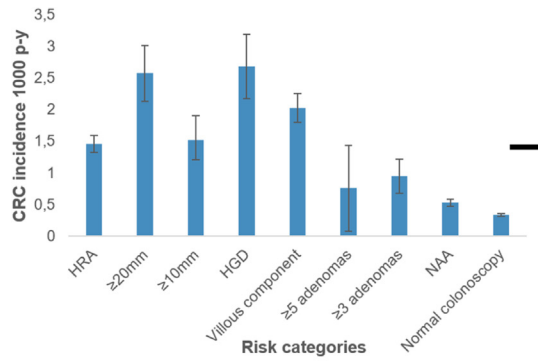
Risk Factors for Metachronous Colorectal Cancer or Advanced Adenomas After Endoscopic Resection of High-risk Adenomas

Sandra Baile-Maxía,[1] Carolina Mangas-Sanjuán,[1] Uri Ladabaum,[2] Cesare Hassan,[3,4] Matthew D. Rutter,[5,6] Michael Bretthauer,[7,8] Lucía Medina-Prado,[1] Noelia Sala-Miquel,[1] Oscar Murcia Pomares,[1] Pedro Zapater,[9] and Rodrigo Jover[1]

[1]Servicio de Medicina Digestiva, Hospital General Universitario Dr Balmis, Instituto de Investigación Biomédica ISABIAL, Universidad Miguel Hernández, Alicante, Spain; [2]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, California; [3]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [4]IRCCS Humanitas Research Hospital, Milan, Italy; [5]North Tees and Hartlepool NHS Foundation Trust, Stockton-On-Tees, Cleveland, Yorkshire, United Kingdom; [6]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, United Kingdom; [7]Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo, Norway; [8]Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway; and [9]Clinical Pharmacology Department, Hospital General Universitario Dr Balmis, Instituto de Investigación Biomédica ISABIAL, CIBERehd, Alicante, Spain



Risk category	RR for CRC risk	
	Compared with NAA	Compared with normal colonoscopy
HRA	2.56 [2.21-2.96]	2.92 [2.29-3.73]
Size ≥ 20mm	3.81 [2.19-6.63]	
Size ≥ 10mm	1.66 [1.30-2.13]	2.61 [2.06-3.32]
HGD	2.89 [1.88-4.44]	6.62 [4.60-9.52]
Villous component	1.75 [1.33-2.31]	3.58 [2.24-5.73]
≥ 5 adenomas	1.36 [0.54-3.46]	
≥ 3 adenomas	1.24 [0.84-1.83]	2.03 [1.40-2.94]

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: **Among the characteristics of high-risk adenomas (HRAs), some may predict a higher risk of metachronous advanced lesions. Our aim was to assess which HRA characteristics are associated with high risk of metachronous colorectal cancer (CRC) or advanced adenomas (AAs).**

METHODS: **We systematically searched Pubmed, EMBASE, and Cochrane for cohort studies and clinical trials of CRC or AA incidence at surveillance stratified by baseline lesion size, histology, and multiplicity. We calculated pooled relative risks (RRs) using a random-effects model. Heterogeneity was assessed with the I^2 statistic.**

RESULTS: **Fifty-five studies were included, with 936,540 patients with mean follow-up 5.4 ± 2.9 years. CRC incidence per 1000 person-years was 2.6 (2.1–3.0) for adenomas ≥20 mm, 2.7 (2.2–3.2) for high-grade dysplasia (HGD), 2.0 (1.8–2.3) for villous component, 0.8 (0.1-1.4) for ≥5 adenomas, 1.0 (0.7–1.2) for ≥3 adenomas. Metachronous CRC risk was higher in adenomas ≥20 mm vs 10 to 19 mm (RR, 2.08; 95% confidence interval [CI], 1.20–3.61), HGD vs low-grade dysplasia (RR, 2.89; 95% CI, 1.88–4.44), villous vs tubular (RR, 1.75; 95% CI, 1.33–2.31). No significant differences in CRC risk were**

