risk category	RR for CRC risk		RR for advanced polyp
	Compared with non-advanced SP	Compared with normal colonoscopy	Compared with non-advanced SP
Advanced SP	1.84 [1.11-3.04]	2.92 [2.26-3.77]	2.05 [1.36-3.09]
SP ≥ 10mm	2.61 [1.43-4.77]	3.52 [2.17-5.69]	1.78 [1.17-2.71]
SP with dysplasia	2.06 [0.41-10.35]	2.71 [2.00-3.67]	1.00 [0.40-2.48]
Proximal SP	1.90 [0.78-4.63]	1.41 [0.56-3.53]	1.16 [0.84-1.59]
≥ 3 SP			1.18 [0.61-2.28]

Background and Aims: Serrated polyps (SPs) are precursors to 15% to 20% of colorectal cancers (CRCs). However, there are uncertainties regarding which SPs require surveillance and at what intervals, with recommendations adapted from those for adenomas in the absence of solid evidence. Our aim was to assess which SP risk characteristics relate to a higher risk of metachronous CRC or advanced polyps.

Methods: We systematically searched PubMed, Embase, and Cochrane for cohort studies, case-control studies, and clinical trials from inception to December 31, 2023, of CRC or advanced polyps (advanced adenoma [AA] or advanced SP) incidence at surveillance stratified by baseline SP size, dysplasia, location, and multiplicity. We defined advanced SPs as those ≥10 mm or with dysplasia. CRC and advanced polyp incidence per 1000 person-years were estimated. We performed a meta-analysis by calculating pooled relative risks (RRs) using a random-effects model.

Results: A total of 5903 studies were reviewed, and 14 were included with 493,949 patients (mean age, 59.5 years; 55% men). The mean follow-up was 4.9 years. CRC incidence per 1000 person-years was 2.09 (95% confidence interval [CI], 1.29-2.90) for advanced SPs, 1.52 (95% CI, 0.78-2.25) for SPs of ≥10 mm, 5.86 (95% CI, 2.16-9.56) for SPs with dysplasia, 1.18 (95% CI, 0.77-1.60) for proximal SPs, 0.52 (95% CI, 0.08-1.12) for ≥3 SPs, 0.50 (95% CI, 0.35-0.66) for nonadvanced SPs, and 0.44 (95% CI, 0.41-0.46) for normal colonoscopy findings. Metachronous CRC risk was higher in advanced SPs versus nonadvanced SPs (RR, 1.84; 95% CI, 1.11-3.04) and versus normal colonoscopy findings (RR, 2.92; 95% CI, 2.26-3.77), in SPs of ≥10 mm versus <10 mm (RR, 2.61; 95% CI, 1.43-4.77) and versus normal colonoscopy findings (RR: 3.52; 95% CI, 2.17-5.69); and in SPs with dysplasia versus normal colonoscopy findings (RR: 2.71; 95% CI, 2.00-3.67). No increase in CRC or advanced polyp risk was found in patients with proximal versus distal SPs, nor in ≥3 SPs versus 1 or 2 SPs.

Conclusions: CRC risk is significantly higher in patients with baseline advanced SPs after 4.9 years of follow-up, with risk magnitudes similar to those described for AA, supporting the current recommendation for 3-year surveillance in patients with advanced SPs. (Gastrointest Endosc 2024;■:1-11.)

(footnotes appear on last page of article)

Most colorectal cancers (CRCs) arise from colonic adenomas following the classic adenoma-carcinoma progression model.[1] However, approximately 15% to 20% of CRCs arise through the CpG island methylator phenotype (CIMP) or serrated pathway, where serrated polyps (SPs) are the precursor lesions.[2] The serrated pathway accounts for an even higher fraction of postcolonoscopy CRCs.[3]

Although there is evidence supporting surveillance in individuals with high-risk adenomas (HRAs),[4-6] there are uncertainties regarding which SPs require surveillance and at what intervals, with recommendations adapted from those for adenomas in the absence of solid evidence. Advanced SPs are defined as an SP of ≥10 mm or with any degree of dysplasia,[7-9] and major society guidelines[7-10] agree on recommending surveillance after resection of these lesions. However, guidelines offer varying recommendations with respect to other potential risk factors, including multiplicity or proximal location.

Identifying which patients require endoscopic surveillance is key, particularly because postpolypectomy surveillance has become one of the main indications for colonoscopy,[11] with the consequent burden on endoscopy units.[12] Also, colonoscopy is an invasive procedure with associated adverse events.[13] Therefore, surveillance colonoscopy should be targeted to individuals who are most likely to benefit, at the minimum frequency required to protect against CRC.

We performed a systematic review and meta-analysis with the aim of (1) comparing metachronous CRC or advanced polyp (advanced adenoma [AA] or advanced SP) incidence in patients with advanced SPs versus those with nonadvanced SPs or normal colonoscopy findings and (2) assessing which specific characteristics of SPs (size, dysplasia, location, and multiplicity) are associated with a higher risk of developing CRC or metachronous advanced polyps.

METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Supplementary Table 1, available online at www.giejournal.org).[14] The protocol was registered prospectively at PROSPERO (CRD42020186548). Based on the design of the majority of studies in this field, we considered patients with baseline SPs with or without synchronous adenomas. To explore the risk of metachronous CRC and advanced polyps attributed exclusively to SPs, we performed a sensitivity analysis focusing on patients with only baseline SPs.

Search strategy

To identify issues of greatest importance for the literature revision, we developed PICO (patient, intervention, comparison, and outcome) questions (Supplementary Table 2, available online at www.giejournal.org). In consultation with a certified medical librarian (C.S.-A), a comprehensive search of the available electronic literature was performed to find studies describing CRC or advanced polyp incidence at surveillance stratified according to baseline polyps' characteristics. Here, we describe the results regarding baseline SPs. Our study of risks after resection of baseline adenomas has been previously published.[15]

We searched the PubMed, Embase, and Cochrane databases from inception to December 2023. The search strategy is shown in Appendix 1 (available online at www.giejournal.org). Language was restricted to English, French, or Spanish. No publication date or status restrictions were imposed. References cited in related articles and meta-analyses were searched for additional eligible studies, referred to as cross-references.

Study selection and data extraction

Two reviewers (S.B.-M. and C.M.-S.) independently screened all titles and abstracts, and after selection of articles fulfilling the eligibility criteria, data extraction was carried out. Disagreement among reviewers was solved through discussion with a third reviewer (R.J.). In those studies that had multiple reports on detection rates in different moments of follow-up, we extracted the data from the overall follow-up period. Studies reporting only adjusted data, without providing crude numbers, were also excluded.

Study type

Cohort studies, case-control studies, and clinical trials were included.[16-29] Studies were excluded if subjects were aged <18 years, had any high-risk condition for CRC (inflammatory bowel disease, hereditary CRC syndromes) or had a personal history of CRC. Additionally, studies were excluded if surveillance was performed within 6 months of baseline colonoscopy or using methods other than colonoscopy. Patients with synchronous serrated and adenomatous lesions were included according to the risk features of the SP. When multiple studies reported outcomes retrieved from

the same population, only 1 study was selected, either the most applicable to our research question or the study reporting the most recent data.

Definitions and outcomes

The terminology and understanding of the SP family has evolved over time. Sessile serrated lesions (SSLs) and traditional serrated adenomas (TSAs) have malignant potential, but small, distal hyperplastic polyps (HPs) do not.[3] However, SSLs and HPs are not always distinguished endoscopically or by pathologists, and proximal and large HPs (or SPs without further subclassification) appear to be associated with CRC risk.[30] Given this, we decided to define SPs broadly as either SSL, TSA, or proximal HP. Advanced SP was defined as an SP of ≥10 mm or with dysplasia. Proximal SP was defined as any lesion proximal to the descending colon in most studies,[19,22,25-27] as proximal to the sigmoid colon in 1 study,[17] and as proximal to the rectum in 1 study.[20] Multiple SPs were considered as ≥3 SSLs, TSAs or proximal HPs. AA was defined as an adenoma of ≥10 mm, containing ≥25% villous component, or with high-grade dysplasia. Metachronous advanced polyp was defined as either metachronous AA or metachronous advanced SP. CRC was defined as invasion of malignant cells through the muscularis mucosa. Normal colonoscopy findings referred to colonoscopy results with no adenomas, SPs, or CRC detected.

The outcomes of the study were to assess the following: (1) the incidence of metachronous CRC per 1000 person-years (p-y) for patients with advanced SP, nonadvanced SP, and normal colonoscopy findings at baseline; (2) the incidence of metachronous CRC per 1000 p-y stratified by the SP risk characteristics of size, dysplasia, location, or multiplicity; (3) the incidence of metachronous advanced polyps per 1000 p-y for patients with advanced SP, nonadvanced SP, and normal colonoscopy findings at baseline; and (4) the incidence of metachronous advanced polyps per 1000 p-y stratified by the 4 SP risk characteristics. Not all of these prespecified outcomes could be assessed for some subgroups, given the scarcity of studies reporting relevant results.

Risk-of-bias assessment

The risk of bias was assessed independently by 2 reviewers (S.B.-M. and C.M.-S.) using the Quality in Prognosis Studies tool.[31] Quality was analyzed based on 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Studies were classified as having either low, moderate, or high risk of bias.

Sensitivity analysis

To explore heterogeneity among studies, 3 sensitivity analyses were conducted. First, a sensitivity analysis was performed including only cohort studies and clinical trials, excluding case-control studies. Second, to explore the risk of metachronous CRC and advanced polyps attributed exclusively to SPs, a sensitivity analysis was performed including only those studies in which patients with SPs did not have synchronous adenomas. Finally, a third sensitivity analysis was performed in the risk group of proximal SPs for studies defining proximal location as proximal to descending colon.

Statistical analysis

The incidence rates of CRC and metachronous advanced polyps per 1000 p-y of follow-up were calculated using the number of events in each risk category and the duration of follow-up, obtained from cohort studies and clinical trials. Unadjusted relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated from extracted data, with a P value of <.05 considered statistically significant. When crude numbers were not available, the study was excluded. Because data were assumed to be heterogeneous, a random-effects meta-analysis using the generic inverse variance weighting method was used. Statistical heterogeneity among studies was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating high heterogeneity. The possibility of publication bias was assessed by inspection of funnel plots. The meta-analysis was performed using Review Manager 5.3 (The Nordic-Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

The initial literature search yielded 5903 studies, of which 5566 remained after removal of duplicates. After applying the selection criteria, the addition of cross-references, and a first screening of the title and abstract, 47 studies were selected and reviewed in detail (Appendix 2, available online at www.giejournal.org), and 14 studies[16-29] were included in the final analysis (Fig. 1). Of those, 11 were cohort studies,[16-18,20,22,24-29] 2 were case-control studies,[19,21] and 1 was a clinical trial.[23] There were a total of 493,949 patients (mean age, 59.5 ± 4.2 years; 55% male) included. The mean duration of follow-up was 4.9 ± 2.6 years (median, 4.4 years; range, 2.1 years). Supplementary Table 3 (available online at www.giejournal.org) provides an overview of the individual studies with their demographic data.

