The prevalence of sessile serrated lesion in the colorectum and its relationship to synchronous colorectal advanced neoplasia: a systemic review and meta-analysis

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Background The aim of this systemic review and meta-analysis was to evaluate the prevalence of sessile serrated lesion (SSL) and its relationship to synchronous colorectal advanced neoplasia.

Materials and methods Comprehensive, computerized research was performed on PubMed and published from 1 January 2010 to 6 July 2018 which searched relevant articles without any language limitations. Clinical trials were included in the narrative systemic review if they matched the following inclusion criteria: (1) published as a case-controlled study, cohort study or cross-sectional study; (2) defined objectively for diagnosis of SSL within the studies; (3) addressed the prevalence and characteristics of SSL. Within these trials, if they met additional criteria involving the reported outcome of risk regarding advanced neoplasia in relation to SSL, they were enrolled into meta-analysis.

Results Forty-one trials were enrolled for the systematic review, with a total of eight analyzed for the meta-analysis. The prevalence of all SSL ranged from 0.038 to 20.23% and the prevalence by pooled analysis was 2.7%. In a subgroup analysis, the overall prevalence of SSL during the periods of 2010–2014 and 2015–2018 was shown to be 2.7 and 2.8%, respectively. We calculated the pooled data on the cancer risk of SSL and the risk of synchronous advanced neoplasia in patients with SSL made available from the eight trials, which resulted in a pooled odds ratio of 3.53 (95% confidence interval 2.39–5.20, I^2 = 4%, P = 0.40).

Conclusion In this systemic review, SSL was found to be associated with an increased risk of synchronous advanced neoplasia in the colorectum. Eur J Gastroenterol Hepatol 33: 1495–1504

Introduction

Colorectal cancer (CRC) is the third and the second most common malignancy in men and women respectively worldwide, resulting in the third highest cancer-related deaths in the world [1]. Although primary screening through a colonoscopy decreases the incidence and mortality of CRC [2], the incidence of interval CRC has been reported to be from 6 to 7.2% in two large population-based cohort studies [3,4]. In 2010, the WHO classification system [5] divided serrated lesions in the colorectum into three major types: hyperplastic polyp (HP), traditional serrated polyp (TSP), and sessile serrated adenoma/polyp (SSA/P), which was recommended to be paraphrased as sessile serrated lesion (SSL) in 2019 [6]. At least some interval CRC cases are considered to have developed from SSLs via the so-called serrated pathway [7,8]. However, the true prevalence of SSL and its characteristics are still unknown due to detection difficulty, as well as poor discrimination by endoscopists and pathologists in daily practice.

In previous meta-analyses, it was confirmed that serrated polyps were associated with an increased risk of synchronous advanced neoplasia in the colorectum [9], and that in proximal and large serrated polyps the risk was higher. However, the direct relationship between SSLs and synchronous advanced neoplasia was not made clear, and thus the application of this datum in clinical practice may be of limited value. The aim of this systematic review and meta-analysis was to evaluate the prevalence and characteristics of SSL and its relationship to synchronous colorectal advanced neoplasia.

Methods

Search strategy and selection criteria

This systematic review was conducted according to prior established statements of preferred reporting items for

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Keywords: meta-analysis, sessile serrated lesion, synchronous colorectal advanced neoplasia, systemic review

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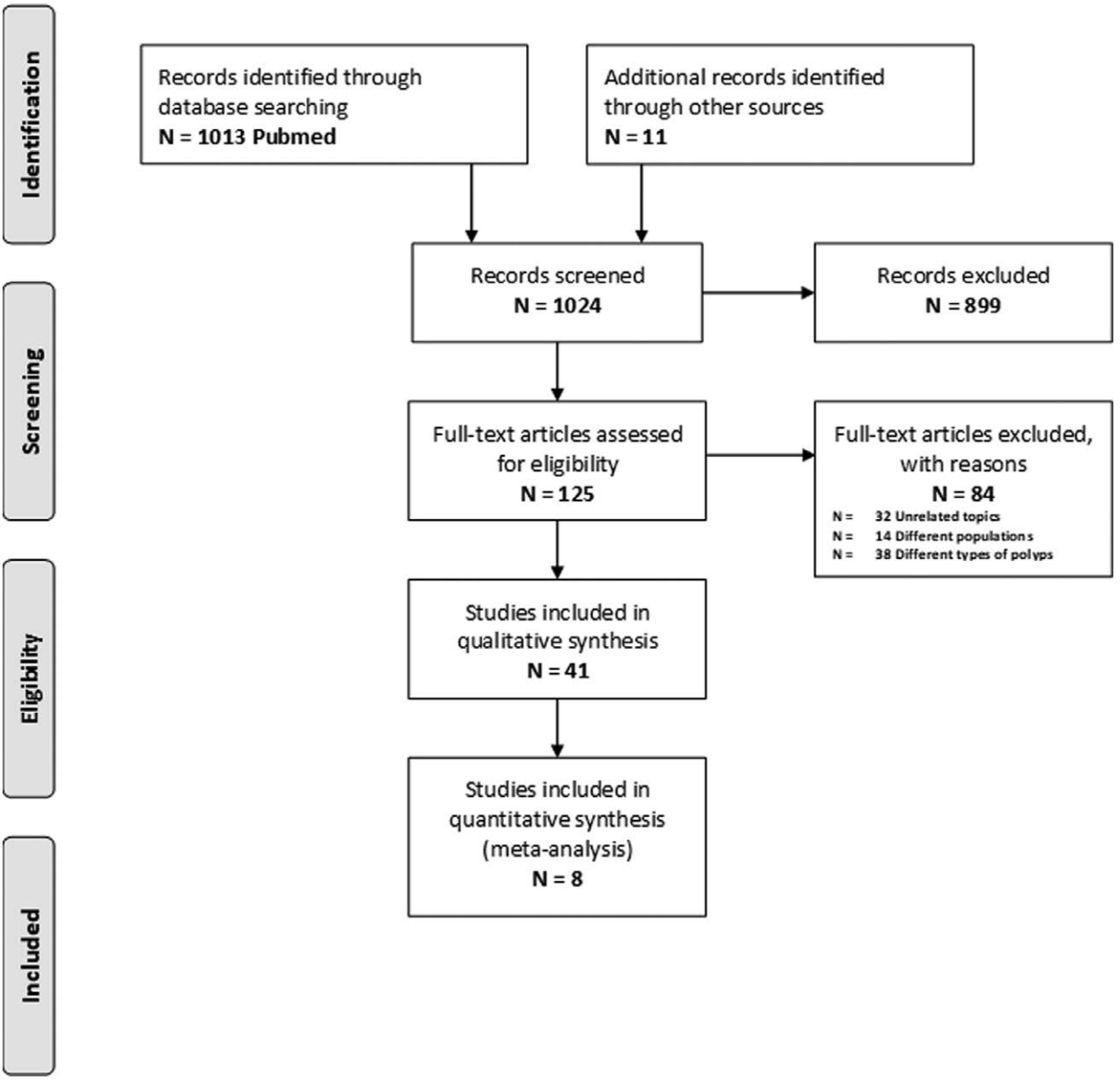