Abbreviations used in this paper: AA, advanced adenoma; ARD, absolute risk difference; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; HRA, high-risk adenoma; LGD, low-grade dysplasia; LRA, low-risk adenoma; NAA, non-advanced adenoma; NNS, number needed to scope; RR, relative risk.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2022.12.005

found in ≥3 adenomas vs 1 to 2 (RR, 1.24; 95% CI, 0.84–1.83), nor in ≥5 adenomas vs 3 to 4 (RR, 0.79; 95% CI, 0.30–2.11). Compared with normal colonoscopy, RR for CRC risk was 2.61 (95% CI, 2.06–3.32) for ≥10mm, 6.62 (95% CI, 4.60–9.52) for HGD, 3.58 (95% CI, 2.24–5.73) for villous component, and 2.03 (95% CI, 1.40–2.94) for ≥3 adenomas. Similar trends were seen for metachronous AAs.

CONCLUSION: **Metachronous CRC risk is highest in patients with baseline adenomas with ≥20 mm or HGD. Multiplicity does not seem to be associated with substantially higher CRC risk in the near term.**

Keywords: Adenomas; Colonoscopy; Colorectal Cancer; Colorectal Neoplasms.

Due to the increasingly widespread use of diagnostic colonoscopy and colorectal cancer (CRC) screening programs, more people are being diagnosed with colonic adenomas and serrated lesions.[1-3] Some of these individuals are considered at high risk of developing future CRC or advanced adenoma (AA), and, therefore, may need to be monitored with periodic surveillance colonoscopies.[4] especially those with risk factors related to size, histology, and number of adenomas detected at index colonoscopy.[5-9] Several major societies have established recommendations for surveillance, with some degree of concordance, but also with discrepancies in the recommended surveillance intervals.[9-13]

Post-polypectomy surveillance is one of the main indications for colonoscopy, accounting for around 20% to 25% of colonoscopies performed at 50 years of age or older in Western countries,[14,15] with a consequent burden on endoscopy units. Until recently, the evidence informing recommendations for surveillance after polyp removal has been of low or moderate quality. It is possible that longer intervals than those currently used in practice may provide the same level of protection against CRC with better cost effectiveness.[16-18]

The ultimate goals of surveillance colonoscopy are the prevention and early detection of CRC.[19] Thus, it is imperative to establish which individuals are at highest risk and might benefit most from surveillance. We performed a systematic review and meta-analysis with the aim of assessing which specific characteristics of high-risk adenoma (HRA) (size, histology, multiplicity) are associated with a higher risk of metachronous CRC or AA.

Methods

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).[20] The protocol was registered prospectively at PROSPERO (CRD42020186548).

Search Strategy

To identify issues of greatest importance for the literature revision, we developed patient, intervention, comparison, and outcome (PICO) questions (Supplementary Table 2). In consultation with a certified medical librarian, a comprehensive search of the available electronic literature was performed to find studies describing CRC or AA incidence at surveillance stratified according to baseline adenoma characteristics. We searched the Pubmed, EMBASE, and Cochrane databases from inception to February 2022. The search strategy is shown in Supplementary Appendix 1. 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.

Study Type

Cohort studies and clinical trials were included. Studies were excluded if subjects were <18 years of age, had any high-risk condition for CRC (inflammatory bowel disease, hereditary CRC syndromes), or 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, if results were presented in terms of advanced colorectal neoplasia without displaying AA and CRC separately, or if data regarding follow-up was not provided. Patients with nonadenomatous lesions (ie, serrated polyps) were not included in the analysis, and patients with synchronous serrated and adenomatous lesions were included according to the risk features of the adenomatous polyp. 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. Prevention trials were eligible if there was no statistically significant difference in the recurrence of adenomas between the intervention and the control group.

Definitions and Outcomes

Non-advanced adenoma (NAA) was defined as 1 to 2 tubular adenomas <10 mm with low-grade dysplasia (LGD). AA was defined as an adenoma ≥10 mm, containing ≥25% villous component, or high-grade dysplasia (HGD). Low-risk adenoma (LRA) was defined as 1 to 2 NAA, whereas HRA was defined as any AA or ≥3 NAA.[10] CRC was defined as invasion of malignant cells through the muscularis mucosa. Normal colonoscopy referred to those colonoscopies where no neoplasia was found.