Overall metachronous CRC incidence

The CRC incidence per 1000 p-y was 2.09 (95% CI, 1.29-2.90) in patients with advanced SPs. In contrast, the incidence rates were 0.50 (95% CI, 0.35-0.66) in patients with nonadvanced SPs and 0.44 (95% CI, 0.41-0.46) in those with normal colonoscopy findings. By SP characteristic, the incidence rates were 1.52 (95% CI, 0.78-2.25) in patients with SPs of ≥10 mm, 5.86 (95% CI, 2.16-9.56) in those with SPs with dysplasia, 1.18 (95% CI, 0.77-1.60) in those with proximal SPs, and 0.52 (95% CI, 0.08-1.12) in those with ≥3 SPs (Fig. 2A).

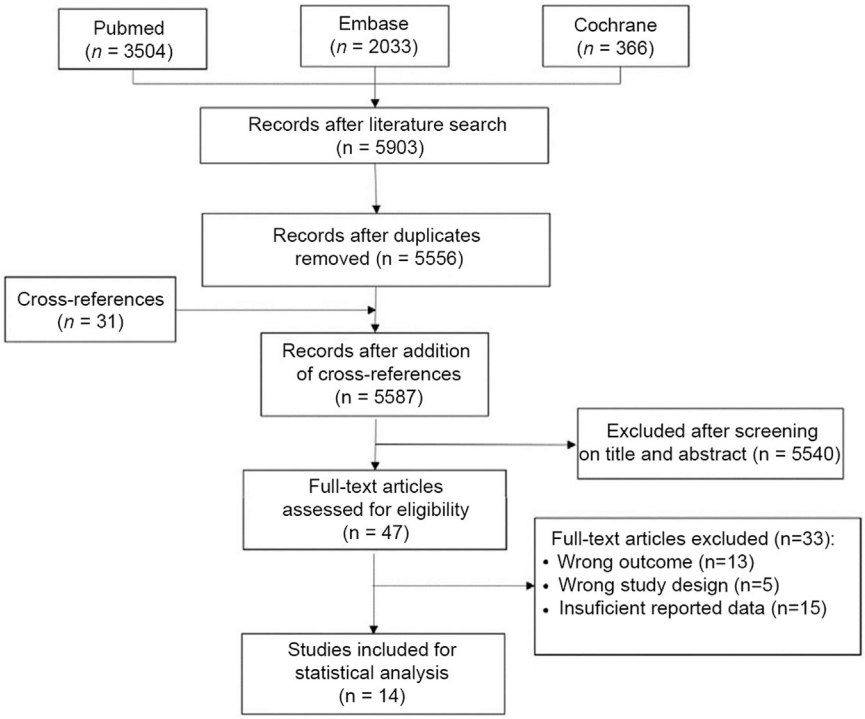


Figure 1. Flow diagram of study selection.

Overall metachronous advanced polyp incidence

The metachronous advanced polyp incidence per 1000 p-y was 55.04 (95% CI, 40.70-69.30) in patients with advanced SPs. In contrast, the incidence rates were 13.38 (95% CI, 9.60-17.20) in patients with nonadvanced SPs and 10.33 (95% CI, 8.60-12.01) in those with normal colonoscopy findings. By SP characteristic, the incidence rates were 70.62 (95% CI, 52.30-88.90) in patients with SPs of ≥10 mm, 93.02 (95% CI, 27.60-158.50) in those with SPs with dysplasia, 45.10 (95% CI, 37.30-52.90) in those with proximal SPs, and 45.46 (95% CI, 26.11-64.84) in those with ≥3 SPs (Fig. 2B).

Advanced SPs as a risk factor for metachronous CRC or advanced polyps

Eleven studies[16,18,19,21-26,28,29] reported the risk of metachronous CRC or advanced polyp incidence in patients with advanced SPs at baseline. The pooled RR for CRC incidence was 1.84 (95% CI, 1.11-3.04; I^2 = 40%) compared with patients with nonadvanced SPs and 2.92 (95% CI, 2.26-3.77; I^2 = 0%) compared with normal colonoscopy findings. The pooled RR for metachronous advanced polyp incidence was 2.05 (95% CI, 1.36-3.09; I^2 = 10%) compared with nonadvanced SPs (Fig. 3).

Impact of SP size

Seven studies[16,19,20,22-25] stratified the risk of metachronous CRC or advanced polyp according to SP size at baseline colonoscopy. The pooled RR for CRC incidence for SPs of ≥10 mm was 2.61 (95% CI, 1.43-4.77; I^2 = 0%) compared with patients with SPs of <10 mm and 3.52 (95% CI, 2.17-5.69; I^2 = 0%) compared to those with normal colonoscopy findings. The pooled risk for metachronous advanced polyp incidence for SPs of ≥10 mm was 1.78 (95% CI, 1.17-2.71; I^2 = 27%) compared with SPs of <10 mm (Fig. 4).

Impact of dysplasia

Four studies[19-21,29] stratified the risk of metachronous CRC or advanced polyp according to the presence of dysplasia in baseline SPs. The RR for CRC incidence for patients with SPs with dysplasia at the index colonoscopy was 2.06 (95% CI, 0.41-10.35; I^2 = 41%) compared to those with SPs without dysplasia and 2.71 (95% CI, 2.00-3.67; I^2 = 0%) compared to those with normal colonoscopy findings. The pooled RR for metachronous advanced polyp incidence was 1.00 (95% CI, 0.40-2.48; I^2 = 0%) compared with SPs without dysplasia (Fig. 5).

Impact of SP location

Seven studies[17,19,20,22,25-27] stratified the risk of metachronous CRC or advanced polyp according to the location of baseline SPs. The RR for CRC incidence for patients with proximal SPs at the index colonoscopy was 1.90 (95% CI, 0.78-4.63; I^2 = 50%) compared to those with distal SPs and 1.41 (95% CI, 0.56-3.53; I^2 = 70%) compared to those with normal colonoscopy findings. The pooled RR for

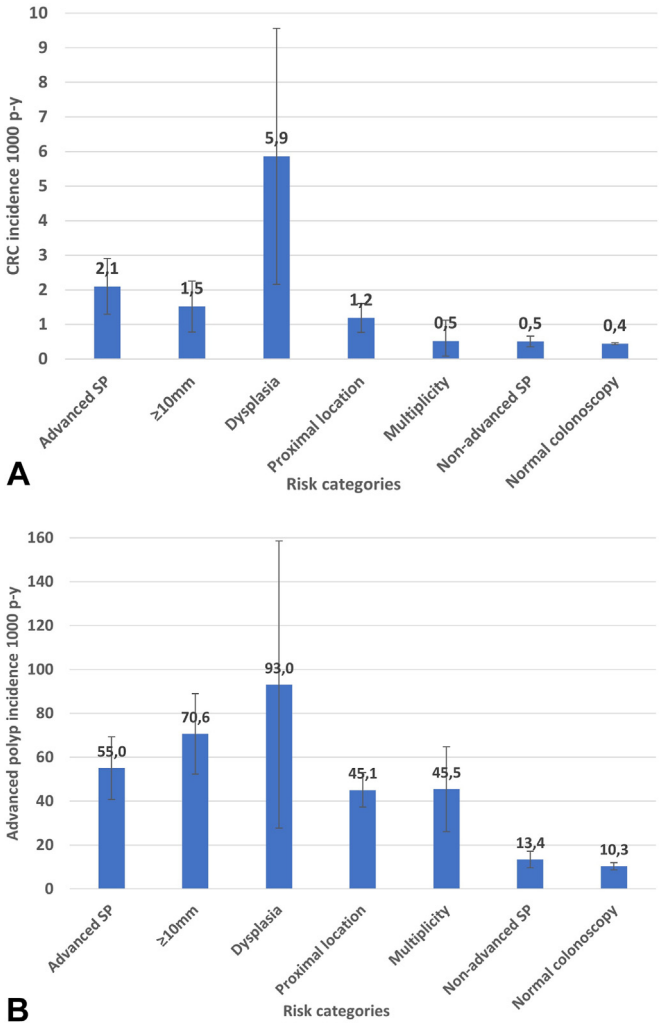


Figure 2. A, CRC and **B,** metachronous advanced polyp incidence per 1000 p-y in each risk category and in the population with nonadvanced SP and normal colonoscopy findings. *CRC*, Colorectal cancer; *p-y*, person-years; *SP*, serrated polyp.

metachronous advanced polyp incidence for proximal SP was 1.16 (95% CI, 0.84-1.59; I^2 = 14%) compared with distal SP (Fig. 6).

Impact of SP multiplicity

Three studies stratified the risk of metachronous CRC or advanced polyp according to the number of baseline SPs.[17,20,22] Of those, only 1 study assessed the risk of CRC incidence for patients with multiple SPs at the index colonoscopy compared with patients with 1 or 2 SPs or normal colonoscopy findings, without finding significant differences.[22] The pooled RR for metachronous advanced polyp incidence for ≥3 SPs compared to 1 or 2 SPs was 1.18 (95% CI, 0.61-2.28; I^2 = 54%) (Fig. 7).

Risk-of-bias assessment

Supplementary Fig. 1 and Supplementary Table 4 (available online at www.giejournal.org) show the risk-of-bias assessment. Supplementary Fig. 2 (available online at www.giejournal.org) shows funnel plots, which are quite symmetric around the *x*-axis, suggesting the absence of publication bias.

Sensitivity analyses

In the sensitivity analysis including only cohort studies and clinical trials (Supplementary Figs. 3-6, available online at www.giejournal.org), patients with advanced SPs and SPs of ≥10 mm continued having higher CRC and advanced polyp risk compared with patients with nonadvanced SP or normal colonoscopy findings. Patients with proximal SPs did not show an increased risk of CRC or metachronous advanced polyps compared to patients with distal SPs or normal colonoscopy findings, and patients with ≥3 SPs did not show an increased risk of advanced polyps compared to those with 1 or 2 SPs. There were insufficient studies to perform this analysis in the group of SPs with dysplasia.

In the sensitivity analysis including only studies in which patients with SPs had no synchronous adenomas, patients with advanced SP continued having an increased risk of metachronous advanced polyps compared to patients with nonadvanced SPs (RR, 1.89; 95% CI, 1.12-3.21) (Fig. 8). There were insufficient studies to perform this analysis for other outcomes or risk groups.

Finally, in the sensitivity analysis including only studies where proximal SPs were defined as proximal to the descending colon, excluding those SPs in the descending colon and sigmoid colon, patients with proximal SPs did not show an increased risk of CRC or metachronous advanced polyps compared to patients with distal SPs or normal colonoscopy findings (Supplementary Fig. 7, available online at www.giejournal.org).

