Serrated Polyps and the Risk of Synchronous Colorectal Advanced Neoplasia: A Systematic Review and Meta-Analysis

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REVIEW

Serrated Polyps and the Risk of Synchronous Colorectal Advanced Neoplasia: A Systematic Review and Meta-Analysis

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OBJECTIVES: **Serrated polyps of the colon comprise a heterogeneous group of lesions with distinct histological and malignant features. The presence of serrated polyps has been associated with synchronous advanced neoplasia, although the magnitude of this relationship is unclear.**

METHODS: **Using studies identified from systematic literature search up to February 2014, we performed a systematic review and meta-analysis to estimate the pooled prevalence of serrated polyps and their association with synchronous advanced neoplasia. Random-effects models were used to combine estimates from heterogeneous studies, and odds ratios (ORs) with 95% confidence intervals (CIs) were presented.**

RESULTS: **Nine studies with 34,084 participants were included. The mean age of subjects was 59.9±6.6 years and 52.5% of the subjects were male. Pooled prevalence of serrated polyps was 15.6% (95% CI, 10.3–22.9%). The pooled OR of advanced neoplasia in individuals with serrated polyps was 2.05 (95% CI, 1.38–3.04). Pooled analysis showed that the presence of proximal serrated polyps (OR=2.77, 95% CI, 1.71–4.46) and large serrated polyps (OR=4.10, 95% CI, 2.69–6.26) was associated with an increased risk of synchronous advanced neoplasia. The pooled OR for advanced neoplasia in individuals with proximal and large serrated polyps was 3.35 (95% CI, 2.51–4.46). Considerable heterogeneity was observed in most analyses.**

CONCLUSIONS: **Our meta-analysis showed that serrated polyps are associated with a more than twofold increased risk of detection of synchronous advanced neoplasia. Individuals with proximal and large serrated polyps have the highest risk. These individuals deserve surveillance colonoscopy.**

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INRODUCTION

Colorectal cancer (CRC) develops from an accumulation of genetic and molecular changes arising within initially normal mucosa. Approximately 15–20% of all sporadic CRCs arise via the serrated pathway (1–3), in which serrated polyps may be the precursor lesions (4–6). Serrated polyps are classified pathologically according to the World Health Organization criteria as hyperplastic polyps (HPs), sessile serrated adenoma/polyps (SSA/Ps) with or without cytological dysplasia, and traditional serrated adenomas (TSAs) (7). Advanced lesions in the serrated pathway are thought to be SSA/Ps with cytologic dysplasia. Earlier colonoscopic studies have also shown variable prevalence rates of these three subtypes of serrated polyps (8–10).

Over the past few years, several studies have highlighted the association between serrated polyps and advanced colorectal neoplasia. Large serrated polyps (LSPs) were found to be strongly associated with synchronous cancer (11), and SSA/Ps have been shown to be associated with an increased risk of metachronous cancer (10,12,13). However, to date, there is no study that has systematically synthesized data from available studies to estimate the prevalence and risk of serrated polyps, and their association with synchronous advanced neoplasia.

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The aim of this systematic review and meta-analysis is to evaluate the risk of serrated polyps and their association with synchronous advanced neoplasia. We also assessed the prevalence of serrated polyps and defined the risk in subjects with proximal serrated polyps (PSPs) or LSPs. In this study, the term "serrated polyps" included HPs, SSA/Ps, and TSAs.

METHODS

Search strategy

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (14), and we followed *a priori* established protocol. Standard guidelines for conducting and reporting meta-analyses AQ1 of observational studies were followed (15). An electronic literature search was conducted of articles published from 1 January 1950 to 20 February 2014 using the keywords "serrated", "polyps", "serrated lesion", "serrated adenoma", "advanced neoplasia", "synchronous", "colon cancer", and "colorectal cancer", alone and in combination, to identify clinical studies in full publications from five computerized databases: MEDLINE (1950 to February 2014), EMBASE (1980 to December 2014), Cochrane Central Register of Controlled Trials and systematic reviews (1991 to the fourth quarter of 2014), Database of Abstracts of Reviews of Effects (1991 to the fourth quarter of 2014), and International Pharmaceutical Abstracts (1970 to December 2014). Manual search was performed for abstracts published in major international conferences, including Digestive Disease Week, United European Gastroenterology Week, and Asia Pacific Digestive Week over the past 5 years. Additional studies were identified through bibliographies of original articles or relevant reviews. Only publications in English were included. Both full articles and abstracts were reviewed. After removal of duplicate references, initial screening of article titles and abstracts was undertaken by two independent members (Q.G. and K.K.F.T.). This process removed articles that were not relevant to our study, including editorials, case reports, and therapeutic approach articles. Potentially relevant articles were obtained in full text and reviewed independently. Predefined criteria were used to determine eligibility for inclusion. Any disagreements were settled by a third reviewer (S.C.N.). We obtained copies of all articles identified as being of potential importance, including contacting authors as necessary.