Fig. 1. PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

systematic reviews and meta-analyses (PRISMA) [10] and meta-analyses Of observational studies in epidemiology [11]. Additionally, we followed the guidelines for reporting systematic reviews and meta-analyses as well as those for observational studies. Comprehensive, computerized research was performed on PubMed (National Library of Medicine, Bethesda, Maryland, USA) and later published during the period 1 January 2010 to 6 July 2018. The keywords (sessile OR serrated), (adenoma[s] OR polyp[s] OR polypoid), (cecum OR cecal OR colon OR colonic OR rectum OR rectal OR colorectal) along with (tumor OR carcinoma OR adenocarcinoma OR malignancy OR malignant OR neoplasm OR neoplastic) were inputted to search for relevant articles without any language limitations. As the standardization for nomenclature and diagnostic criteria was first established in 2010 by the consensus conference of the Working Group of Gastroenterological Pathology of the German Society of Pathology [12], we restricted our search for articles to those only published after 1 January 2010. Additional studies were manually identified from bibliographies of the original articles or any relevant reviews. Both the titles and abstracts were reviewed, and initial screening was undertaken by two independent reviewers after removal of any duplicated articles. Potentially relevant articles were obtained in full-text and reviewed independently in accordance with the pre-defined criteria. We also contacted the authors if necessary, and any disagreements were settled by a third reviewer.

Clinical trials were included in the systematic review if they matched the following inclusion criteria: (1) published as a case-controlled study, cohort study or cross-sectional study; (2) SSL (SSA, SSP, or SSA/P) being defined objectively within the study; (3) addressed the prevalence and characteristics of SSL. The studies which met the additional inclusion criteria involving risk of advanced neoplasia in relation to SSL were enrolled into the meta-analysis. The exclusion criteria were unrelated topics; exclusive specific populations such as children, as well as patients diagnosed with inflammatory bowel disease and polyposis

Table 1. Narrations of enrolled trials

Author	Year	Country	Study type	No. of subjects	Patient source	Exclusion criteria
Liu *et al.*	2018	China	Retrospective cohort (single-center)	38 981	Conventional colonoscopy in symptomatic patient	1. Poor bowel preparation or incomplete colonoscopy 2. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 3. Patients with a history of IBD, CRC, or history of colorectal resection
Turner *et al.*	2018	USA	Retrospective cohort (multi-center)	483 998	Therapeutic colonoscopy with polypectomy	Masses, nodules, or any other descriptions of a mucosal lesion were excluded
Davenport *et al.*	2018	USA	Retrospective cohort (multi-center)	6404	Conventional colonoscopy	1. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 2. Patients with a history of IBD, CRC, or history of colorectal resection 3. Any history of cancer except for non-melanoma skin cancer
Maratt *et al.*	2017	USA	Retrospective cohort (single-center)	2416	Surveillance colonoscopy	1. Colonoscopy for an indication other than surveillance of polyps 2. A prior colonoscopy within 3 years 3. Incomplete examination, missing pathology, or a personal history of inflammatory bowel disease or CRC 4. Colonoscopies with missing prior pathology were excluded given the difficulty in assessing for risk factors with unknown polyp history 5. Only colonoscopies performed by gastroenterologists were included in this study
Ferreira *et al.*	2017	Portugal	Retrospective cohort (single-center)	654	Surveillance colonoscopy or positive Fecal Occult Blood Test (FOBT)	Patients referred for colonoscopy for other indications, including surveillance after resection of colorectal lesions and a family history of CRC or adenomas, were excluded from the analysis
Sonnenberg *et al.*	2017	USA	Retrospective cohort (multi-center)	813 057	Conventional colonoscopy	Not mentioned
Wong *et al.*	2017	Australia	Retrospective cohort (single-center)	2064	Conventional colonoscopy	Not mentioned
Bettington *et al.*	2017	Australia	Retrospective cohort (single-center)	707	Conventional colonoscopy	Inpatients were excluded from the study
Chang *et al.*	2017	Taiwan	Retrospective cohort (single-center)	6198	Surveillance colonoscopy	Personal histories of CRC, colectomy, hereditary polyposis, or inflammatory bowel disease were excluded
IJspeert *et al.*	2017	European	Prospective cohort (multi-center)	243 450	Surveillance colonoscopy (gFOBT/FIT or not)	1. Colonoscopies performed before 2009 and/or in individuals aged below 50 were excluded 2. IBD and/or a known hereditary CRC syndrome were excluded
Cao *et al.*	2016	China	Retrospective cohort (single-center)	28 981	Conventional colonoscopy in symptomatic patient	1. <20 years old 2. Patients with any kinds of polyposis syndromes 3. Patients with a history of CRC or inflammatory bowel disease 4. Patients with a history of colonic resection or polypectomy 5. Patients with any emergent and therapeutic colonoscopy 6 Patients with inadequate bowel preparation and had incomplete colonoscopy
Laird-Fick *et al.*	2016	USA	Retrospective cohort (multi-center)	13 881	Specimens from colonoscopy	Not mentioned
IJspeert *et al.*	2016	Netherlands	Retrospective cohort (single-center)	3364	Conventional colonoscopy	1. All colonoscopies done by an endoscopist who performed fewer than 40 procedures were also excluded 2. Incomplete colonoscopies were excluded
Saiki *et al.*	2016	Japan	Retrospective cohort (single-center)	15 326	Therapeutic colonoscopy with endoscopic resection	Not mentioned
Pereyra *et al.*	2016	Argentina	Retrospective cohort (single-center)	4550	Surveillance colonoscopy in OPD	Patients with a medical history or with a diagnosis of inflammatory bowel disease, SPS, familial adenomatous polyposis, or Lynch syndrome, and those with inadequate bowel preparation or incomplete colonoscopies were excluded
Kawasaki *et al.*	2016	Japan	Retrospective cohort (single-center)	5078	Serrated specimens from colonoscopy resected endoscopically or surgically	1. Patients with hereditary polyposis syndromes and serrated polyposis were excluded 2. We also excluded patients with serrated lesions and conventional adenomas with areas of adenocarcinoma that had invaded the proper muscular layer 3. Furthermore, we excluded patients with polyps less than 5 mm in diameter and mixed polyps with combined areas of serrated and conventional adenoma histology or those with combined areas of serrated histology
Chino *et al.*	2016	Japan	Retrospective cohort (single-center)	1858	Therapeutic colonoscopy with endoscopic resection	Lesions that were extracted via cold biopsy or hot biopsy were excluded, as the biopsy material was unsatisfactory (it only included the mucosal surface) and might be not suitable for a pathological diagnosis of SSL, Hp, or mixed