DISCUSSION

This systematic review and meta-analysis synthesizes all the available evidence on which SP characteristics at baseline best predict the risk of metachronous CRC or advanced polyps. Our findings can help standardize postpolypectomy surveillance guidelines for serrated lesions. Our results show that patients with advanced SPs are at a clinically meaningful higher risk of developing CRC than patients with nonadvanced SPs or normal colonoscopy findings. This higher risk for metachronous advanced polyps seems to be maintained even in patients with advanced SPs without synchronous adenomas, according to the results of our sensitivity analysis. Regarding individual characteristics of SPs, patients with SPs of ≥10 mm have a higher risk of metachronous CRC compared with individuals with SPs of <10 mm or normal colonoscopy findings, and patients with baseline SPs with dysplasia have a higher risk of metachronous CRC compared with normal colonoscopy findings. In contrast, current evidence did not identify

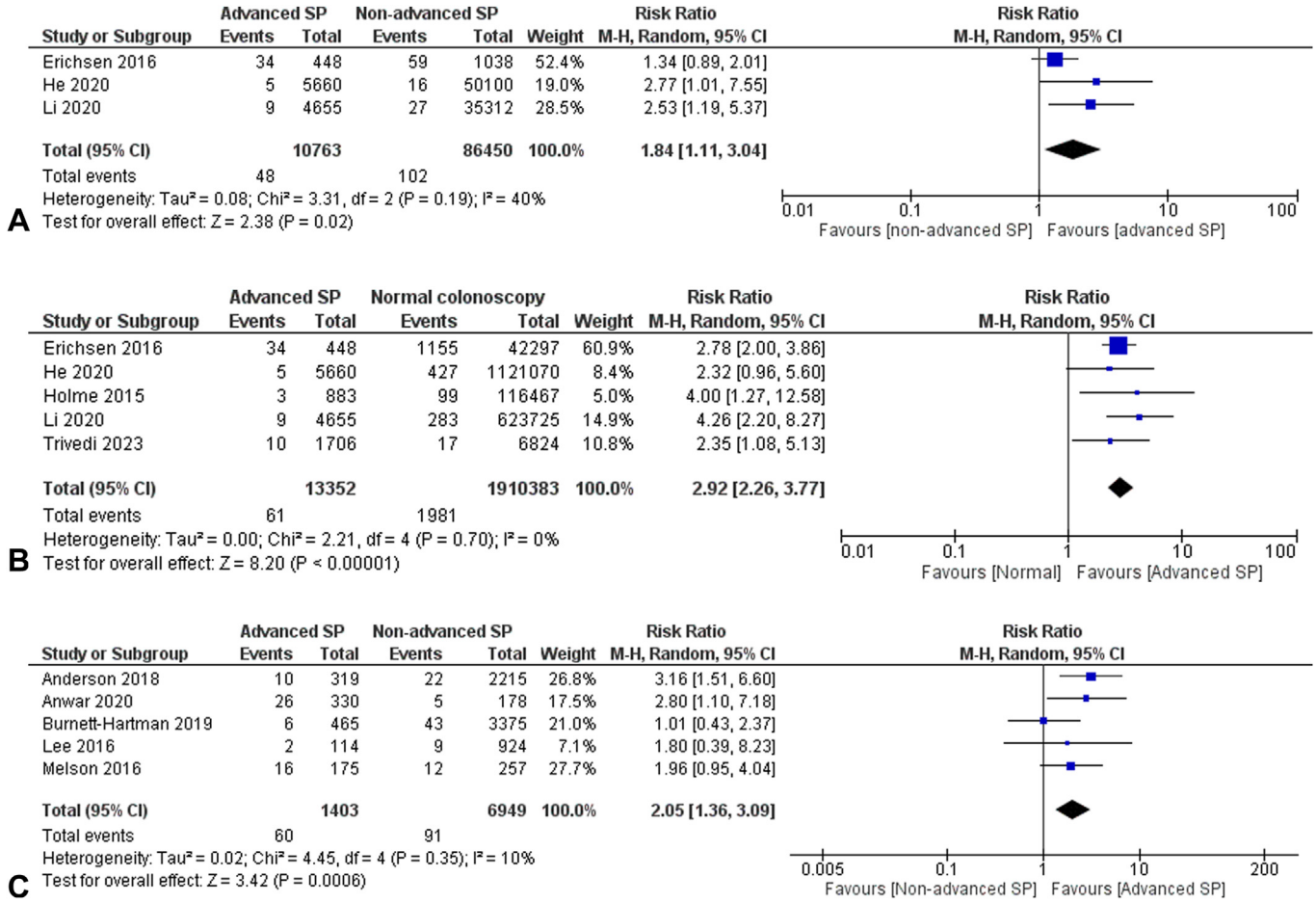


Figure 3. Risk ratio for CRC incidence in 1000 p-y in the advanced SP group compared to **A,** the nonadvanced SP group and **B,** the group with normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y in the advanced SP group compared to the nonadvanced SP group. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *M-H*, Mantel-Haenszel; *p-y*, person-years; *SP*, serrated polyp.

proximal location or multiplicity as risk factors for higher CRC risk over a mean follow-up period of 4.9 years.

Medical societies tend to agree on recommending surveillance after resection of advanced SPs, defined as those of ≥10 mm or with any degree of dysplasia.[7-10] According to our analyses, these were the 2 risk characteristics to confer an increased risk of metachronous CRC, and therefore our results support that definition of advanced SP in guidelines.

In a case-control study, Erichsen et al[21] showed that patients with SSL with dysplasia had almost twice the risk of CRC after 10 years of follow-up compared with patients with SSL without dysplasia or patients with conventional adenomas. Our results show a CRC incidence of 5.86 (95% CI, 2.16-9.56) per 1000 p-y in patients with SPs with dysplasia and a higher CRC risk compared to patients with normal colonoscopy findings. However, we did not observe a significantly higher risk compared to SPs without dysplasia, probably because of the scarcity of studies.

In our study, patients with proximal SPs did not show a higher risk of CRC or advanced polyps compared to those with distal SPs or normal colonoscopy findings. To date, major society guidelines do not consider proximal SP location as an independent risk factor to determine the need for surveillance. Similarly, a recent study showed that patients with proximal SPs did not have an increased risk of CRC compared to patients with distal SPs.[22] However, another study observed an increased risk of CRC with both large and small proximal SPs after 3 years.[25]

Regarding SP multiplicity, the U.S. Multi-Society Task Force (USMTF) on Colorectal Cancer[7] recommends surveillance for any number of SPs, with a closer interval as the number increases. In contrast, the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/Public Health England (PHE) guidelines[10] recommend 3-year surveillance in patients with ≥5 nondysplastic small SPs, and ESGE guidelines[9] do not recommend surveillance for only small nondysplastic SPs (except for serrated polyposis syndrome). Our results show that patients with multiple nonadvanced SPs (regardless of distal HP) do not appear to have an increased risk of metachronous advanced polyps.

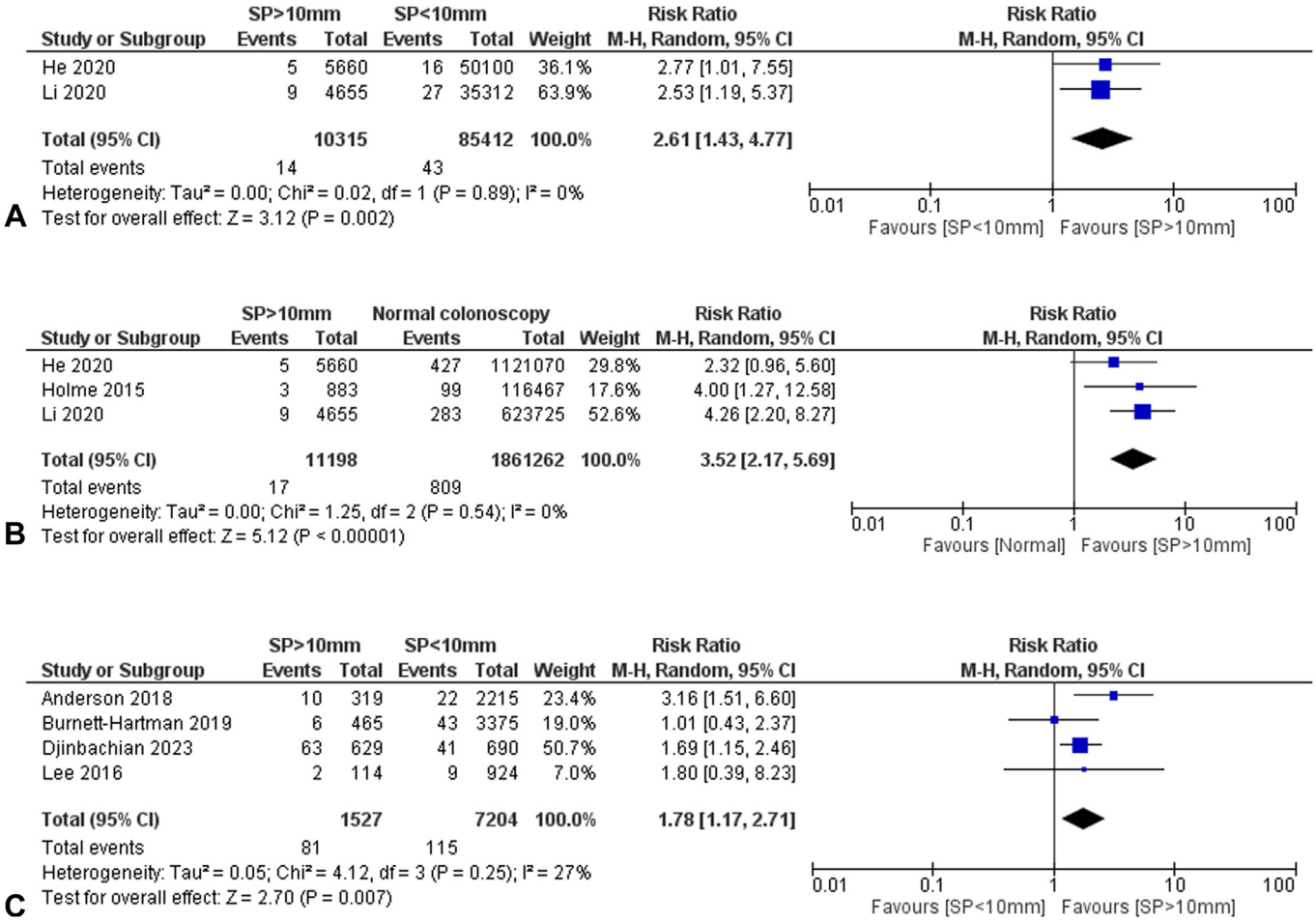


Figure 4. Risk ratio for CRC incidence in 1000 p-y comparing SPs of ≥10 mm **A,** to SPs of <10 mm and **B,** to normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing SPs of ≥10 mm to SPs of <10 mm. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

To our knowledge, only 1 study has assessed CRC risk after resection of multiple SPs,[22] without significant differences between patients with ≥3 SPs compared to 1 or 2 SPs. Our results, along with those of recently published studies,[17,20,22] may help to clarify that patients with multiple nonadvanced SPs do not have an increased risk of metachronous CRC or advanced polyps and that longer surveillance intervals (or even no need for surveillance) may be considered in these individuals.