Inclusion criteria

Clinical studies were eligible for this meta-analysis if they met the following criteria: (i) clinical studies that have addressed the prevalence of serrated polyps; (ii) the definition of serrated polyps was clearly defined in the studies; and (iii) studies have reported the outcome of risk of advanced neoplasia or CRC with serrated polyps. For the purpose of this study, serrated polyps were classified as HPs, SSA/Ps (with or without dysplasia), or TSAs. SSA/P with cytological dysplasia is a more advanced lesion in the progression to cancer compared with those without dysplasia. LSPs were defined as serrated polyps with a diameter of ≥10 mm. PSPs were defined as serrated polyps located proximal to the splenic flexure. Advanced adenoma was defined as an adenoma measuring ≥10 mm in diameter, with villous or tubulovillous architecture, high-grade dysplasia, or intramucosal carcinoma, or any combinations thereof. Advanced neoplasia included advanced adenoma or cancer.

Data extraction and quality assessment

Data were extracted directly into a Microsoft EXCEL database that included predefined fields set up to capture all aspects of study design, quality of studies, and outcome measures including the odds ratio (OR) and 95% confidence intervals (CIs). Two researchers independently assessed studies for eligibility and extracted data on primary author, year/time period of publication, source of population, study design, study size, study setting, definition of serrated polyps, prevalence of serrated polyps, size and location of serrated polyps, and advanced neoplasia. When initial conclusions did not agree among reviewers, a meeting was held to discuss these studies to reach a joint conclusion. All studies were judged using factors recommended by the Standards for the Reporting of Observational Studies in Epidemiology Group (16). We used the Newcastle–Ottawa Scale for assessing the quality of cohort or case–control studies (17), and the standard that was recommended by Agency for Healthcare Research and Quality for assessment of cross-sectional studies (18).

Outcome measures

The main outcome measure was the risk of synchronous advanced neoplasia associated with serrated polyps. Secondary outcomes included the risk of advanced neoplasia with PSPs and/or LSPs, the prevalence of serrated polyps, and the risk of serrated polyps and advanced neoplasia at different sites of the colon.

Data synthesis

The results from observational studies were analyzed using Review Manager V.5.1 (Nordic Cochrane Centre, Copenhagen, Denmark) and CMA 2.0 (Biostat, Englewood, NJ) (19). ORs with 95% CIs were used to evaluate the risk of synchronous colorectal advanced neoplasia. Weighted summaries were determined using meta-analysis models if a given result was reported by ≥4 studies. Tests for heterogeneity were performed for each meta-analysis using the I^2 statistic (I^2 <25% and I^2 >50% reflect small and large inconsistency, respectively). If the χ^2 test (P>0.1) was not significant in the heterogeneity test, it showed that the research was not heterogeneous, and hence we used fixed-effects models; otherwise, we used random-effects models. Subgroup meta-analyses were performed on cancer, LSPs, or PSPs.

RESULTS

Search results

The results of the search strategy have been summarized in **Figure 1**. The initial search identified 1,544 abstracts. The majority of abstracts were excluded, as they were not relevant to the search topic. A total of 68 English language abstracts

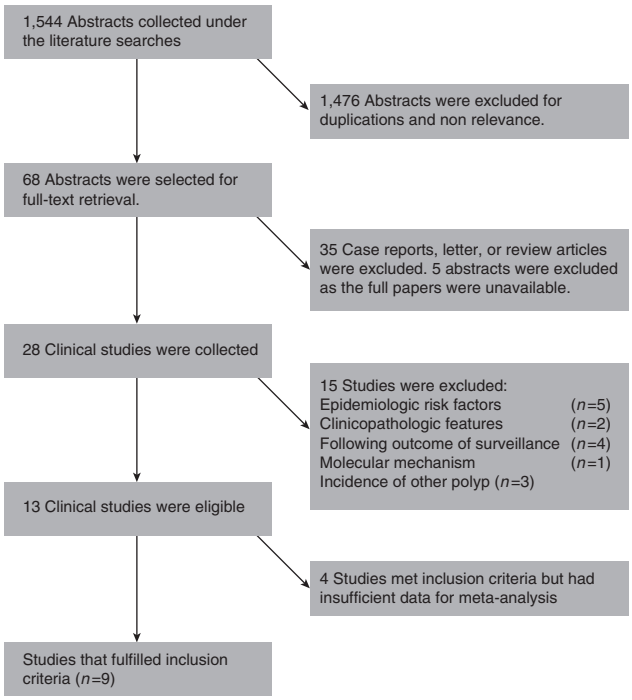


Figure 1. Flow diagram on the literature search.

that involved human subjects were retrieved, and 28 potentially relevant studies were reviewed (10,11–13,20–43). After exclusion of 15 studies that did not report the information of interest (12,21,23–25,28–30,32,33,35–39) and 4 studies that had insufficient data for meta-analysis (13,22,31,41), our final analysis included nine studies published between 2009 and 2014.