The primary outcomes were: (1) The incidence of metachronous CRC per 1000 person-years by HRA characteristic; (2) The comparison of incidence of metachronous CRC between the HRA groups and the LRA or normal colonoscopy groups. The secondary outcomes were: (1) Absolute risk difference (ARD) per 1000 person-years and number needed to scope (NNS) to detect an additional case of CRC between the different HRA groups vs LRA and normal colonoscopy groups; (2) The comparison of incidence of metachronous AA between the different HRA groups and the LRA or normal colonoscopy groups; (3) The comparison of CRC mortality between the different HRA groups and the LRA or normal colonoscopy groups. Not all these prespecified outcomes could be assessed for some HRA groups, especially CRC mortality or comparisons with normal colonoscopy, 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.[21] 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 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 for the outcome of CRC incidence for those studies that included a colonoscopy quality assessment, excluding those procedures where inadequate bowel preparation was found or cecal intubation was not reached. Second, a sensitivity analysis was performed including only those studies with a follow-up time longer than 5 years, to explore the risk of metachronous CRC in the intermediate long term. Finally, a third sensitivity analysis was performed for studies in which most of the patient enrolment was from 2005 onwards, the period in which an increasing number of publications addressed the quality of colonoscopy and its role in the adenoma detection rate. This included studies in which recruitment began in 2005 or later,[24,26,41,43,53,59,60,63,66] but also some studies in which recruitment began before 2005.[18,45,61,65]

What You Need To Know

Background

Some of the characteristics of high-risk adenomas (size, histology, multiplicity) may be associated with a higher risk of metachronous advanced lesions than others, and therefore, not all of these features may warrant close endoscopic surveillance.

Findings

Metachronous colorectal cancer risk is highest in patients with baseline adenomas with size ≥20 mm or high-grade dysplasia and also significantly high for adenomas of ≥10 mm or with a villous component. Multiplicity does not seem to be associated with a substantially higher colorectal cancer risk in the near term.

Implications for patient care

Patients with baseline adenomas with size ≥10 mm, high-grade dysplasia, or villous component have a clear indication for surveillance, whereas persons with multiple adenomas without these features may not benefit from near-term endoscopic surveillance.

Statistical Analysis

Unadjusted relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated from extracted data. When crude numbers were not available, the study was excluded. Incidence of CRC and AA per 1000 person-years of follow-up was calculated using the number of events in each risk category and the duration of follow-up. The ARD for CRC was estimated as the difference in CRC incidence between each HRA group and patients with NAA or normal colonoscopy. The NNS was calculated as the inverse of ARD. 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 an 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 5187 studies, of which 4840 remained after removal of duplicates. After

applying the selection criteria and addition of cross-references, 201 studies were selected and reviewed in detail, and 55 studies[7,17,18,22-73] were included in the final analysis (Figure 1). Of those, 53 were cohort studies,[7,17,18,22-36,38-71,73] and 2 were clinical trials.[37,72]There was a total of 936,540 patients (mean age, 60.9 ± 9.9 years; 60% males) included. The mean duration of follow-up was 5.4 ± 2.9 years (median, 4.2 years; range, 12.3 years). Supplementary Table 3 provides an overview of the individual studies with their demographic data.

Supplementary Figure 1 and Supplementary Tables 4 and 5 show the risk of bias assessment. Supplementary Figure 2 shows funnel plots, which are quite symmetrical around the x-axis, suggesting the absence of publication bias.

CRC Incidence per 1000 Person-years

The CRC incidence per 1000 person-years was 1.46 (95% CI, 1.32–1.60) in patients with HRA. By HRA characteristic, the incidence rates were 2.58 (95% CI, 2.14–3.02) in patients with adenomas ≥20 mm, 1.52 (95% CI, 1.21–1.91) in adenomas ≥10 mm, 2.68 (95% CI, 2.18–3.20) in adenomas with HGD, 2.03 (95% CI, 1.80–2.26) in adenomas with villous component, 0.76 (95% CI, 0.08–1.44) in ≥5 adenomas, and 0.95 (95% CI, 0.68–1.22) in ≥3 adenomas. In contrast, the incidence rates were 0.53 (95% CI, 0.47–0.59) in patients with NAA and 0.34 (95% CI, 0.32–0.36) in normal colonoscopy (Figure 2, *A*).