Our systematic review and meta-analysis has several strengths. We pooled all data on the risk of CRC after resection of advanced SPs. Previous meta-analyses have examined the CRC and metachronous neoplasia risk in patients with SPs and synchronous AA versus AA alone[32,33] or the risk of synchronous neoplasia in patients with SPs.[34] Our expansive search aimed to cover all available evidence, resulting in pooled data from 14 studies with almost 500,000 patients with a mean follow-up of 4.9 years. Our main outcomes were clinically relevant, including CRC incidence. We extracted raw data from each study and used p-y of follow-up for our analysis to try to minimize heterogeneity among studies.

The main limitation of this study is that, in many studies, patients with SPs also had synchronous adenomas, which could overestimate the metachronous CRC risk attributable independently to the presence of SPs. There is evidence showing that patients with HRA and synchronous SSP or TSA are at higher risk of metachronous advanced neoplasia compared to those with HRA alone.[16,32] In this regard, recent guidelines[10] are already considering synchronous adenomas and SP together for risk stratification and surveillance recommendations.

In our meta-analysis, of the 11 studies evaluating the risk of metachronous CRC or advanced polyps in patients with advanced SPs at baseline, only 5 reported data for patients with SPs without synchronous adenomas.[16,18,19,26,28] Of the remaining 6 studies, 1 included patients with SPs with up to 2 nonadvanced adenomas,[23] and the others did not offer any information on the characteristics of the synchronous adenomatous lesions. In our sensitivity analysis of

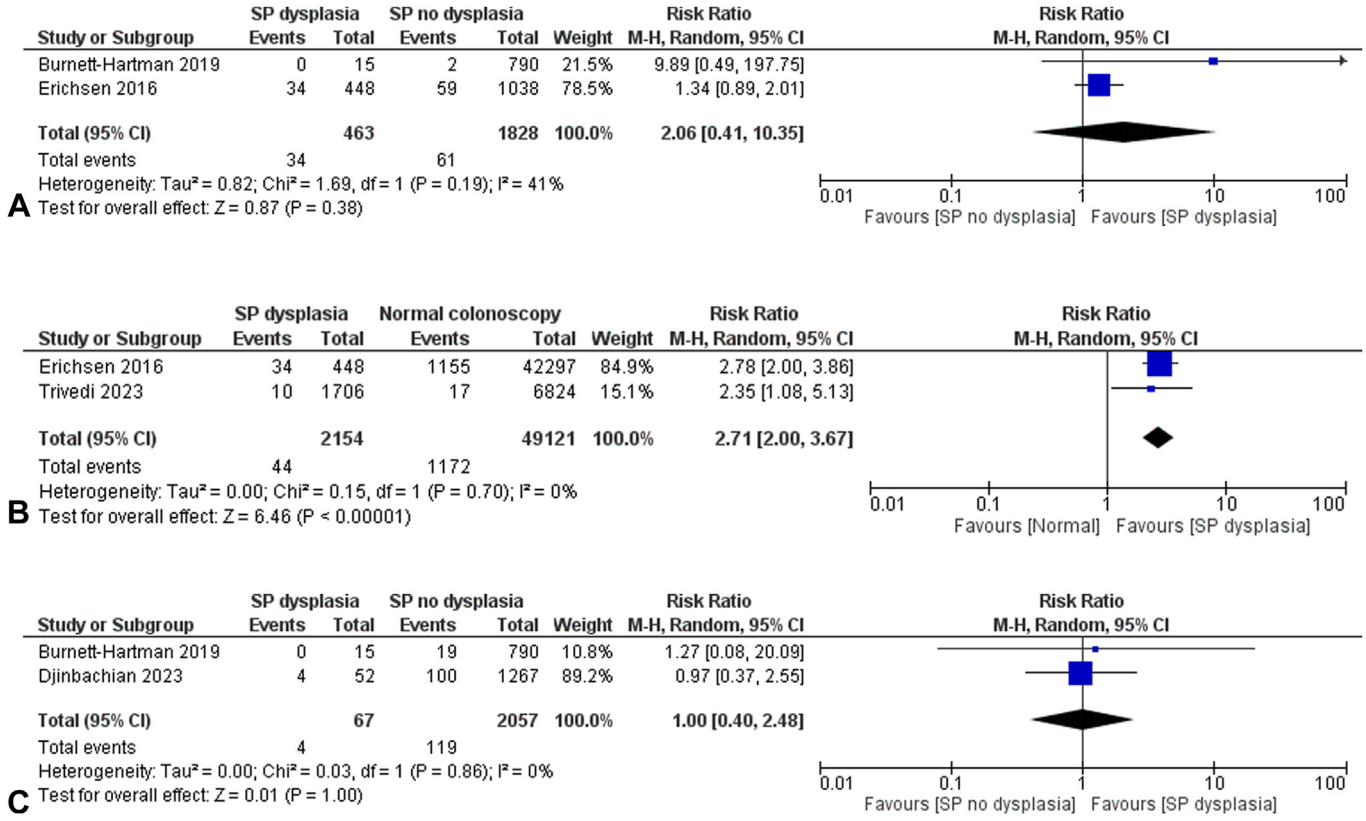


Figure 5. Risk ratio for CRC incidence in 1000 p-y in patients with SP with dysplasia compared to **A,** those with SP without dysplasia and **B,** those with normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y in patients with SP with dysplasia compared to SP without dysplasia. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

studies in which patients with advanced SPs had no synchronous adenomas, advanced SPs were still associated with a clinically meaningful higher metachronous advanced polyp risk. Despite this limitation, published data on the fraction of patients with advanced SPs with synchronous AA (17%-30%)[16,18,20,27-29] and comparisons to our recently published results for patients with baseline adenomas[15] suggest that synchronous AAs cannot explain away the magnitude of the metachronous lesion risks observed after the detection of advanced SPs (Supplementary Table 5, available online at www.giejournal.org).

The fact that we included in our analysis proximal or ≥10-mm HPs may also be considered as a potential limitation. Regarding SP subtype, only the USMTF guidelines[7] offer different recommendations depending on the histology (HP, SSL, or TSA), whereas the ESGE[9] and BSG/ACPGBI/PHE guidelines[10] do not take the polyp subtype into account and, instead, consider size and dysplasia (and also multiplicity for BSG/ACPGBI/PHE). One study[35] evaluated the implications of considering the SP subtype by comparing the surveillance recommendations given following either the USMTF or ESGE guidelines, with 90% of patients having an identical recommended interval. This, together with the rarity of HPs in the proximal colon and the fact that SSLs are difficult to differentiate from HPs, including high interobserver variability,[30] suggests that guiding surveillance based on distinguishing SSLs from HPs, once size and dysplasia have been taken into account, may be unnecessary.

Our study has additional limitations. First, most available studies are observational, with the inherent risk of bias (especially attrition bias). Second, high heterogeneity was observed among studies, with differences in design, population size, follow-up time, and colonoscopy indications. For some analyses, there were few available studies, which could affect the power to find statistically significant results. Although the primary studies performed a variety of multivariate analysis, the fact that each one of them controlled for different variables precluded a quantitative synthesis of these or the extraction of adjusted data. Also, some studies had to be excluded because they did not provide unadjusted data. In most studies, only total follow-up time was provided, without specifying the actual interval of surveillance, preventing us from addressing the appropriate intervals of surveillance. Inadequate surveillance intervals could have affected metachronous CRC risk. Some studies might have only accounted for CRC found at surveillance and not interval CRC, potentially underestimating the risk. Because SPs are considered more difficult to identify and remove completely,[36] evaluation of metachronous outcomes becomes more challenging because we might have been

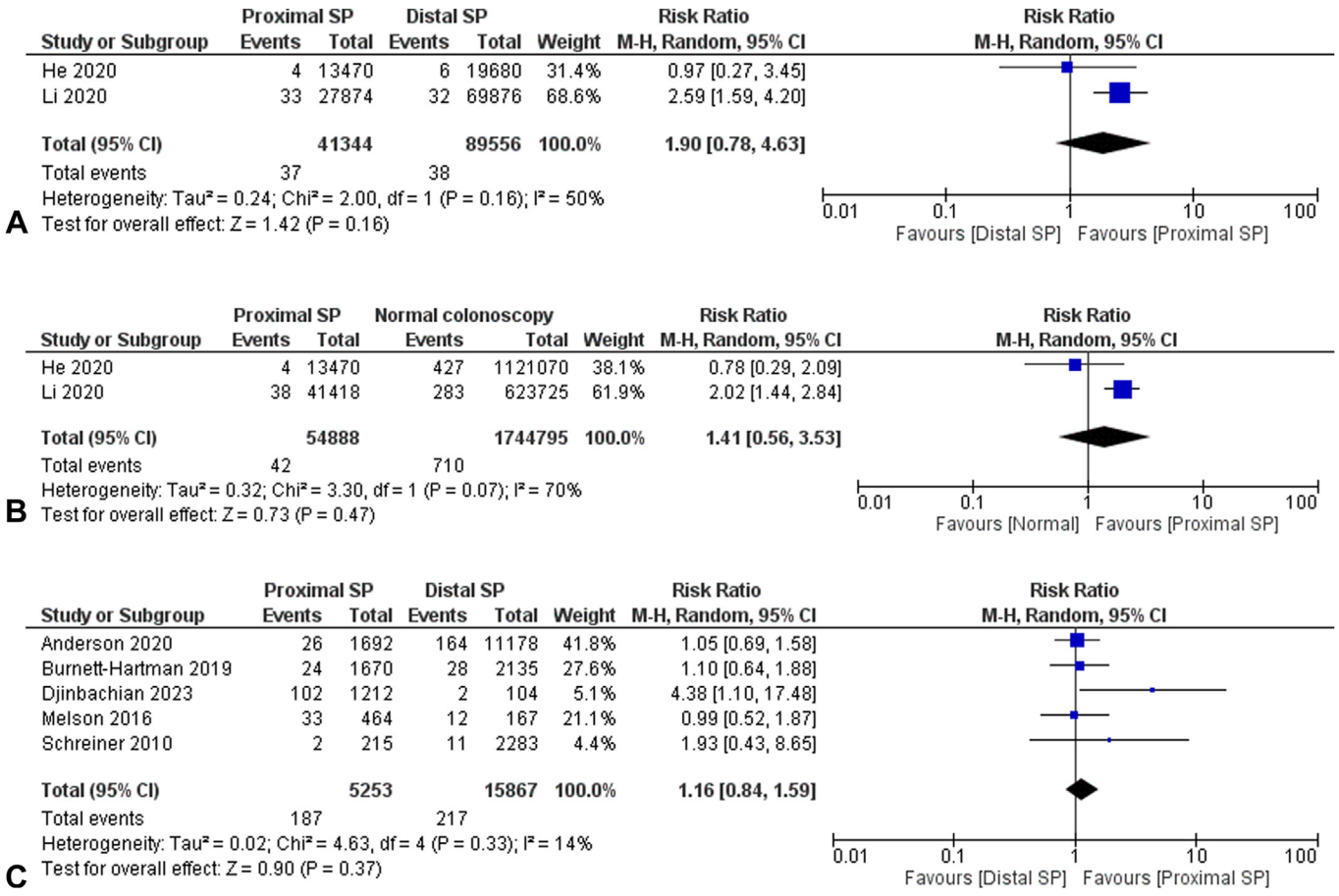


Figure 6. Risk ratio for CRC incidence in 1000 p-y comparing patients with proximal SP to **A,** those with distal SP and **B,** those with normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y in patients with proximal SP compared to distal SP. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