Study and patient characteristics

Nine studies with a total of 34,084 patients (10,11,20,26, 27,34,40,42,43) met inclusion criteria and were included in the meta-analysis. The study characteristics are shown in **Table 1**. There were seven cross-sectional studies, one cohort study, and one randomized-controlled trial. Four studies were from Europe, two from United States, one from Japan, and two from Hong Kong. Seven studies consisted of consecutive average-risk asymptomatic subjects who had undergone screening colonoscopy and two studies included both symptomatic and asymptomatic patients (11,27). The mean age of enrolled subjects was 59.9±6.6 years (range 43–75), and the proportion of male was 52.5%, apart from one study in which 97% of the subjects were male (34). The number of participants in the individual trial ranged from 985 to 10,199. All studies included were published as full articles.

Serrated polyps and risk of synchronous advanced neoplasia

The prevalence of serrated polyps in included studies ranged from 5.6 to 28.7% (42,43). On pooled analysis, the prevalence of serrated polyps was 15.6% (95% CI, 10.3–22.9%, **Figure 2**). The overall prevalence of PSPs and LSPs ranged from 3.7 to 12.2%

Table 1. Description of the included studies

Author	Country	Year	Study type	Number of subjects	Patient source	Mean age (years)	Male	Prevalence of serrated polyps		Quality
								PSP	LSP	
Li *et al.*(10)	America	2009	Cross-sectional multicenter	4,714	Asymptomatic	69	44.5%	NA	2.3%	9
Hiraoka *et al.* (11)	Japan	2010	Cross-sectional multicenter	10,199	Symptomatic/asymptomatic	58.9	51.5%	NA	1.4%	10
Schreiner *et al.* (34)	America	2010	Cohort multicenter	3,121	Asymptomatic	62.4	96.7%	7.9%	1.4%	8[a]
Rondagh *et al.* (27)	Netherlands	2011	Cross-sectional single center	2,309	Symptomatic/asymptomatic	58.4	46.1%	3.8%	2.9%[b]	9
Buda *et al.*(20)	Italy	2012	Cross-sectional single center	985	Asymptomatic	53	38.0%	4.8%	0.3%	10
Leung *et al.* (40)	Hongkong	2012	Cross-sectional multicenter	1,282	Asymptomatic	49.1	48.4%	7.2%	2.3%	9
Álvarez *et al.* (26)	Spain	2013	RCT multicenter	5,059	Asymptomatic	59	48.6%	6.5%	1.8%	9[c]
Hazewinkel *et al.* (42)	Netherlands	2014	Cross-sectional multicenter	1,426	Asymptomatic	60	51.0%	12.2%	2.6%	9
NG *et al.*(43)	Hongkong	2014	Cross-sectional multicenter	4,989	Asymptomatic	58	45.5%	3.7%	0.4%	9

LSP, large serrated polyp; PSP, proximal serrated polyp; RCT, randomized clinical trial.
[a]The quality of this study was assessed using the Newcastle–Ottawa Scale (NOS).
[b]In this article, LSP was defined as serrated polyps with a diameter of ≥6mm.
[c]The study was reported as a randomized clinical trial, but the data were extracted as a cross-sectional study, and hence the standard recommended by Agency for Healthcare Research and Quality (AHRQ) was used.