(*Continued*)

Table 1. (*Continued*)

Author	Year	Country	Study type	No. of subjects	Patient source	Exclusion criteria
Wallace *et al.*	2016	USA	Retrospective cohort (multi-center)	233	Conventional colonoscopy	1. Patients were excluded if they were unable to speak English, cognitively unable to provide informed consent, symptomatic, and/or had a personal history of colorectal neoplasia (polyps and or cancer) 2. Patients which did not have visualization to the cecum were excluded (n = 4)
Kharlova *et al.*	2015	Russia	Retrospective cohort (single-center)	440	Specimens from colonoscopy	Not mentioned
Rotondano *et al.*	2015	Italy	Prospective cohort (multi-center)	2468	Conventional colonoscopy	Patients with BBPS scores ≤2 were excluded from the analysis
Yang *et al.*	2015	USA	Retrospective cohort (multi-center)	11 201	Specimens from colonoscopy	After excluding patients who had previously been designated as having borderline or indeterminate serrated polyp
Zhu *et al.*	2015	USA	Retrospective cohort (single-center)	428	Specimens from colonoscopy	Because of the small number of MP (n = 5), they were excluded
Ross *et al.*	2015	USA	Retrospective cohort (single-center)	2833	Surveillance colonoscopy	1. Suspicions of having a colon cancer syndrome based on a family or personal history of cancer 2. Multiple first-degree relatives with a colon cancer history or one first-degree relative younger than 45 years of age at time of diagnosis of colon cancer 3. Personal history of Crohn's disease or ulcerative colitis 4. Previous colonoscopy or colon resection
Ng *et al.*	2015	China	Retrospective cohort (multi-center)	4989	Surveillance colonoscopy	Small (<5 mm) hyperplastic polyps at or distal to the splenic flexure were excluded in the analysis
Abdeljawad *et al.*	2015	USA	Retrospective cohort (single-center)	1910	Surveillance colonoscopy	Patients who underwent diagnostic colonoscopy (for evaluation of symptoms such as abdominal pain, anemia, altered bowel habits), who had a personal history of inflammatory bowel disease or a family history of familial adenomatous polyposis, or who underwent surveillance colonoscopy (post-polypectomy or post-CRC resection) were excluded
Sanaka *et al.*	2014	USA	Retrospective cohort (single-center)	2167	Surveillance colonoscopy	1. Poor bowel preparation or incomplete colonoscopy 2. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 3. Patients with a history of IBD, CRC, or history of colorectal resection
Pereyra *et al.*	2014	Argentina	Prospective cohort (single-center)	272	Surveillance colonoscopy	1. Poor bowel preparation or incomplete colonoscopy 2. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 3. Patients with a history of IBD, CRC
Kim *et al.*	2014	Korea	Retrospective cohort (single-center)	28 544	Surveillance colonoscopy	1. Poor bowel preparation or incomplete colonoscopy 2. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 3. Patients with a history of IBD, CRC
Bouwens *et al.*	2014	Netherlands	Retrospective cohort (single-center)	7433	Conventional colonoscopy	1. Poor bowel preparation or incomplete colonoscopy 2. Patients with polyposis syndrome (such as FAP, juvenile polyposis, Peutz–Jeghers syndrome, and Cronkhite–Canada syndrome) 3. Patients with a history of IBD, CRC 4. Patients <18 years of age
Bettington *et al.*	2014	Australia	Prospective cohort (single-center)	3603	Specimens from colonoscopy	Excluding serrated polyp unclassified and GCHPs
Hazewinkel *et al.*	2014	Netherlands	Prospective cohort (multi-center)	1426	Surveillance colonoscopy	Eligible persons were not invited or were excluded if they had undergone a full colonic examination in the previous 5 years, were scheduled for surveillance colonoscopy because of a personal history of CRC, adenomas, or inflammatory bowel disease, or had end-stage disease with a life expectancy of less than 5 years
Buda *et al.*	2012	Italy	Prospective cohort (single-center)	985	Surveillance colonoscopy	Exclusion criteria included alarm symptoms of disease of the lower gastrointestinal tract (recent onset of abdominal pain that normally would require medical evaluation, change in bowel habits), unexplained weight loss, occult anemia, rectal bleeding, and previous colonoscopy performed for any reasons. Patients with family history of CRC or adenomatous polyps, personal history of inflammatory bowel disease, hereditary non-polyposis CRC, familial and hyperplastic polyposis, previous colonic resection were excluded. Additional exclusion criteria were an unsatisfactory colonic preparation precluding a complete examination