AA Incidence per 1000 Person-years

The AA incidence per 1000 person-years was 27.73 (95% CI, 26.77–28.68) in patients with HRA. By HRA characteristic, the incidence rates were 90.88 (95% CI, 80.76–101.01) in patients with adenomas ≥20 mm, 44.12 (95% CI, 39.51–34.92) in adenomas ≥10 mm, 46.64 (95% CI, 40.57–52.71) in adenomas with HGD, 40.16 (95% CI, 38.45–41.88) in adenomas with villous component, 51.02 (95% CI, 48.85–53.18) in ≥5 adenomas, and 30.17 (95% CI, 27.01–33.34) in ≥3 adenomas. In contrast, the incidence rates were 10.82 (95% CI, 10.52–11.38) in patients with NAA and 5.31 (95% CI, 5.08–5.54) in normal colonoscopy (Figure 2, *B*).

NNS and ARD Estimation

NNS with their 95% CI for CRC and AA incidence for each HRA characteristic compared with NAA or normal colonoscopy are shown in Figures 2, *C–D* and Supplementary Table 6. The characteristics with the lowest NNS compared with NAA were adenoma size ≥20 mm (NNS, 480), and HGD (NNS, 531), and the characteristic with the highest NNS was multiplicity (≥5 adenomas, 4726; ≥3 adenomas, 9720). ARD per 1000 person-years estimates are shown in Supplementary Table 7.

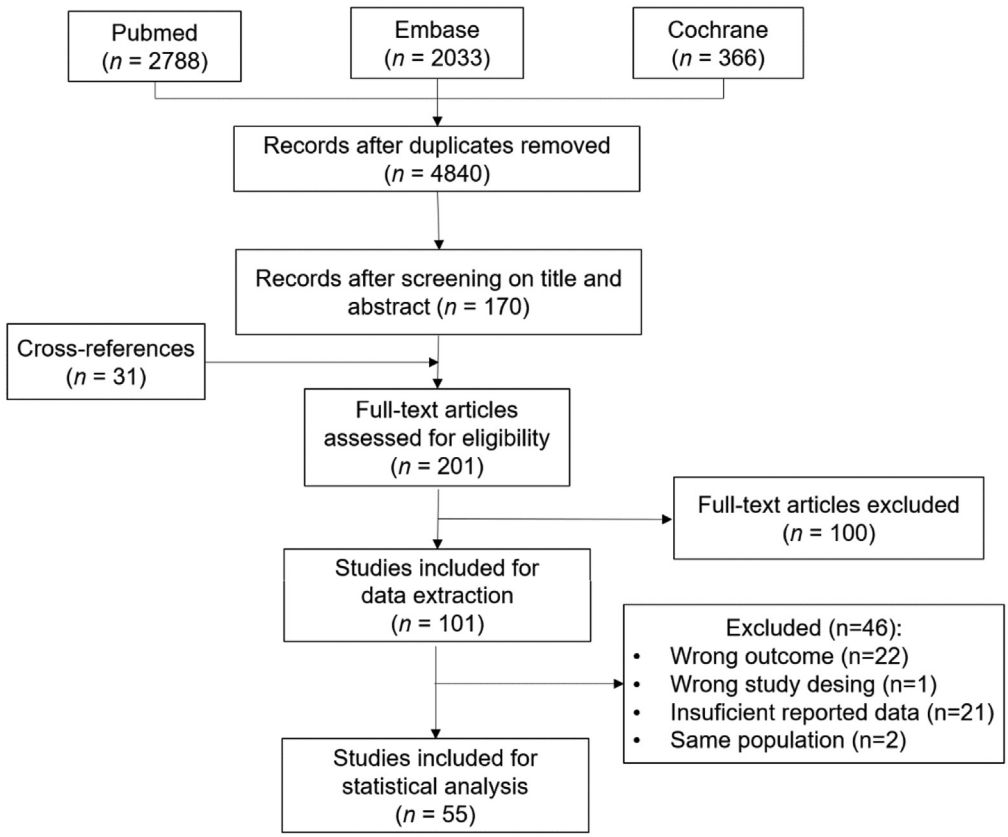


Figure 1. Flow diagram of study selection.