AQ17 AQ18

REVIEW

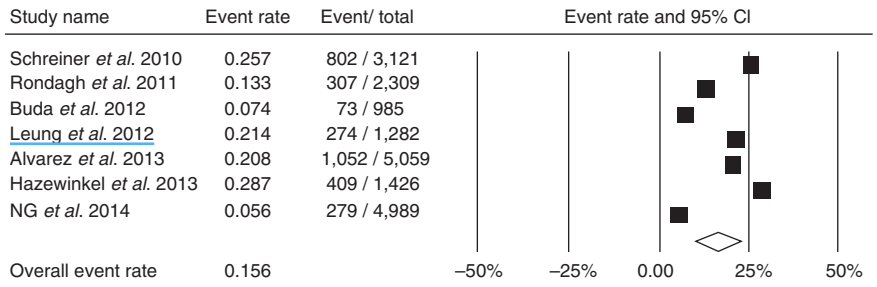
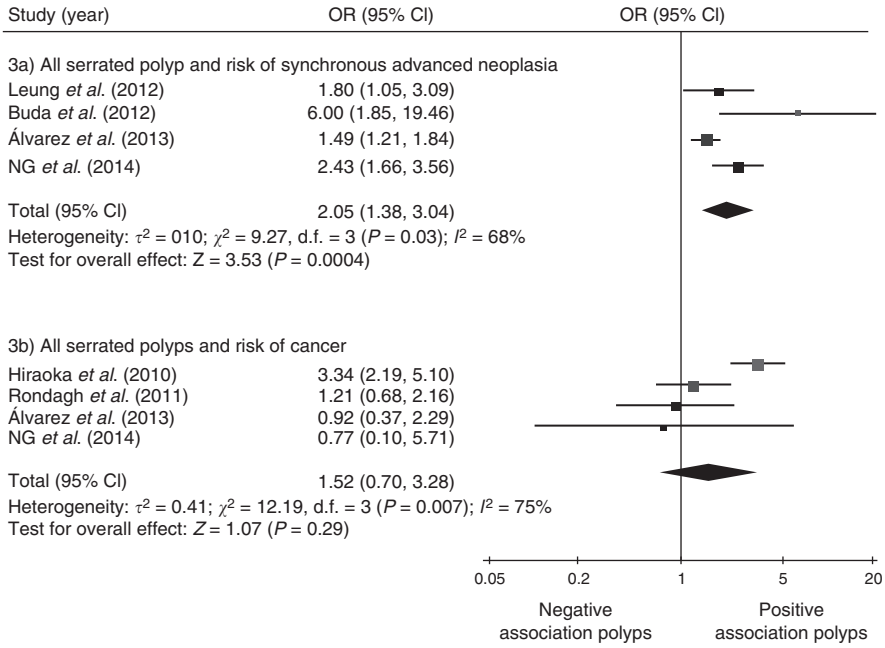


Figure 2. Forest plots of pooled prevalence of all serrated polyps. CI, confidence interval.

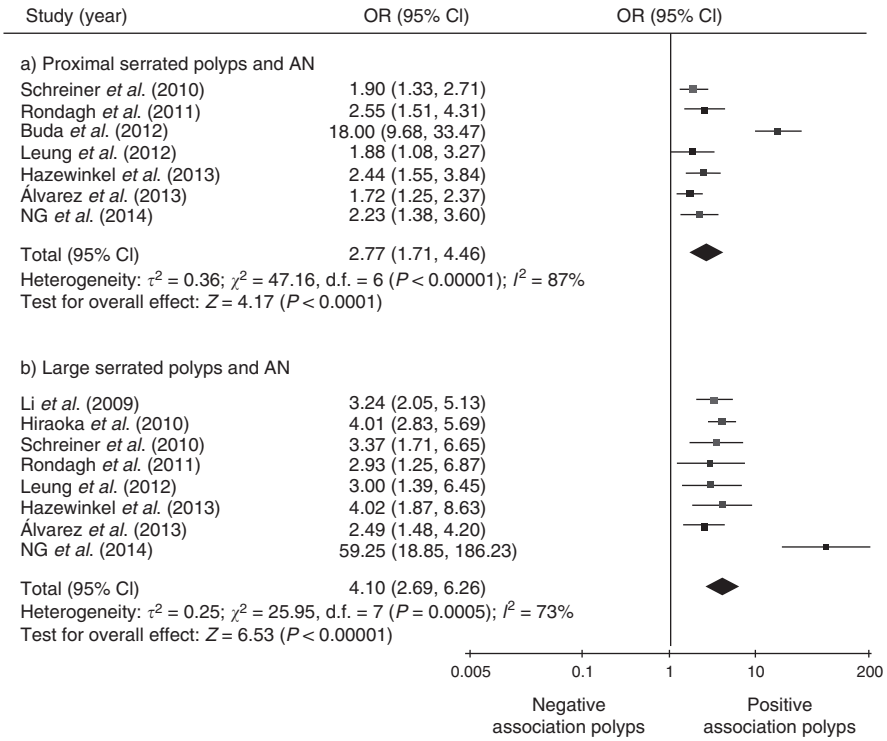


AQ12 **Figure 3.** Forest plots of all serrated polyps and risk of synchronous advanced neoplasia and cancer. CI, confidence interval; OR, odds ratio.

(42,43), and from 0.3 to 2.6% (20,42), respectively. The pooled prevalence of PSPs was 6.1% (95% CI, 4.5–8.4%) and that of LSPs was 1.5% (95% CI, 1.1–2.1%). Advanced neoplasia was detected in 4.1 to 15.4% (11,42) of subjects. Data on the risk of serrated polyps and synchronous advanced neoplasia were available from four studies (20,26,40,43). Individuals with serrated polyps were more likely to have synchronous advanced neoplasia, with a pooled OR of 2.05 (95% CI, 1.38–3.04, I^2=68%), as shown in **Figure 3a**. Subgroup analysis was performed to determine the association of serrated polyps and CRC. Among four studies with limited data available (11,26,27,43), the presence of serrated polyps was not significantly associated with synchronous CRC (OR=1.52, 95% CI, 0.70–3.28, I^2=75%, **Figure 3b**).