(*Continued*)

Table 1. (Continued)

Author	Year	Country	Study type	No. of subjects	Patient source	Exclusion criteria
Salaria *et al.*	2012	Netherlands	Retrospective cohort (single-center)	93	Specimens from colonoscopy	Not mentioned
Teriaky *et al.*	2012	Canada	Retrospective cohort (multiple center)	33	Conventional colonoscopy	Not mentioned
Freedman *et al.*	2011	USA	Retrospective cohort (multiple center)	1486	Surveillance colonoscopy	Exclusion criteria included (1) personal history of GI malignancy, (2) colonic surgery, (3) symptoms or signs indicating a need for colonoscopy, (4) personal history of idiopathic colitis, (5) personal history of colonic polyposis syndrome, and (6) inability to intubate the cecum. We excluded participants with 7 PMPs in order to prevent inclusion of patients with polyposis syndromes from skewing the results. Participants with inadequate bowel preparations that prevented complete colonoscopy were excluded from polyp detection analyses
Wang *et al.*	2010	China	Retrospective cohort (multiple center)	5347	Conventional colonoscopy	Not mentioned
Hetzel *et al.*	2010	USA	Retrospective cohort (single-center)	7192	Surveillance colonoscopy	After excluding data from endoscopists performing less than 100 colonoscopies
Gurudu *et al.*	2010	USA	Retrospective cohort (single-center)	5991	Conventional colonoscopy	Not mentioned
Lu *et al.*	2010	Canada	Retrospective cohort (single-center)	2046	Specimens from colonoscopy	Patients with inflammatory bowel disease were excluded. There were no patients with familial adenomatous polyposis syndrome
Lash *et al.*	2010	USA	Retrospective cohort (multiple center)	179 111	Conventional colonoscopy	Not mentioned
Pai *et al.*	2010	USA	Retrospective cohort (single-center)	950	Surveillance colonoscopy	Patients with inflammatory bowel disease and polyposis syndromes (familial adenomatous polyposis, HPS, juvenile polyposis syndrome and Peutz–Jeghers syndrome) were excluded

CRC, colorectal cancer; FAP, familial adenomatous polyposis; IBD, inflammatory bowel disease; SSL, sessile serrated lesion.

syndrome; study design including animal study, review articles, or diagnostic methods for adenoma detection. A detailed PRISMA flowchart is outlined in Fig. 1. We defined a large SSL as one with a diameter of ≥10 mm, and proximal SSL as being located proximal to the splenic flexure. Advanced adenoma was defined as one with a size ≥10 mm, having villous or tubulovillous architecture, high-grade dysplasia, or intramucosal carcinoma. Advanced neoplasia was defined to include advanced adenoma and invasive cancer.

Data extraction and quality assessment

The following variables were extracted independently by two investigators: the first author, year of publication, country of study, study design, sample size, participants' characteristics, exclusion criteria, risk of bias in enrolled studies, demography of population with SSL, adenoma detection rate, size and percentage of dysplastic change in SSL, prevalence of SSL in different situations (study population, all polyps, or only serrated polyps), and percentage of large SSLs and proximal SSLs within all the SSLs. We also calculated outcome measurements, including the odds ratio (OR) and 95% confidence interval (CI).

Two authors evaluated the risk of bias in all studies independently, based upon the Newcastle–Ottawa Scale (NOS) assessment tool [13]. In addition, assessment of methodological qualities regarding enrolled trials was also performed independently in order to discriminate factors from three aspects: bowel preparation, experience of the endoscopist, and quality of the pathologist. Disagreements were discussed until a consensus was reached. A third investigator was consulted whenever necessary.

Data synthesis and statistical analysis

The results were analyzed using Comprehensive Meta-analysis 2.0 software (Biostat, Englewood, New Jersey, USA) and Review Manager V.5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark). An OR with a 95% CI was used to present the risk of synchronous colorectal advanced neoplasia in patients with SSL. These were totally produced using a random effect model to allow for the expected heterogeneity amongst the enrolled studies.

Heterogeneity of the outcome measures was examined using the Cochrane I^2 statistic. We regarded an I^2 less than 25% as mild heterogeneity, 25–50% as moderate heterogeneity, and higher than 50% as severe heterogeneity. If the χ^2 test showed $P > 0.05$ it was not considered significant in the heterogeneity test of the research. We checked for publication bias by carrying out visual inspection of the funnel plot.

Results

Literature search and eligible studies

The detailed searching strategy is summarized in Fig. 1. Initially, we identified 1024 abstracts and reviewed 125 articles with full-text articles independently after the exclusion of 899 studies which were not relevant to our topic. This resulted in 41 enrolled trials for the systematic