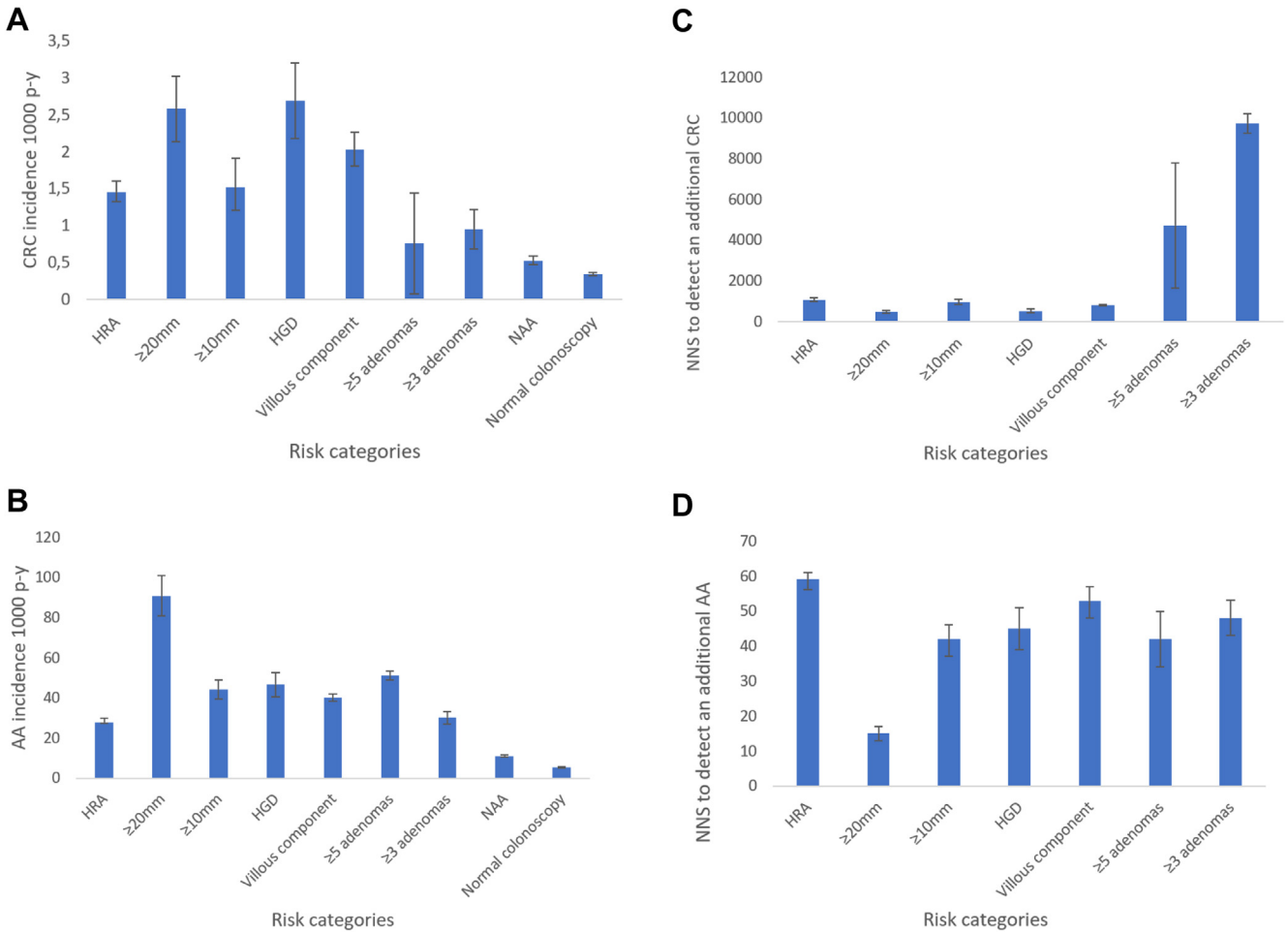


Figure 2. CRC (*A*) and AA (*B*) incidence per 1000 person-years in each high-risk category and in the population with NAA and normal colonoscopy. NNS to detect one additional CRC (*C*) or AA (*D*) for each HRA characteristic compared with NAA.