PSPs and risk of synchronous advanced neoplasia

Seven papers reported PSPs and the risk of synchronous advanced neoplasm (20,26,27,34,40,42,43). PSPs were defined as serrated polyps located proximal to the splenic flexure in all studies. Among them, six papers have included average-risk patients who underwent screening colonoscopy, and one study has included a majority of symptomatic subjects (27). Individuals with PSPs were more than twice as likely to have synchronous advanced neoplasia (OR=2.77, 95% CI, 1.71–4.46, I^2=87%, **Figure 4a**) than those without PSPs. It has been estabilised that individuals with a family history of CRC have an elevated risk of developing CRC compared with those without such a history (44,45). Two out of seven studies have included individuals with a family history of CRC (34,43). Exclusion of the two studies that have included these high-risk individuals did not significantly alter the risk estimate of synchronous advanced neoplasia in individuals with serrated polyps (OR=3.18, 95% CI, 1.55–6.49, I^2=81%). Heterogeneity exists between studies (I^2=87%) in random-effects model. The removal of one study with a particularly high OR when compared with the remaining studies (Buda *et al.* (20), OR=18) led to a considerable decrease in the heterogeneity (OR=2.02, 95% CI, 1.70–2.39, χ^2=2.72, d.f.=5, P=0.74, I^2=0%).



AQ14 **Figure 4.** Forest plots of large or proximal serrated polyps and risk of synchronous advanced neoplasia. CI, confidence interval; OR, odds ratio.

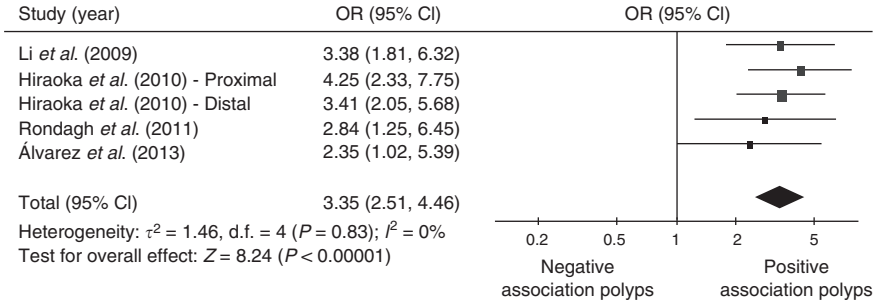


Figure 5. Forest plots of large and proximal serrated polyps and risk of synchronous advanced neoplasia. CI, confidence interval; OR, odds ratio.

LSPs and risk of synchronous advanced neoplasia

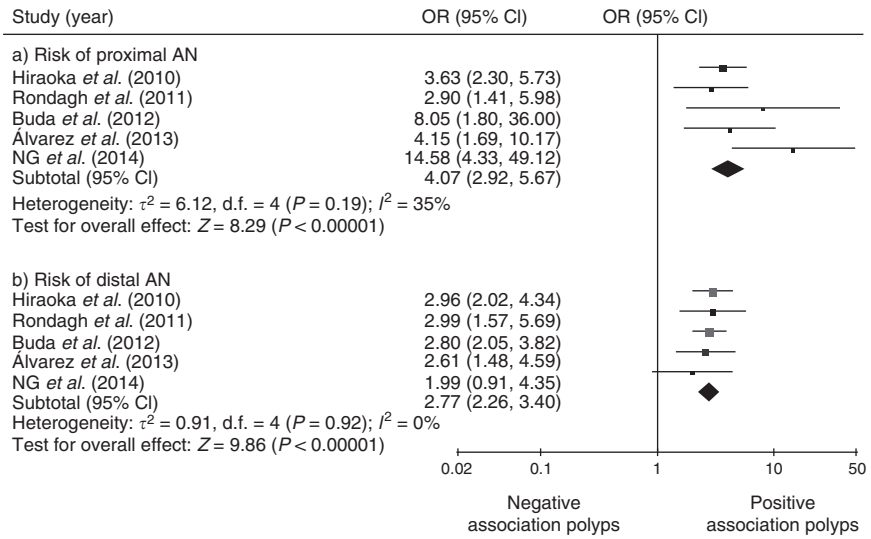
Eight papers reported the presence of LSPs and the risk of synchronous advanced neoplasm (10,11,26,27,34,40,42,43). Serrated polyps ≧10 mm were considered as LSPs. We found that LSPs were associated with an increased risk of synchronous advanced neoplasia. The pooled estimate for the OR of synchronous advanced neoplasia in subjects with LSPs was 4.10 (95% CI, 2.69–6.26) with evidence of relatively high heterogeneity (I^2=73%) among the included studies, as shown in **Figure 4b**. Similarly, following the exclusion of the one study that reported an extremely high OR (OR=59.25) possibly owing to the small number of LSPs (only 0.4%) (43), there was no heterogeneity between the remaining studies (OR=3.38, 95% CI, 2.75–4.15, χ^2=2.66, d.f.=6, P=0.85, I^2=0%).