Table 2. Characteristics of sessile serrated polyps from enrolled trials

Author	Mean age (years)	Male (%)	ADR (%)	Size (mm)	Dysplasia (%)	Prevalence of SSL (%)	Prevalence of SSL in all polyps (%)	Prevalence of SSL in serrated polyps (HP, TSP, SSL) (%)	Prevalence of large SSL in SSL (%) (≥10 mm)	Prevalence of proximal SSL in SSL (%)
Liu *et al.*	57.8	57	NA	NA	98.6 (dysplasia)	0.18	NA	23.4	NA	NA
Turner *et al.*	NA	NA	NA	NA	3.71 (HGD, CIS)	NA	4.69	14.58	33.57	NA
Davenport *et al.*	57.8	64	NA	NA	NA	3.34	8.38	27.65	NA	NA
Maratt *et al.*	61.4	61	31.4	NA	NA	7.86	16.18	NA	NA	61.2
Ferreira *et al.*	NA	NA	36	NA	NA	1	2.78	NA	NA	NA
Sonnenberg *et al.*	NA	45	NA	NA	NA	8.3	NA	24.73	NA	NA
Wong *et al.*	NA	NA	34.6	8.78	NA	3.15	9.23	31.7	NA	NA
Bettington *et al.*	58.3	52.4	48	7.61	1.85 (dysplasia)	20.23	19.15	42.52	NA	65.56
Chang *et al.*	NA	NA	27.1	10.1	NA	1.44	NA	NA	49.44	NA
IJspeert *et al.*	NA	NA	43.08	NA	12.18 (Dysplasia)	2.98	NA	NA	NA	NA
Cao *et al.*	60.3	63.6	31.7	NA	90.9 (dysplasia)	0.038	0.12	7.2	9.1	54.5
Laird-Fick *et al.*	NA	48.4	NA	NA	NA	NA	4.5	NA	NA	NA
IJspeert *et al.*	NA	NA	38.5	5	18.5 (Dysplasia)	8.2	9.4	28.91	NA	75.6
Saiki *et al.*	65.7	68.6	NA	8.8	4 (dysplasia)	NA	3	33.05	NA	61.7
Pereyra *et al.*	59	45	NA	9.9	6.9 (HGD)	4.07	NA	NA	61.4	75.3
Kawasaki *et al.*	65	50.9	NA	12.9	13 (HGD, CIS)	NA	0.86	23.84	NA	83.1
Chino *et al.*	62	64.7	NA	8	1 (HGD, CIS)	NA	2.1	23.14	31	60
Wallace *et al.*	NA	NA	37	NA	NA	4.48	NA	11.63	NA	NA
Kharlova *et al.*	62.3	33.3	NA	6	25 (dysplasia)	NA	5.45	19.8	NA	29
Rotondano *et al.*	NA	NA	23	NA	6.06 (HGD, CIS)	NA	3.72	19.1	NA	54.5
Yang *et al.*	61	46.3	NA	NA	5.02 (LGD, HGD, CIS)	NA	NA	NA	NA	80
Zhu *et al.*	63.4	63.8	NA	NA	NA	NA	NA	16	NA	30
Ross *et al.*	NA	58.65	41	NA	NA	8.2	NA	NA	NA	NA
Ng *et al.*	NA	NA	31.9	NA	NA	1.2	3.78	21.51	NA	NA
Abdeljawad *et al.*	NA	NA	NA	7.13	5.8 (dysplasia)	8.1	5.9	38.93	22.67	86.2
Sanaka *et al.*	NA	50	25.2	NA	NA	1.8	NA	NA	NA	NA
Pereyra *et al.*	NA	NA	NA	10.3	14 (LGD)	7.7	8	18.68	NA	94
Kim *et al.*	NA	60.1	27.4	NA	NA	0.5	1.38	3.32	NA	NA
Bouwens *et al.*	63.1	47.9	28.5	NA	9.5 (HGD)	1.88	2.85	9.58	NA	64.7
Bettington *et al.*	59	44.5	NA	8.48	3.52 (dysplasia)	16.8	12.1	25.49	NA	80.1
Hazewinkel *et al.*	60	51.5	29.4	5	26.1	4.8	7.3	14.92	16.36	59.5
Buda *et al.*	NA	NA	14.8	5.8	18	2.3	10.85	27.4	3.6	63.6
Salaria *et al.*	63	53.8	NA	4.6	NA	NA	NA	NA	NA	92.47
Teriaky *et al.*	66	32	NA	11	3	NA	NA	NA	35	70
Freedman *et al.*	60.9	38.5	66.5	NA	NA	7.86	6.94	21.74	4	95
Wang *et al.*	NA	NA	NA	NA	NA	NA	0.49	10.1	NA	NA
Hetzel *et al.*	58	50	42.9	NA	NA	0.64	1.35	4.49	NA	NA
Gurudu *et al.*	65.9	53	NA	8.1	NA	2.9	NA	NA	31	67
Lu *et al.*	63	56.5	NA	6	NA	NA	1.5	4.41	13.6	53.1
Lash *et al.*	62	45.7	NA	NA	15.1 (dysplasia)	1.19	1.16	3.2	NA	81.2
Pai *et al.*	62.6	48.3	NA	NA	NA	NA	4.3	NA	NA	54

ADR, adenoma detection rate; CIS, carcinoma *in situ*; HGD, high-grade dysplasia; HP, hyperplastic polyp; LGD, low-grade dysplasia; NA, not available; SSL, sessile serrated lesion; TSP, traditional serrated polyp.

review (summarized in Table 1), with eight of the trials being analyzed for meta-analysis.

Characteristics and clinical parameters of included studies

The characteristics of SSL extracted from the enrolled trials are shown in Table 2. The mean age of subjects ranged between 57.8 and 66 years, with the proportion of male subjects more than 50% in 17 out of 28 trials. The mean size of SSL ranged from 5 to 10 mm in 13 trials, was larger than 10 mm in four trials and was less than 5 mm in only one trial. The event rate of SSL with dysplasia was varied, ranging from 1.0 to 98.6%. The prevalence of all SSL ranged from 0.038 to 20.23%, with the overall prevalence by pooled analysis being 2.7% (95% CI 1.9–3.9%, Fig. 2). In subgroup analysis the overall prevalence of SSL during the periods 2010–2014 and 2015–2018 showed 2.7% (95% CI 1.2–6.0%) and 2.8% (95% CI 1.9–4.1%), respectively (Supplementary Figures 1 and 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A654*). Regarding geography, the overall prevalence by pooled analysis was 0.4% (95% CI 0.2–0.9%) in Eastern countries and 4.3% (95% CI 3.0–6.1%) in Western countries (Supplementary Figures 3 and 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A654*). The percentage of SSL in all polyps ranged from 0.12 to 19.15%, while in serrated polyps (including HP, TSP, and SSL) the proportions were from 3.2 to 42.52%. The percentage of large SSLs amongst all the SSLs was 3.6–61.4%, while proximal SSLs within all the SSLs ranged from 29 to 94%.