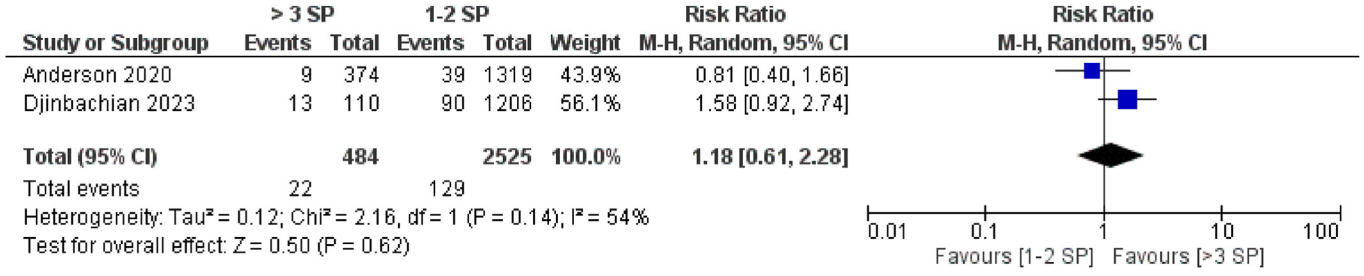


Figure 7. Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing patients with 3 SPs to those with 1 or 2 SPs. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

detecting previously missed or incompletely resected lesions. Finally, we did not consider clinical characteristics of the patients, such as smoking habit or obesity, that have proven to be risk factors for SP,[37] or emerging factors that might inform surveillance recommendations in the future, including quality indicators of the endoscopists[38] or molecular markers.[39]

In summary, our results show that patients with advanced SP have a higher risk of metachronous CRC compared to individuals with nonadvanced SP or normal colonoscopy findings. Specifically, patients with SPs of ≥10 mm have a higher risk of metachronous CRC compared with individuals with nonadvanced SPs or normal colonoscopy findings, and patients with baseline SPs with dysplasia have a higher risk of metachronous CRC compared with patients with normal colonoscopy findings. The comparatively high metachronous CRC incidence in these patients probably justifies surveillance. In contrast, the current available evidence does not identify proximal SP or multiple SPs as factors that increase the risk of metachronous CRC over the next 5 years.

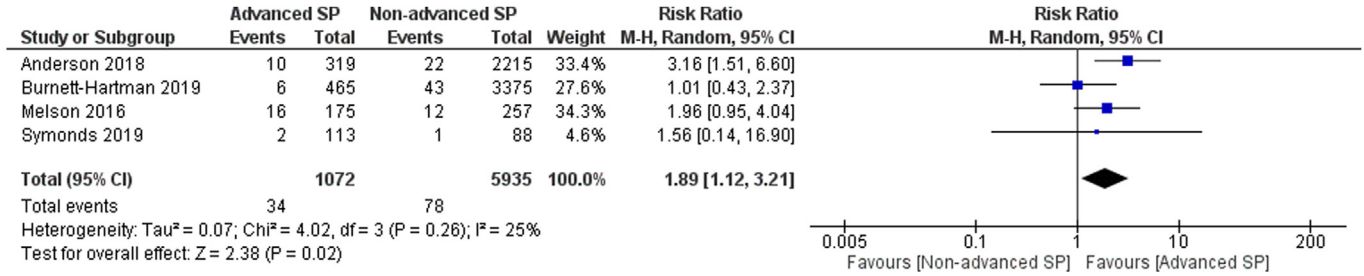


Figure 8. Sensitivity analysis including only studies where patients with SP had no synchronous adenomas. Metachronous advanced polyp incidence in 1000 p-y for patients with advanced SP compared to those with nonadvanced SP. *CI*, Confidence interval; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

Therefore, surveillance may not be indicated for these SP features alone. The relative scarcity of studies on CRC incidence and mortality as well as the impact of surveillance in patients with SPs highlights the need for dedicated studies on the efficacy of surveillance in patients with SPs.[40]

DISCLOSURE

The following authors disclosed financial relationships: U. Ladabaum: Advisor for UniversalDx, Lean Medical, Vivante, and Kohler Ventures; consultant for Medtronic, Clinical Genomics, Guardant Health, Freenome and CheckCap. C. Hassan: Consultant for ERBE, Fujifilm, Odin, and Olympus; R. Jover: Advisor for MSD, Norgine, Alpha.Sigma, and GI Supply. All other authors disclosed no financial relationships.

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Abbreviations: AA, advanced adenoma; ACPGBI, Association of Coloproctology of Great Britain and Ireland; BSG, British Society of Gastroenterology; CI, confidence interval; CRC, colorectal cancer; ESGE, European Society of Gastrointestinal Endoscopy; HP, hyperplastic polyp; HRA, high-risk adenoma; p-y, person-years; PHE, Public Health England; RR, relative risk; SP, serrated polyp; SSL, sessile serrated lesion; TSA, traditional serrated adenoma; USMTF, U.S. Multi-Society Task Force.

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APPENDIX 1

PubMed (National Library of Medicine)

(human[MeSH Terms]) AND ((((((risk*[Title/Abstract]) OR (risk factors[MeSH Terms])) AND (("Colorectal Neoplasms"[Mesh]) OR ("COLONIC NEOPLAS*"[Title/Abstract] OR "COLON NEOPLAS*"[Title/Abstract] OR "COLON TUMOR*"[Title/Abstract] OR "COLONIC TUMOR*"[Title/Abstract] OR "COLORECTAL NEOPLAS*"[Title/Abstract] OR "CANCER OF COLON"[Title/Abstract]))) AND ((colonoscopy*[Title/Abstract]) OR ("Colonoscopy"[Mesh]))) AND (((((((("Colonic Polyps"[Mesh]) OR ("Adenoma"[Mesh])) OR (adenoma*[Title/Abstract])) OR (postpolypectomy*[Title/Abstract])) OR ("polyp removal"[Title/Abstract])) OR ("serrated polyp*"[Title/Abstract])) OR ("serrated lesion*"[Title/Abstract])) OR ("colon polyp*"[Title/Abstract])) OR ("colonic polyp*"[Title/Abstract]))) NOT (("Inflammatory Bowel Diseases"[MeSH Terms] OR "Neoplastic Syndromes, Hereditary"[MeSH Terms])))

Embase (Elsevier)

#1	'colon tumor'/exp
#2	colonic AND neoplasm:ti,ab
#3	'colonic neoplasm':ti,ab
#4	'colonic neoplasms':ti,ab
#5	'colonic cancer':ti,ab
#6	'colonic cancers':ti,ab
#7	'colon neoplasm':ti,ab
#8	'colon neoplasms':ti,ab
#9	'colonic tumor':ti,ab
#10	'colonic tumors':ti,ab
#11	'colon tumor':ti,ab
#12	'colon tumors':ti,ab
#13	'cancer of the colon':ti,ab
#14	'colorectal tumor'/exp
#15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	'colon polyp'/exp
#17	'colon polyp':ti,ab
#18	'colon polyps':ti,ab
#19	'colonic polyp':ti,ab
#20	'colonic polyps':ti,ab
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#23	'polyp removal':ti,ab
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#48	#15 AND #43 AND #44 AND #47
#49	#29 OR #30 OR #31
#50	#39 AND #49
#51	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #50
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#53	#15 AND #43 AND #47 AND #51 AND [embase]/lim
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#55	#53 AND #54
#56	'inflammatory bowel disease'/exp OR 'inflammatory bowel disease'
#57	'inflammatory bowel disease'/exp OR 'inflammatory bowel disease'
#58	#56 OR #57
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#60	#55 NOT #58 AND ([medline]/lim OR [pubmed-not-medline]/lim)
#61	#59 NOT #60

Cochrane Library

#1	(polypectom*):ti,ab,kw (Word variations have been searched)
#2	(colon*):ti,ab,kw (Word variations have been searched)
#3	MeSH descriptor: [Colorectal Neoplasms] explode all trees

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Continued

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#6	MeSH descriptor: [Risk Factors] explode all trees
#7	(RISK*):ti,ab,kw (Word variations have been searched)
#8	#6 OR #7
#9	MeSH descriptor: [Adenoma] explode all trees
#10	(adenoma*):ti,ab,kw (Word variations have been searched)
#11	#9 or #10
#12	MeSH descriptor: [Colonoscopy] explode all trees
#13	(colonoscop*):ti,ab,kw (Word variations have been searched)
#14	#12 or #13
#15	#2 AND #4
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#18	("RECTAL NEOPLASM*"):ti,ab,kw (Word variations have been searched)
#19	("COLON TUMOR*"):ti,ab,kw (Word variations have been searched)
#20	("CANCER OF THE COLON*"):ti,ab,kw (Word variations have been searched)
#21	("COLON CANCER*"):ti,ab,kw (Word variations have been searched)
#22	#3 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#1 OR #4 OR #5 OR #11
#24	#22 AND #23 AND #8 AND #14

APPENDIX 2

Insufficient reported data

1. Tao EW, Wang YF, Zou TH, et al. Relationship between serrated polyps and synchronous and metachronous advanced neoplasia: A retrospective study. J Dig Dis 2020;21:558-65.
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Wrong outcome

1. Álvarez C, Andreu M, Castells A, et al. Relationship of colonoscopy-detected serrated polyps with synchronous advanced neoplasia in average-risk individuals. Gastrointest Endosc 2013;78:333-41.e1.
2. 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.
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Wrong study design