Proximal LSPs and risk of synchronous advanced neoplasia

We investigated whether LSPs located at the proximal colon will further influence the risk of advanced neoplasia. Four of nine publications have reported PSPs and LSPs and risk of synchronous advanced neoplasia (10,11,26,27). The combined OR from these studies was 3.35 (95% CI, 2.51–4.46), with no evidence of heterogeneity (I^2=0%; **Figure 5**).

LSPs or PSPs and risk of synchronous advanced neoplasia according to location

Studies have shown that clinical and biologic differences exist between colorectal neoplasia in the proximal and distal colon (46,47). We next analyzed the association between LSPs or PSPs and synchronous advanced neoplasia in the right or left colon.



AQ16 **Figure 6.** Forest plots of large or proximal serrated polyps and the risk of synchronous advanced neoplasia according to location. CI, confidence interval; OR, odds ratio.

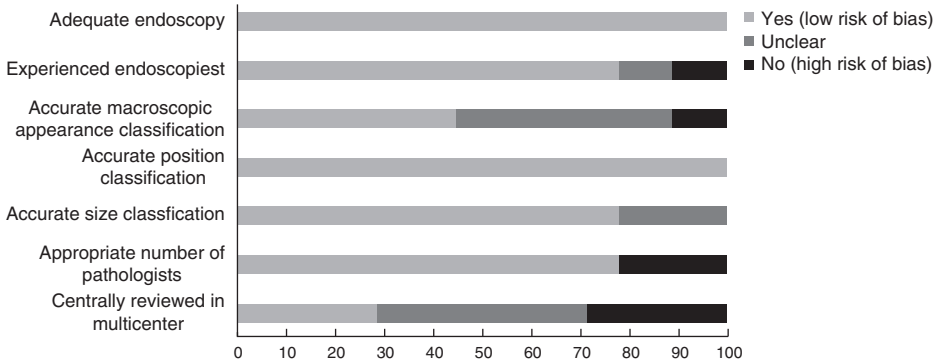


Figure 7. Methodological quality and risk of bias for studies included in systematic review.

Our analyses revealed that the risk presented by the presence of LSPs or PSPs was high for advanced neoplasia in both right and AQ2 left colons (right colon: OR=4.07, 95% CI, 2.92–5.67; left colon: OR=2.77, 95% CI, 2.26–3.40; **Figure 6a,b**).

Methodological quality and risk of bias of included studies

In all but one study, colonoscopies were performed by experienced endoscopists. One study reported that several trainees AQ3 joined in performing the procedures (27). Standard examination with white-light, high-definition colonoscopes was performed, with supplementation by narrow-band imaging when suspected lesions were detected (40). Selective chromoendoscopy was used in one study in order to better visualize the borders of nonpolypoid lesions before endoscopic removal (27). Macroscopic appearance of the polyp was classified according to the Paris endoscopic classification (48) in four studies (11,20,27,42), classified into protruded or flat type in one study (26), and not mentioned in the remaining four studies (10,34,40,43). The same definition for polyp size estimation and lesion location was used in all the included studies: (i) The junction of the splenic flexure and the descending colon, as determined by the endoscopist, defined the border between the proximal and the distal colon and (ii) the size of the polyps resected with polypectomy was measured just after resection or estimated visually using a standard biopsy forceps. The histology of polyps was interpreted by a single pathologist in two studies, by two pathologists in three studies, and by a committee of pathologist in four studies. Central review of polyps was performed in 2 out of 7 (29%) of the multicenter studies. Among the included studies, there was variable risk of bias as shown in **Figure 7**, detailed in **Table 2**.

DISCUSSION

Serrated polyps of the colorectum are characterized histologically by a serrated (or saw-toothed) appearance of the crypt epithelium (7). Different subtypes of serrated polyps have different molecular profiles and variable potential to develop into malignant disease. Because of the potential clinical importance, recent studies have

Table 2. Assessment of bias risk of the included studies

Study	Adequate endoscopy	Experienced endoscopist	Accurate macroscopic appearance classification	Accurate position classification	Accurate size classification	Appropriate number of pathologists	Centrally reviewed in multicenter
Li *et al.* (10)	YES	YES	UNCLEAR	YES	YES	YES	NO
Hiraoka *et al.* (11)	YES	YES	YES	YES	YES	YES	YES
Schreiner *et al.* (34)	YES	YES	UNCLEAR	YES	UNCLEAR	YES	YES
Rondagh *et al.* (27)	YES	NO	YES	YES	YES	YES	NA
Buda *et al.* (20)	YES	YES	YES	YES	YES	YES	NA
Leung *et al.* (40)	YES	YES	UNCLEAR	YES	YES	NO	UNCLEAR
Álvarez *et al.* (26)	YES	YES	NO	YES	UNCLEAR	YES	NO
Hazewinkel *et al.* (42)	YES	YES	YES	YES	YES	YES	UNCLEAR
NG *et al.* (43)	YES	UNCLEAR	UNCLEAR	YES	YES	NO	UNCLEAR

AQ19 NO (high risk of bias); YES (low risk of bias).

reported emerging data to support the association between serrated polyps and advanced colorectal neoplasia.