In Fig. 3, we have calculated the pooled data on the risk of synchronous advanced neoplasia in patients with SSL made available from the 8 trials, and revealed an overall OR of 3.53 (95% CI 2.39–5.20, I^2 = 4%, P = 0.40) without detection in the heterogeneity test. This result indicates that individuals with SSL may be more vulnerable to developing synchronous advanced neoplasia. However, in Fig. 4, the shape of the funnel plot of the enrolled trials appears to be asymmetrical by inspection, indicating the potential existence of publication bias.

We evaluated eight trials and conducted a meta-analysis using the NOS assessment tool to detect any risk of bias for the cross-sectional study (Table 3). The scores in all the trials were less than seven points, which suggests

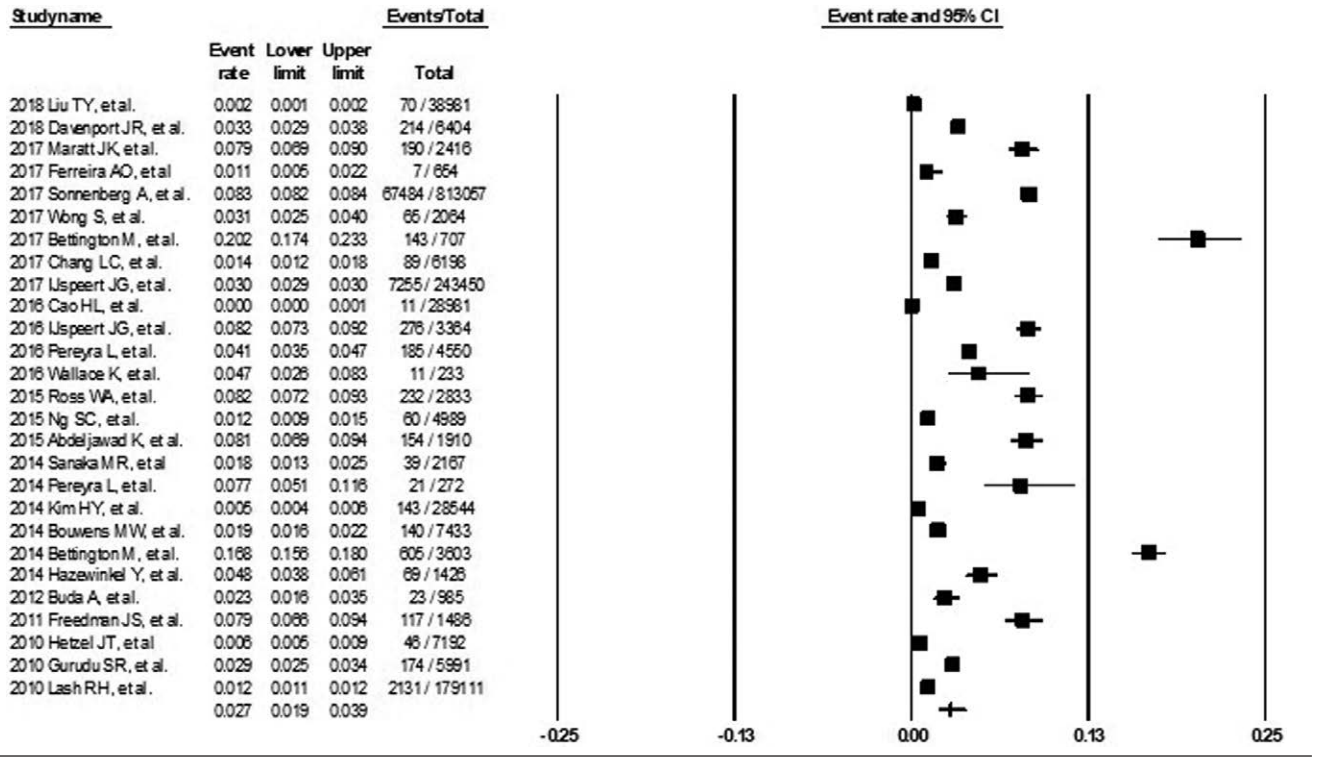

Fig. 2. Pooled prevalence of sessile serrated lesion in screening population.

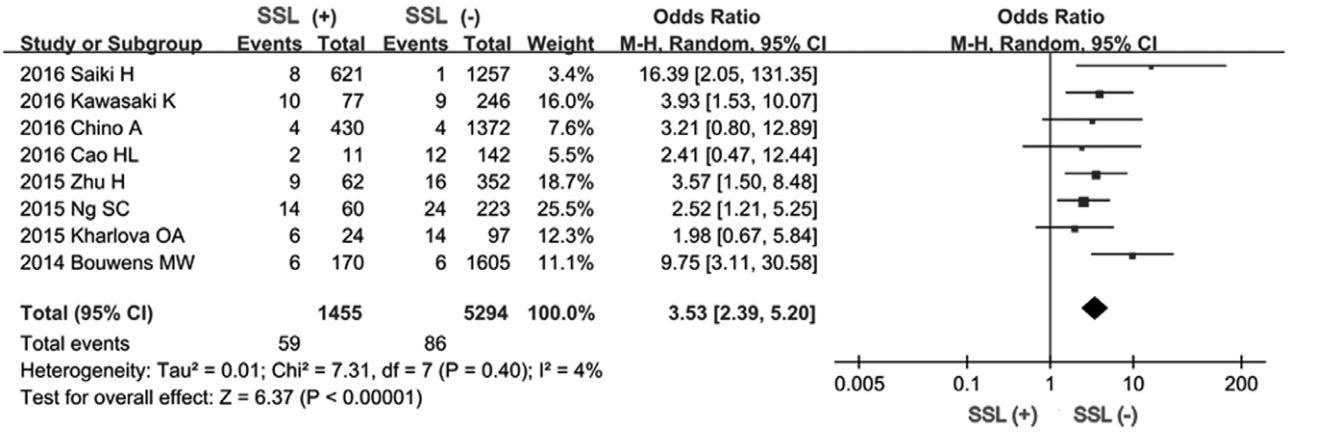

Fig. 3. Forest plot of pooled ORs on the risk of sessile serrated lesion and synchronous advanced neoplasia. OR, odds ratio.