1. Boregowda U, Umapathy C, Echavarria J, Saligram S. Risk of metachronous neoplasia with high-risk adenoma and synchronous sessile serrated adenoma: a systematic review and meta-analysis. Diagnostics (Basel) 2023;13:1569.
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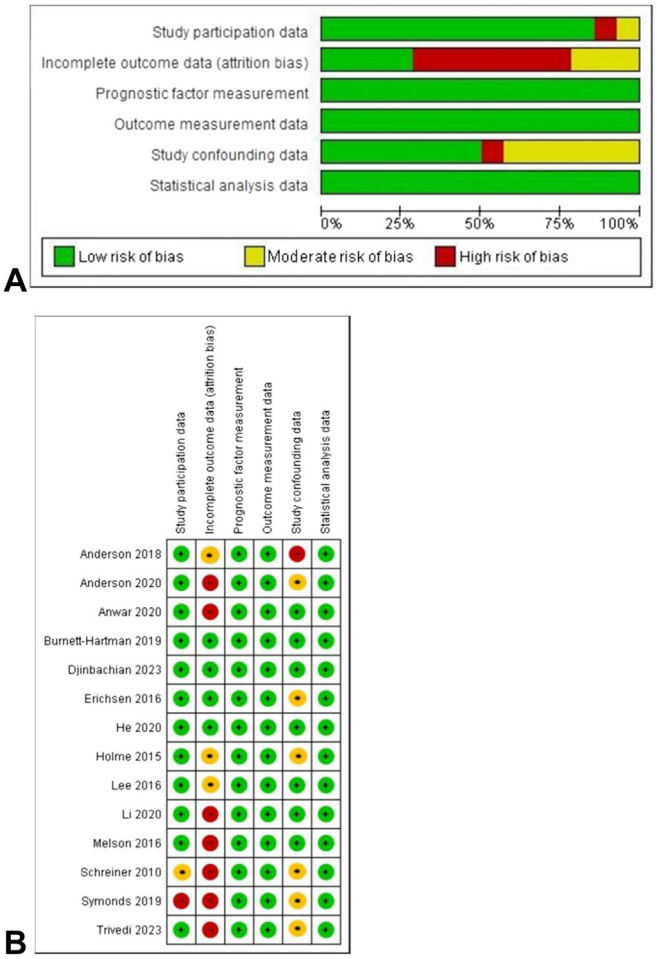
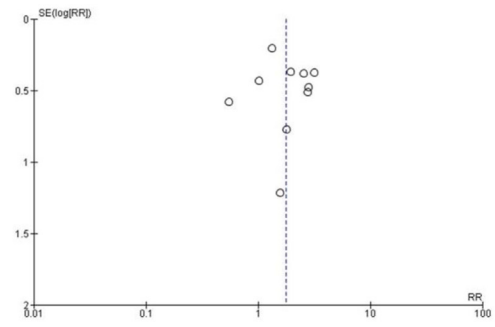
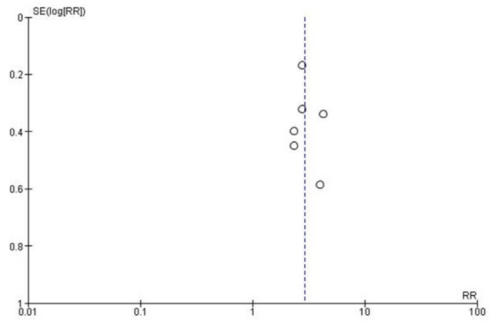


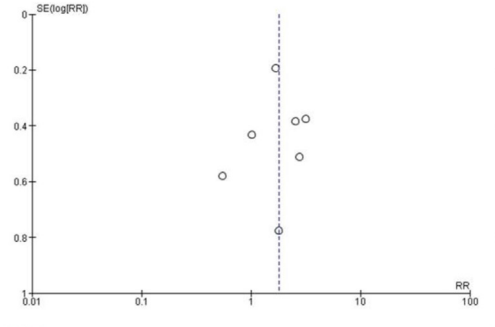
Supplementary Figure 1. Risk-of-bias analysis. The authors' judgment about each risk-of-bias item is **A,** presented as a percentage across all included studies and **B,** presented individually for each included study.



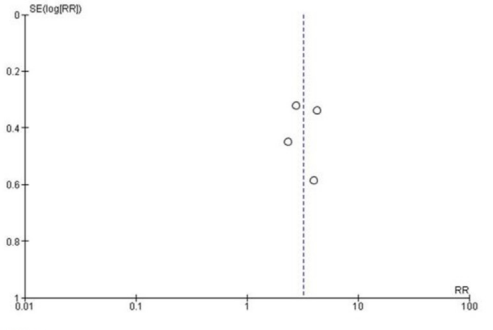
Caption
Funnel plot of comparison: 1 ASP vs NASP, outcome: 1.3 AP + CRC.



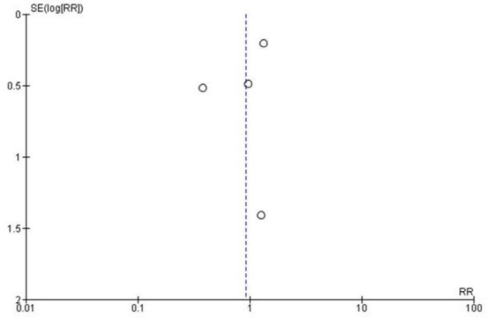
Caption
Funnel plot of comparison: 2 ASP vs NC, outcome: 2.3 AP + CRC.



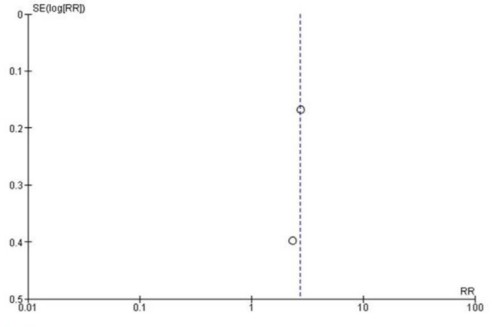
Caption
Funnel plot of comparison: 3 SP>10mm vs SP<10mm, outcome: 3.3 AP + CRC.



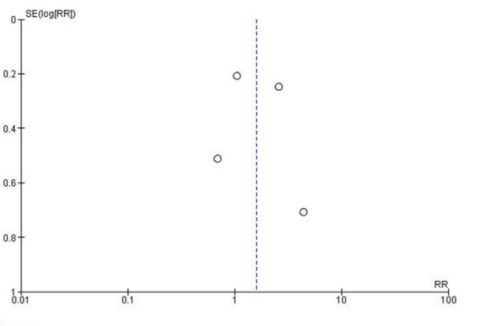
Caption
Funnel plot of comparison: 4 SP>10mm vs NC, outcome: 4.3 AP + CRC.



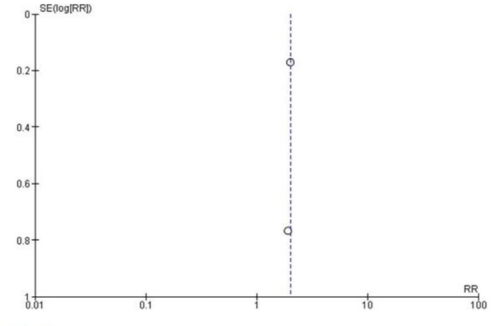
Caption
Funnel plot of comparison: 5 SP dysplasia vs SP no dysplasia, outcome: 5.3 AP + CRC.



Caption
Funnel plot of comparison: 6 SP dysplasia vs NC, outcome: 6.3 AP + CRC.

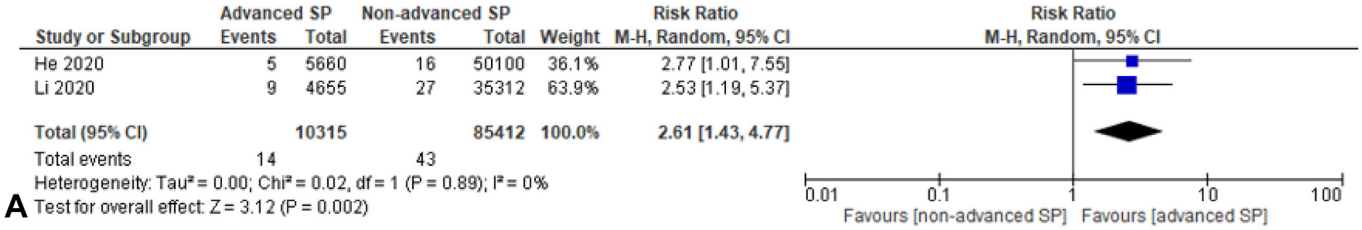


Caption
Funnel plot of comparison: 7 Proximal SP vs distal SP, outcome: 7.3 CRC + AP

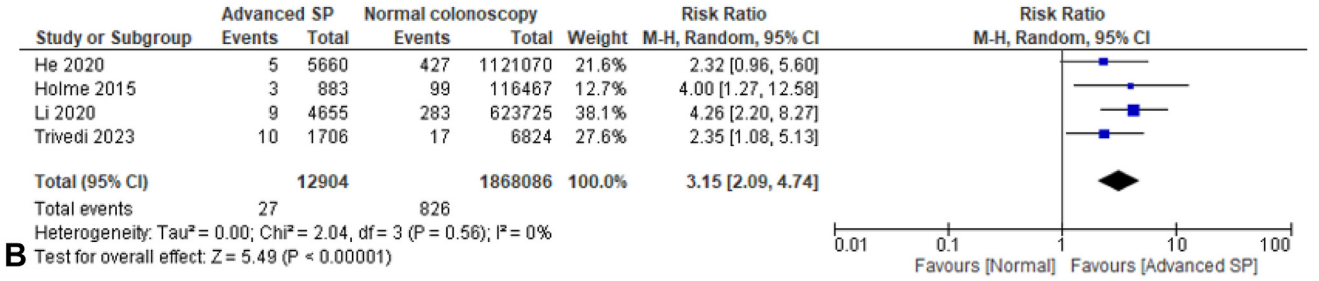


Caption
Funnel plot of comparison: 8 Proximal SP vs NC, outcome: 8.3 AP + CRC.

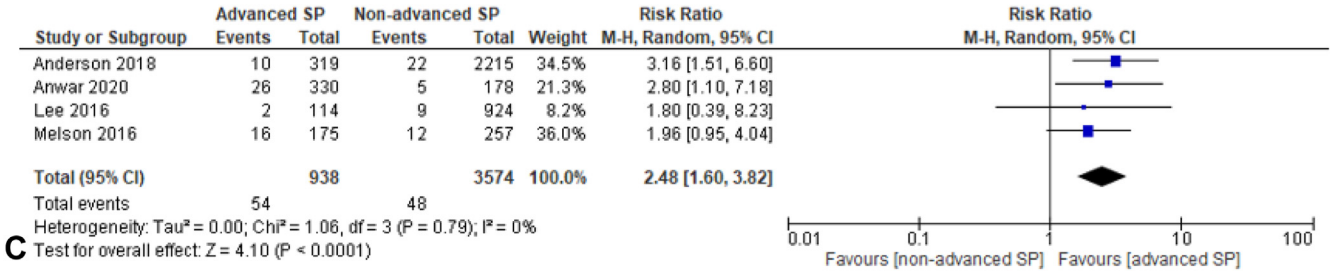
Supplementary Figure 2. Funnel plots assessing risk of publication bias. *AP*, Advanced polyp; *ASP*, advanced serrated polyp; *CRC*, colorectal cancer; *NASP*, non-advanced serrated polyp; *NC*, normal colonoscopy; *RR*, relative risk; *SE*, standard error; *SP*, serrated polyp.