Our meta-analysis showed that serrated polyps are associated with a more than twofold risk of synchronous advanced neoplasia. This risk is particularly high for PSPs and LSPs. To the best of our knowledge, this is the first systematic review and meta-analysis to estimate the prevalence of serrated polyps among studies published in the past 5 years and to summarize the magnitude of risk of serrated polyps and advanced colorectal neoplasia. We did not find a significant association between serrated polyps and synchronous CRC (OR=1.52, 95% CI, 0.70–3.28). However, this finding is based on limited studies, and there was high heterogeneity because of a small proportion of patients with CRC (only ~2.5%).

The pooled prevalence of serrated polyps was 15.6%. The most striking finding is the strong risk relationship between the presence of PSPs and synchronous advanced neoplasia (OR=2.77, 95% CI, 1.71–4.46). Serrated polyps may be more easily missed because of their flat morphology and ambiguous color particularly in the proximal colon, whereby the endoscopic view is often not clear enough because of the insufficient bowel preparation. Once a PSP is identified, further careful inspection will likely result in an incremental increase in rates of detection of other lesions. Another interesting observation was that the association between PSPs and synchronous advanced colorectal neoplasia was not affected by the presence of a family history of colorectal cancer (OR=3.18, 95% CI, 1.55–6.49 vs. OR=2.77, 95% CI, 1.71–4.46). A family history of colorectal cancer has been shown to be a predictor of proximal AQ4 adenomas and PSPs (34,38,49). An alternative pathway such as the BRAF-serrated pathway might predispose patients with a family history of CRC to PSPs that is associated with an increased risk of adenoma and colorectal neoplasia (38). However, our study did not detect family history of colorectal cancer to be an independent potential risk factor in PSPs with synchronous advanced neoplasia. This is most likely because individuals with a family history of CRC were excluded from the majority of the included studies. Only two of the articles included a family history of CRC patients (13.9% of totally enrolled 3,121 patients and 14% of totally enrolled patients 4,989, respectively) (34,43). The ratios of men and women in each study were similar, with the exception of one VA study (34), whereby 97% of patients were male. Exclusion of this study AQ5 from the analysis did not alter the OR (OR=2.98).

On the other hand, we found that LSPs were independently associated with synchronous advanced colorectal neoplasia (OR=4.10, 95% CI, 2.69–6.26). One study also confirmed that LSPs were associated with an increased risk of CRC (OR=3.34) (11). It has been AQ6 found that LSPs may share some molecular features with certain types of CRCs such as CpG island hypermethylation and BRAF mutations that may result in progression to CRC (6,7). Our findings imply that LSPs should be considered an important marker for synchronous advanced colorectal neoplasia. Patients with LSPs should be considered a high-risk group for developing CRC. However, some of the studies reported the prevalence rate of serrated polyp ≧5 mm, but the OR with synchronous advanced neoplasia was lacking. Therefore, we strongly suggested using the 10-mm cutoff AQ7 for LSPs because this is widely accepted in standard clinical practice. Moreover, our study included a subanalysis of the association between the risk of synchronous advanced colorectal neoplasia and LSPs with proximal location. It is not surprising that we found that AQ8 patients with PSPs and LSPs are associated with a nearly threefold risk of detection of synchronous advanced neoplasia (OR=3.35, 95% CI, 2.51–4.46). Early research has suggested that proximal-located serrated polyps have higher malignant potential compared with distal-located serrated polyps (50), but this finding may relate to the small size of serrated polyps in the distal colon instead of the location of the polyps. In this meta-analysis, two papers reported that the strength of the association between LSPs and advanced neoplasia was similar for both proximal and distally located lesions. The relationship needs to be validated in further analysis.

Last, our analyses revealed that the risk presented by the presence of LSPs or PSPs was quite high for advanced neoplasia in both right and left colons. There are likely to be biological differences between proximal and distal CRCs (51). It has been reported that high-risk polyp may lead to advanced neoplasias that occur AQ9 predominantly in the proximal colon (20). According to our

findings, patients with either LSPs or PSPs are associated with a high risk of detecting synchrnous advanced neoplasia at both sites of the colon.