a low quality. In methodological assessment (Table 4), adequate bowel preparation was available in three of the eight trials. The purpose of a colonoscopy; screening, diagnostic or therapeutic, and the quality of the colonoscopy, whether or not performed by experienced endoscopists were mentioned in only one study but not in the others. An appropriate number of pathologists or a blind reevaluation by an experienced pathologist was achieved in all studies, however, the pathological diagnoses were not reviewed centrally because all trials were conducted by a single center.

Discussion

In this meta-analysis, we comprehensively evaluated the prevalence and characteristics of SSL and its relationship to synchronous colorectal advanced neoplasia. The prevalence of SSL was 2.7% (95% CI 1.9–3.9%) and was not distinct between the periods of 2010–2014 and 2015–2018. The OR regarding the relationship between SSL and the risk of synchronous colorectal advanced neoplasia was 3.53 (95% CI 2.39–5.20), with low heterogeneity ($P = 0.40$).

The prevalence of SSL has been reported quite differently in previous literature [14–19]. In the first place, there can be a large gap between the true prevalence of SSL and the reported SSL detection rates, the detection rates have been varied amongst medical centers [17–20]. It is obvious that all SSLs are not detected during a colonoscopy due to their obscure appearance and the endoscopist's lack of knowledge [20]. Even if an SSL is detected, it may not be recognized as such and its histology may not be confirmed by either resection or biopsy. Additionally, the histological specimen may not be diagnosed as SSL due to the pathologist's lack of knowledge and because the pathological criteria have not necessarily been clear enough [21–25]. Significant interobserver variations in both identifying and classifying serrated lesions amongst

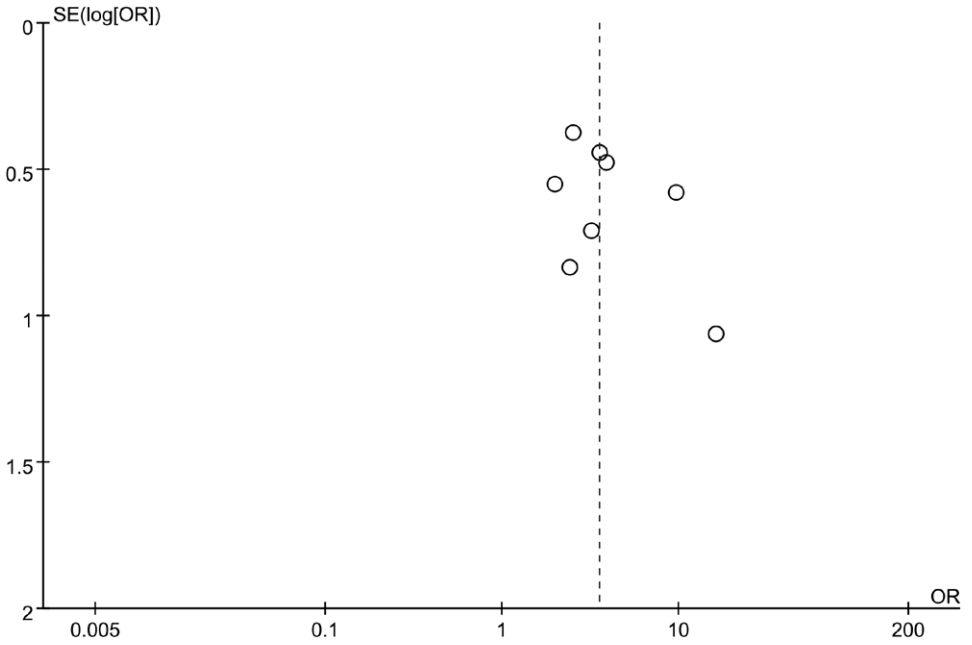

Fig. 4. Funnel plot of enrolled trials evaluating the risk of sessile serrated lesion and synchronous advanced neoplasia.

Table 3. Assessment of risk of bias in cross-sectional trials by Newcastle-Ottawa Scale tool

Author	Year	Selection	Comparability	Outcome	Score
Cao *et al.*	2016	3	0	2	5
Kawasaki *et al.*	2016	2	0	2	4
Chino *et al.*	2016	2	0	2	4
Saiki *et al.*	2016	2	0	2	4
Zhu *et al.*	2015	3	0	3	6
Kharlova *et al.*	2015	2	0	2	4
Ng *et al.*	2015	3	0	2	5
Bouwens *et al.*	2014	3	0	3	6

pathologists have been reported [26]. Thus, SSL detection rates are both endoscopist-dependent and pathologist-dependent. More and more articles concerning SSL are now being published, although this does not, of course, imply that the prevalence of SSL is becoming higher. Reasons for this phenomenon are attributed mainly to two reasons. One is the increasing use of high-definition endoscopes and image-enhanced endoscopy. The other and the more important reason is that there is an increased awareness by endoscopists and pathologists concerning SSL. Some reports have described that the SSL detection rate has been recently increasing [27,28], although this phenomenon was not confirmed in the present study. This may mean that the detection rate has become rather stable after the WHO classification and from when the diagnostic criteria were published in 2010. On the other hand, it is possible that the prevalence of SSL may still be underestimated.