HRA as Risk Factor for Metachronous CRC and AA and CRC Mortality

Twenty-seven studies[18,22,24,26,28,30,33,34,37,44-46,48,50,51,56,57-59,60,61-63,68,70,72,73] reported the risk of metachronous CRC or AA incidence, and 4 studies[18,30,45,71] reported the risk of CRC mortality in patients with HRA at baseline colonoscopy. The pooled RR for CRC incidence was 2.56 (95% CI, 2.21–2.96; $I^2 = 0\%$) compared with patients with NAA, and 2.92 (95% CI, 2.29–3.73; $I^2 = 61\%$) compared with normal colonoscopy (Figure 3). The pooled RR for AA incidence was 2.35 (95% CI, 2.0–2.76; $I^2 = 83\%$) compared with NAA and 4.51 (95% CI, 3.56–5.71; $I^2 = 73\%$) compared with normal colonoscopy. The pooled RR for CRC mortality was 1.94 (95% CI, 1.23–3.07; $I^2 = 32\%$) compared with NAA and 2.41 (95% CI, 1.83–3.19; $I^2 = 0\%$) compared with normal colonoscopy (Supplementary Figure 3).

Size of Adenomas as Risk Factor for Metachronous CRC and AA

Sixteen studies stratified the risk of metachronous CRC or AA according to adenoma size in baseline colonoscopy.[17,18,23,25,27,29,30,38,39,43,47,49,51,54,64,73] The risk for metachronous CRC was higher in patients with adenoma size of ≥20 mm at index colonoscopy vs adenomas <20 mm (RR, 2.98; 95% CI, 1.43–6.19; $I^2 = 88\%$), in those with adenoma size of 10 to 19 mm vs <10 mm (RR, 1.73; 95% CI, 1.31–2.29; $I^2 = 0\%$) and in adenoma ≥10 mm vs <10 mm (RR, 1.66; 95% CI, 1.30–2.13; $I^2 = 0\%$) or vs normal colonoscopy (RR, 2.61; 95% CI, 2.06–3.32; $I^2 = 0\%$) (Figure 4). The risk for metachronous AA is shown in Supplementary Figure 4.

Histological Features as Risk Factors for Metachronous CRC and AA

Thirteen studies stratified the risk of metachronous CRC or AA according to the grade of dysplasia of baseline adenomas.[17,18,23,25,27,29,35,36,38,44,47,51,52] The RR for CRC incidence for patients with HGD at index colonoscopy was 2.89 (95% CI,1.88–4.44; $I^2 = 60\%$) compared with LGD, and 6.62 (95% CI, 4.60–9.52; $I^2 = 0\%$) compared with normal colonoscopy (Figure 5). The RR for AA incidence is shown in Supplementary Figure 5.