A

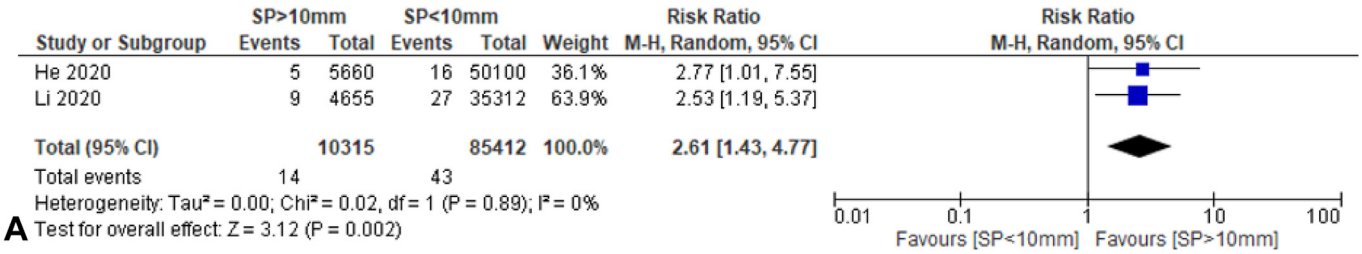


B



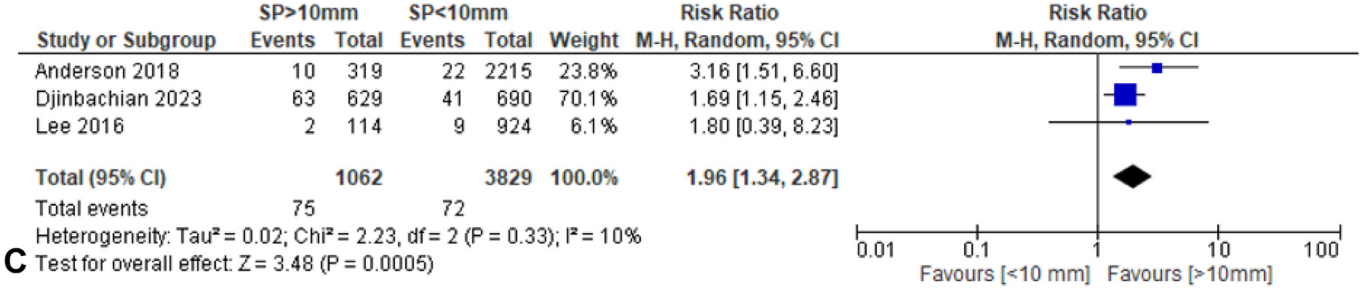
C

Supplementary Figure 3. Sensitivity analysis including only cohort studies and clinical trials (excluding case-control studies). Risk ratio for CRC incidence in 1000 p-y comparing **A,** advanced SP to nonadvanced SP and **B,** advanced SP to normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing advanced SP to nonadvanced SP. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.



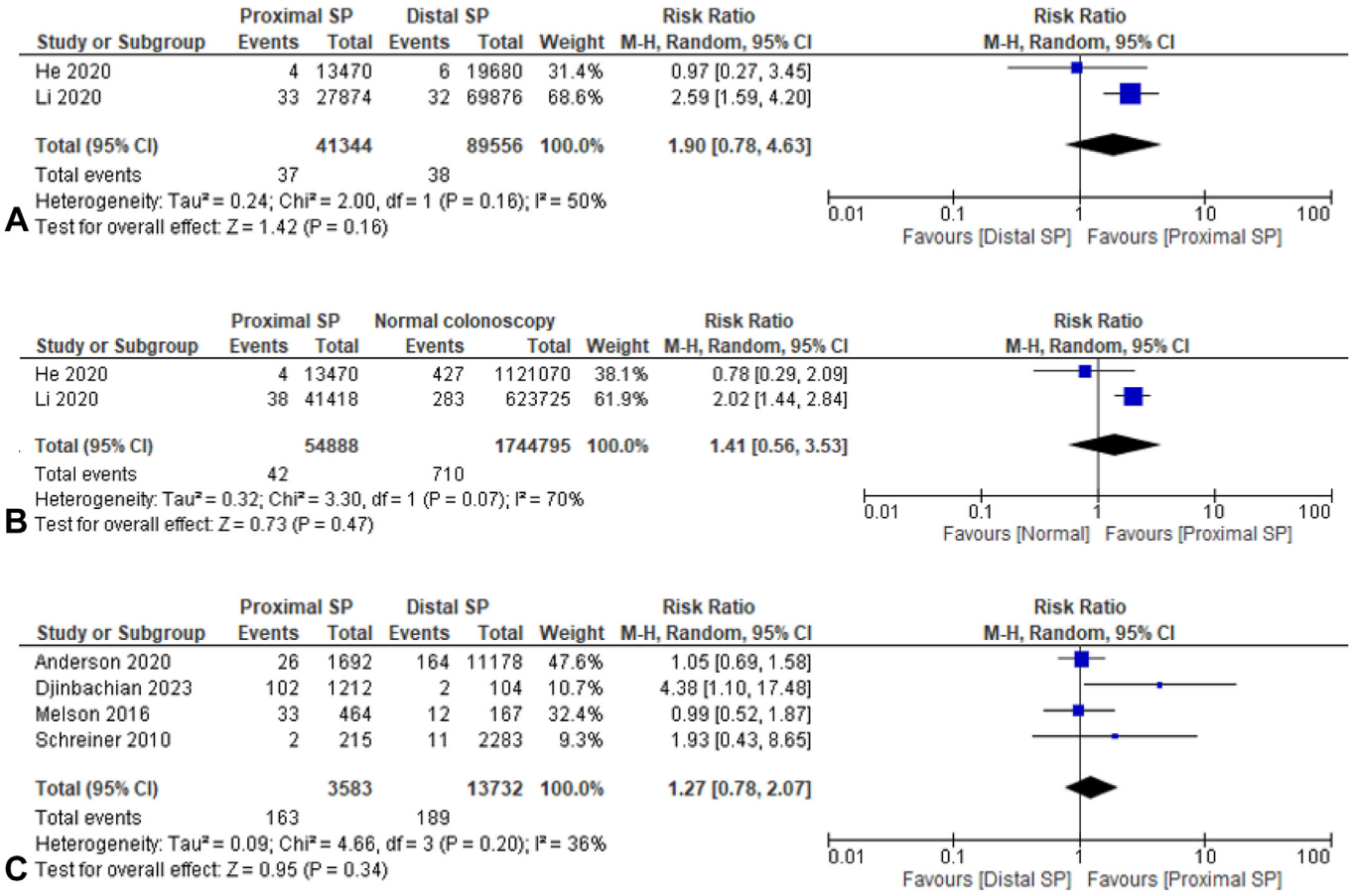
A

B

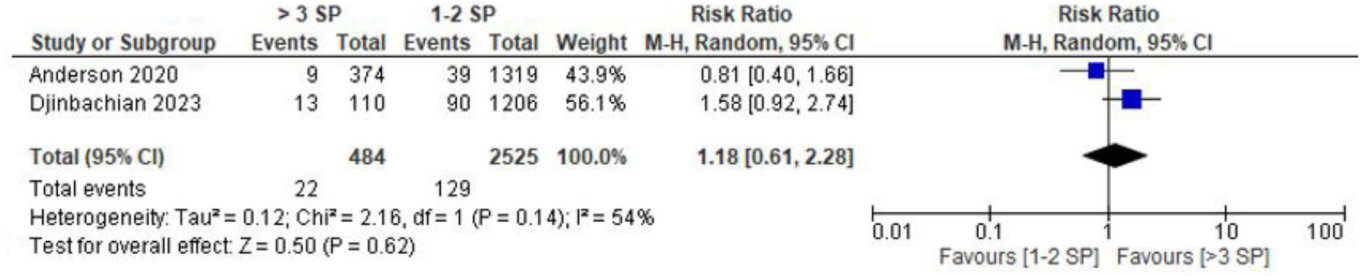


C

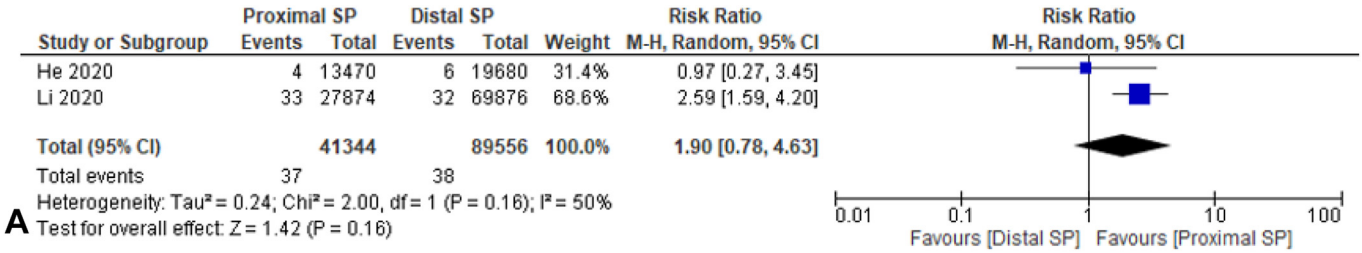
Supplementary Figure 4. Sensitivity analysis including only cohort studies and clinical trials (excluding case-control studies). Risk ratio for CRC incidence in 1000 p-y comparing SPs of ≥10 mm **A,** to SPs of <10 mm and **B,** SPs of ≥10 mm to normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing SPs of ≥10 mm to SPs of <10 mm. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.



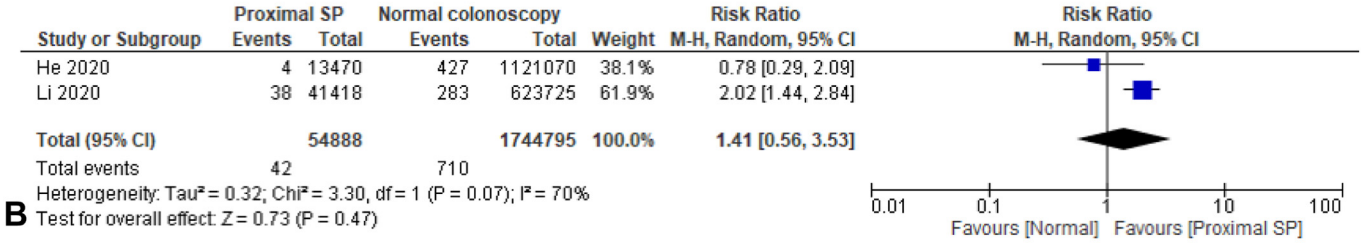
Supplementary Figure 5. Sensitivity analysis including only cohort studies and clinical trials (excluding case-control studies). Risk ratio for CRC incidence in 1000 p-y comparing **A,** proximal SP to distal SP and **B,** proximal SP to normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing proximal SP to distal SP. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.