Our study has several clinical implications. It highlights the emerging importance of serrated polyps as markers of neoplasia, if not a premalignant lesion. Although these lesions can be difficult to detect with standard white-light endoscopy, it is likely that missed or undetected serrated polyps eventually develop into tumors and contribute to interval CRC. It is important for gastroenterologists to optimize their ability to detect these lesions especially when the bowel preparation is not ideal especially in the right colon. Currently, the interval of the surveillance has not yet been definitively determined, but it seems that if the lesions are large and/or proximal to sigmoid then the surveillance should be stricter and more frequent. The strengths of this meta-analysis include a comprehensive and systematic literature search with well-defined inclusion criteria and quantitative and qualitative assessment of several subtypes of serrated polyps, including prevalence and outcomes of advanced neoplasia. We also evaluated the stability of findings and identify potential factors that are responsible for inconsistencies.

Our study also has several limitations. First, in most of the multicenter studies, the pathologic criteria for the diagnosis of serrated polyps were not centrally reviewed, and this may lead to interobserver variation among pathologists in the differentiation of some of the polyps. Second, serrated polyps were not further distinguished into their three subtypes in most studies, and hence the precise association between each serrated polyp subtype (HPs, SSAs, and TSAs) and synchronous advanced neoplasia could not be determined. Owing to limited data from existing studies, we were unable to accurately estimate whether there was any increased risk among those with only small distal HPs or small distal SPs. It would be expected that this group would not have an increased risk of synchronous advanced neoplasia. However, future studies will be needed to study these subsets of lesions separately. A majority of the papers have not provided data on the proportion AQ10 of patients with SSA/Ps as the only lesion. Unpublished data from our group reported that this rate may increase up to 93.3% (among 60 patients with sessile serrated polyps, 56 had sessile serrated polyp as the only lesion) (43), but more data from other countries are needed. Third, there may be possible confounding factors that are associated with the risk of advanced neoplasia, for example, dietary patterns, cigarettes or alcohol use, and socioeconomic factors that could not be determined in our study. Such data are either incomplete or lacking from the original publications. Fourth, some results of our pooled estimates suffered from heterogeneity mainly driven by two papers. For instance, we noted a high heterogeneity (I^2=87%) resulting from the study of Buda *et al.* (20) (OR=18). In that study, the prevalence of serrated polyps (~7%) as well as adenomas (14.8%) was lower when compared with other studies. It is likely that small rectal hyperplastic polyps may not have been recorded, leading to a relatively lower prevalence of overall serrated polyps. Nonetheless, a significant association remained even after removal of this study, with a considerable decrease in heterogeneity (OR=2.02, I^2=0%). Similarly, a separate study with relatively small number of LSPs (0.4%) and a lower rate of serrated polyps (5.6%) may have contributed to the high heterogeneity (I^2=73%) (43). Despite exclusion of this study, the asscociation between LSPs and synchronous advanced neoplasia remained significant. Fifth, neither the management nor the surveillance strategy of serrated polyps is available from the original paper, and hence we could not provide more information about that. Last, some unpublished studies cannot be identified through the literature search in the databases, and publication bias may exist in this meta-analysis. Statistical evaluations for the publication bias, including the funnel plot assessment and trim-and-fill method for model adjustment, cannot be applied with the limited number of included trials.

In summary, this study is the first to show in a comprehensive and systematic way the positive association between serrated polyps and synchronous advanced neoplasia. PSPs and LSPs were independently associated with a twofold to fourfold increased risk of synchronous advanced colorectal neoplasia. Future studies are needed to elucidate whether serrated polyps and synchronous advanced colorectal neoplasia may define a high-risk phenotype, and which subsets of serrated polyps leave patients at highest risk of synchronous lesions, in order to ascertain whether these individuals require more intensive surveillance.

CONFLICT OF INTEREST

Guarantor of the article: Siew C. Ng.

Specific author contributions: Qinyan Gao, Kelvin K.F. Tsoi, Hoyee W. Hirai, and Martin C.S. Wong (study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content). Francis K.L. Chan, Justin C.Y. Wu, James Y.W. Lau, and Joseph J.Y. Sung (technical and material support). Siew C. Ng (study concept and design and study supervision). All authors have read and approved the final manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Serrated polyps, according to the World Health Organization (WHO) criteria, can be classified into hyperplastic polyps, sessile serrated adenoma/polyps (SSA/Ps) with or without cytological dysplasia, or traditional serrated adenomas (TSAs).
- ✓ Serrated polyps have been reported to disproportionally contribute to interval cancers, and SSA/Ps have been shown to be associated with an increased risk of metachronous cancer.

WHAT IS NEW HERE

- ✓ From studies published in the past 5 years, the prevalence of serrated polyps ranged from 5.6 to 28.7%.
- ✓ In pooled analysis, serrated polyps are associated with an increased risk of detection of synchronous advanced neoplasia.
- ✓ Proximal and/or large serrated polyps are associated with a greater risk of detection of synchronous advanced neoplasia, and these patients have an increased risk of advanced neoplasia in both sides of the colon.

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