The prevalence of SSL was different between the East and the West in the present review. However, this difference may be attributed to lack of knowledge, difficulty in detection and unestablished diagnostic criteria in some countries. The true prevalence of SSL is important to clarify because screening a rare premalignant precursor would not be reasonable during a routine colonoscopy. Regarding the true prevalence of SSL, there has been debate until now [29]. Crockett and Nagtegaal [30] reported that the detection rate of SSL was 2–8% in average-risk populations receiving a colonoscopy, which was even higher than that involving experienced endoscopists and centers. Many factors are important to assure there is no missed diagnosis of SSL, including excellent bowel preparation [31], appropriate screening [32], and good discrimination by endoscopists and pathologists during daily practice [32,33]. An inadequate quality of bowel preparation is relevant to decreased adenoma detection rates [34]. Once a good quality of bowel preparation has been achieved after complete cleansing maneuvers have been performed, endoscopists could then conduct an appropriate screening and determine a surveillance interval for each patient. When a lesion suspected to be SSL is observed through white-light imaging, endoscopists could then zoom in and investigate with image-enhanced endoscopy techniques. Although the gold standard of endoscopic diagnostic criteria of SSL has not yet been well established, some specific features have been reviewed thoroughly [35,36]. Even after successful endoscopic resection, both endoscopists and pathologists should suspect the lesion to be SSL when a serrated lesion larger than 5 mm in the right colon is found. One meta-analysis [37] showed that the OR for changing the pathological diagnosis from HP to SSL for proximal location and a size ≥5 mm was 4.40 (95% CI 2.78–6.96%) and 8.336 (95% CI 4.96–15.57), respectively. In our study, the overall prevalence by pooled analysis was 2.7% (95% CI 1.9–3.9%), and in subgroup analysis, the overall prevalence of SSL was not significantly different between the periods of 2010–2014 and 2015–2018. This is true as well regarding the geography between Eastern and Western countries, which indicates that the true prevalence of SSL may still be underestimated in the real world. Because the detection rate of SSL has not improved since 2010, optimizing detection, accurate diagnosis, and resection of SSL must be encouraged and warranted in the future.

The demography of a population and the characteristics of SSL are also controversial among studies. The majority of patients enrolled in our articles were older than 60 years with a male predominance, with the average size

Table 4. Assessment of methodological bias of enrolled trials

Author	Year	Adequate endoscopy	Experienced endoscopists	Accurate macroscopic/size classification	Accurate position classification	Appropriate number of pathologists or blinded reevaluation with experienced pathologist	Centrally reviewed in a multi-center
Cao *et al.*	2016	Yes	Unclear	Yes	Yes	Yes	No (single-center)
Kawasaki *et al.*	2016	No	Yes	Yes	Yes	Yes	No (single-center)
Chino *et al.*	2016	No	Unclear	Yes	Yes	Yes	No (single-center)
Saiki *et al.*	2016	Unclear	Unclear	Yes	Yes	Yes	No (single-center)
Zhu *et al.*	2015	No	No	Yes	Yes	Yes	No (single-center)
Kharlova *et al.*	2015	No	Unclear	Yes	Yes	Yes	No (single-center)
Ng *et al.*	2015	Yes	Unclear	Yes	Yes	Yes	No (single-center)
Bouwens *et al.*	2014	Yes	No	Yes	Yes	Yes	No (single-center)

of the lesions being larger than 5 mm. The event rate of SSL with dysplasia, as well as the percentage of large SSL or proximal SSL, varied widely. It is difficult to draw any conclusions related to lifestyle factors from our review due to insufficient information. Current evidence has revealed that older age and gender are not storing risk factors for SSL, while white race, family history of CRC, and a personal history of premalignant serrated polyps are consistent risk factors for SSL in studies conducted by Western countries [30,38]. Compared to the demographic features, several lifestyle factors, particularly smoking and alcohol intake, may be associated with SSL [39]. When compared with conventional adenoma, smoking, BMI, and alcohol intake were more strongly associated with serrated polyps [40]. The percentage of SSL with an advanced histology are also varying among studies, ranging from 0.9 to 15% [41]. Additionally, SSL patients with an advanced histology tended to be of an older age and female, with diagnosis at a proximal location [42].

There is consistent evidence showing that individuals with SSL have an increased risk of synchronous and metachronous advanced neoplasia when compared to those without polyps [9,29,37,43]. Erichsen *et al.* performed a large population-based study in Denmark to evaluate the risk of metachronous CRC relevant to SSL, and reported that patients with SSL were at an increased risk for developing CRC with an adjusted OR from 2.75 to 4.76 based upon different background polyps. There is no systematic review available which has clarified the relationship between SSL and synchronous advanced neoplasia [9,30]. Although we have shown that SSL is associated with an increased risk of synchronous colorectal advanced neoplasia, there is no direct pathological evidence to demonstrate that synchronous colorectal advanced neoplasm has ever originated from an SSL or a conventional adenoma. Thus, further investigation is warranted.

There are several limitations to this meta-analysis. First, it is challenging to estimate the actual prevalence of SSL when selection bias exists due to inconsistent terminology, changing pathological diagnostic criteria, and lack of adequate endoscopy facilities and experienced endoscopists. And as the endoscopic and pathological images of sessile polyps were read in each hospital and not centrally reviewed in any trial, interobserver bias may have occurred. Second, there is the potential existence of publication bias and methodological bias. Because the present data are limited, further multi-center prospective studies would be needed. Third, we did not analyze the relationship between synchronous colorectal advanced neoplasia and any potential confounding factors, such as smoking, alcohol consumption, BMI, or the event rate of SSL with dysplasia, due to the insufficient data obtained from the enrolled studies.

In summary, we reviewed the prevalence and characteristics of SSL and demonstrated that SSL is associated with an increased risk of synchronous advanced neoplasia in the colorectum.

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Conflicts of interest

There are no conflicts of interest.

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