Supplementary Figure 6. Sensitivity analysis including only cohort studies and clinical trials (excluding case-control studies). Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing ≥3 SPs to 1 or 2 SPs. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.



A



B

C

Supplementary Figure 7. Sensitivity analysis including only studies where proximal SP was defined as proximal to the descending colon, excluding those SPs in the descending colon and sigmoid colon. Risk ratio for CRC incidence in 1000 p-y comparing **A,** proximal SP to distal SP and **B,** proximal SP to normal colonoscopy findings. **C,** Risk ratio for metachronous advanced polyp incidence in 1000 p-y comparing proximal SP to distal SP. *CI*, Confidence interval; *CRC*, colorectal cancer; *df*, degrees of freedom; *p-y*, person-years; *SP*, serrated polyp.

SUPPLEMENTARY TABLE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)

Section and topic	Item number	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	4, 5
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7, 8
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved; whether they worked independently; and if applicable, details of automation tools used in the process.	7, 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report; whether they worked independently; any processes for obtaining or confirming data from study investigators; and if applicable, details of automation tools used in the process.	7, 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses) and, if not, the methods used to decide which results to collect.	8, 9
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8, 9
Study risk-of-bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used; how many reviewers assessed each study and whether they worked independently; and if applicable, details of automation tools used in the process.	9
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item 5]).	7, 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conversions.	8, 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8, 9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, metaregression).	9, 10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9, 10

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Section and topic	Item number	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias caused by missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9, 10
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	10, 11, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria but that were excluded, and explain why they were excluded.	Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary Table 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Fig. 1, Supplementary Tables 4 and 5
Results of individual studies	19	For all outcomes, present, for each study, (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Figs. 2-7
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Supplementary Fig. 1, Supplementary Tables 4 and 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figs. 2-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figs. 2-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary Fig. 3-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Fig. 1, Supplementary Tables 4 and 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figs. 3-7
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14-16
	23b	Discuss any limitations of the evidence included in the review.	17, 18
	23c	Discuss any limitations of the review processes used.	17, 18
	23d	Discuss implications of the results for practice, policy, and future research.	18, 19
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed or state that a protocol was not prepared.	7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	not available
Support	25	Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors in the review.	3
Competing interests	26	Declare any competing interests of review authors.	3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms, data extracted from included studies, data used for all analyses, analytic code, and any other materials used in the review.	3

From Page et al[14] (https://doi.org/10.1136/bmj.n71). For more information, visit: https://www.prisma-statement.org/.

SUPPLEMENTARY TABLE 2. PICO (patient, intervention, comparison, and outcome) questions developed by the authors to identify the issues of greatest importance for the literature revision

Question	Population	Intervention	Comparison	Outcome
Do patients with advanced SP have a higher risk of metachronous CRC or advanced polyp?	Patients with advanced SPs	Colonoscopy	- Patients with nonadvanced SPs - Population with normal colonoscopy findings	- CRC - Advanced polyp
Do patients with SP of ≥10 mm have a higher risk of metachronous CRC or advanced polyp?	Patients with SPs of ≥10 mm	Colonoscopy	- Patients with SPs of <10 mm - Patients with nonadvanced SPs - Population with normal colonoscopy findings	- CRC - Advanced polyp
Do patients with SP with dysplasia have a higher risk of metachronous CRC or advanced polyp?	Patients with SPs with dysplasia	Colonoscopy	- Patients with SP without dysplasia - Patients with nonadvanced SP - Population with normal colonoscopy findings	- CRC - Advanced polyp
Do patients with ≥3 SP have a higher risk of metachronous CRC or advanced polyp?	Patients with ≥3 SPs	Colonoscopy	- Patients with <3 SPs - Population with normal colonoscopy findings	- CRC - Advanced polyp
Do patients with proximal SP have a higher risk of metachronous CRC or advanced polyp?	Patients with proximal SP	Colonoscopy	- Patients with distal SPs - Population with normal colonoscopy findings	- CRC - Advanced polyp

CRC, Colorectal cancer; *SP*, serrated polyp.

SUPPLEMENTARY TABLE 3. Characteristics of the included studies

Study	Design	Years of subject enrollment	Sample size, n	Male, %	Mean age, y	Mean time of follow-up, y
Anderson et al, 2018[16]	Prospective cohort	2004-2015	5433	49.7	61	4.9
Anderson et al, 2020[17]	Prospective cohort	2005-2018	8560	55.2	59	4.5
Anwar et al, 2021[18]	Retrospective cohort	2004-2019	2035	57.1	65.3	3.3
Burnett Hartman et al, 2019[19]	Case-control	1998-2007	918	45.3	NA	5
Djinbachian et al, 2023[20]	Retrospective cohort	2010-2019	1425	53.3	61.9	2.9
Erichsen et al, 2016[21]	Case-control	1977-2009	10,150	45.9	NA	5.9
He et al, 2020[22]	Prospective cohort	1976-1989	122,899	17	58	10
Holme et al, 2015[23]	Clinical trial	1999-2001	91,175	53	56	10.9
Lee et al, 2016[24]	Retrospective cohort	2003-2011	11,042	67.3	51.6	3
Li et al, 2020[25]	Retrospective cohort	2006-2016	233,393	42	NA	3.6
Melson et al, 2016[26]	Retrospective cohort	2005-2011	788	35.6	58.2	3.8
Schreiner et al, 2010[27]	Retrospective cohort	1994-1997	3121	97	NA	5.5
Symonds et al, 2019[28]	Retrospective cohort	2000-2014	2157	58.7	64.2	50.3 months
Trivedi et al, 2023[29]	Retrospective cohort	1999-2018	853	96	NA	2

NA, Not available; *y*, years.

SUPPLEMENTARY TABLE 4. Items for consideration in the risk-of-bias assessment using the Quality in Prognosis Studies tool

Domains	Rating	Prompting items for consideration
Study participation	High bias	Cohort of person that participated in screening Methods of recruitment, period of recruitment, or inclusion or exclusion criteria not adequately described
	Moderate bias	Differences in participants and nonparticipants accounted for in the analysis Small differences in study population compared with target population
	Low bias	No differences in study population compared with target population
Study attrition	High bias	A >40% loss to follow-up at surveillance Reasons for loss to follow-up not provided and participants lost to follow-up not described
	Moderate bias	A 20% to 40% loss to follow-up at surveillance
	Low bias	A <20% loss to follow-up at surveillance
Prognostic factor measurement	High bias	A clear description of high-risk characteristics is not provided.
	Moderate bias	A description of high-risk characteristics is provided, but the measurement method is inadequate. The method is not the same for all participants.
	Low bias	A clear description is provided, and the method of measurement is valid and reliable.
Outcome measurement	High bias	Method of outcome measurement is different for case and control groups.
	Moderate bias	CRC/adenoma/polyp based on questionnaire data and verification through medical records
	Low bias	CRC/adenoma/polyp based on questionnaire data and verification through histology Data analyzed per subgroup of method of verification
Study confounding	High bias	No measurement of important confounders (family or personal history of CRC, hereditary syndromes, IBD) No adjustment and unequal distribution
	Moderate bias	Matching or adjustment for age and gender No adjustment and equal distribution
	Low bias	Matching or adjustment for multiple relevant confounders
Statistical analysis and reporting	High bias	Advanced polyps at surveillance are not part of the primary analysis and therefore not discussed in the statistical analysis of the methods.
	Moderate bias	Only multivariate model reported without explanation how this was conducted Reporting of only summary estimates without raw data
	Low bias	Adjustment for factors prespecified in statistical analysis, raw data present Only raw data presented

CRC, Colorectal cancer; *IBD*, inflammatory bowel disease.

SUPPLEMENTARY TABLE 5. Risk of CRC and AA in the different risk categories of adenomas and SP

Adenomas				Serrated polyps					
							RR for advanced polyp risk compared with nonadvanced SP		
Risk category	CRC incidence, 1000 p-y (95% CI)	RR (95% CI) for CRC risk compared with NAA	RR for AA risk compared with NAA	Risk category	CRC incidence 1000 p-y (95% CI)	RR (95% CI) for CRC risk compared with nonadvanced SP	All studies	No synchronous adenoma	Patients with no synchronous adenoma, %
HRA	1.46 (1.32-1.60)	2.56 (2.21-2.96)	2.35 (2.00-2.76)	Advanced SP	2.09 (1.29-2.90)	1.84 (1.11-3.04)	2.05 (1.36-3.09)	1.89 (1.12-3.21)	76.4
Size ≥ 10 mm	1.52 (1.21-1.91)	1.66 (1.30-2.13)	1.96 (1.26-3.05)	Size >10 mm	1.52 (0.78 -2.25)	2.61 (1.43-4.77)	1.78 (1.17-2.71)	NA	51.3
HGD	2.68 (2.18-3.20)	2.89 (1.88-4.44)	1.86 (1.05-3.30)	Dysplasia	5.86 (2.16-6.56)	2.06 (0.41-10.35)	1.00 (0.40-2.48)	NA	22.4
≥3 adenomas	0.95 (0.68-1.22)	1.24 (0.84-1.83)	2.26 (1.70-3.02)	≥3 SPs	0.52 (0.08-1.12)	NA	1.18 (0.61-2.28)	NA	NA
NA	NA	NA	NA	Proximal SP	1.18 (0.77-1.60)	1.90 (0.78-4.63)	1.16 (0.84-1.59)	NA	66.2
NAA	0.53 (0.47-0.59)	NA	NA	Nonadvanced SP	0.50 (0.35-0.66)	NA	NA	NA	NA
Normal colonoscopy findings	0.34 (0.32-0.36)	NA	NA	Normal colonoscopy findings	0.44 (0.41-0.46)	NA	NA	NA	NA

Synchronous HRA cannot explain the metachronous CRC incidence observed in patients with advanced SP, given that (1) 76.4% of these patients do not have synchronous adenoma and (2) the incidence of CRC per 1000 p-y in persons with baseline HRA is 1.46 (95% CI 1.32-1.60) compared with 2.09 (95% CI 1.29-2-90) in persons with baseline advanced SP.

AA, Advanced adenoma; *CRC,* colorectal cancer; *CI,* confidence interval; *HGD,* high-grade dysplasia; *HRA,* high-risk adenoma; *NAA,* nonadvanced adenomas; *p-y,* person-years; *RR,* relative risk; *SP,* serrated polyp.