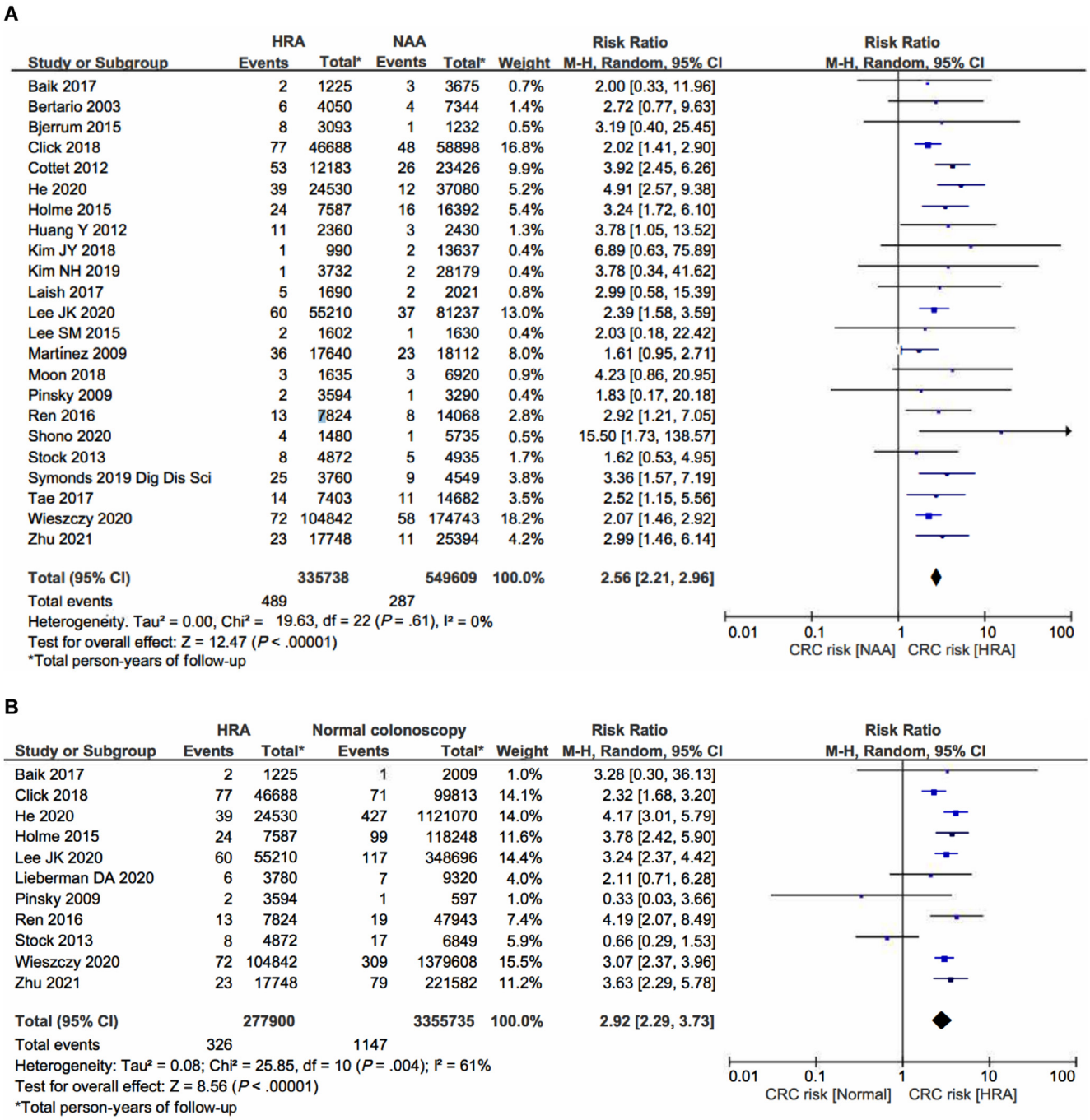


Figure 3. RR for CRC incidence in 1000 person-years in the HRA group compared with the NAA group (*A*) and the normal colonoscopy group (*B*).

Seventeen studies stratified the risk of meta chronous CRC or AA according to the histology (tubular, tubulo-villous, or villous) of baseline adenomas.[17,18,23,25,27,29,31,36-39,43,44,47,49,51,64] The RR for CRC incidence for patients with villous or tubulo-villous adenomas at index colonoscopy was 1.75 (95% CI, 1.33–2.31; $I^2 = 42\%$) compared with tubular adenomas, and 3.58 (95% CI, 2.24–5.73; $I^2 = 53\%$) compared with normal colonoscopy (Figure 5). The RR for AA incidence is shown in Supplementary Figure 5.

Multiplicity of Adenomas as Risk Factor for Metachronous CRC and AA

Twenty-five studies stratified the risk of metachronous CRC or AA according to the number of adenomas in baseline colonoscopy.[17,18,27,32,36,38-42,44,47-49,51,53,55,65,67-69,73] The risk for metachronous CRC was not significantly higher in patients with ≥5 adenomas at index colonoscopy compared with those with <5 adenomas (RR, 1.22; 95% CI, 0.49–3.06; $I^2 = 0\%$); nor in

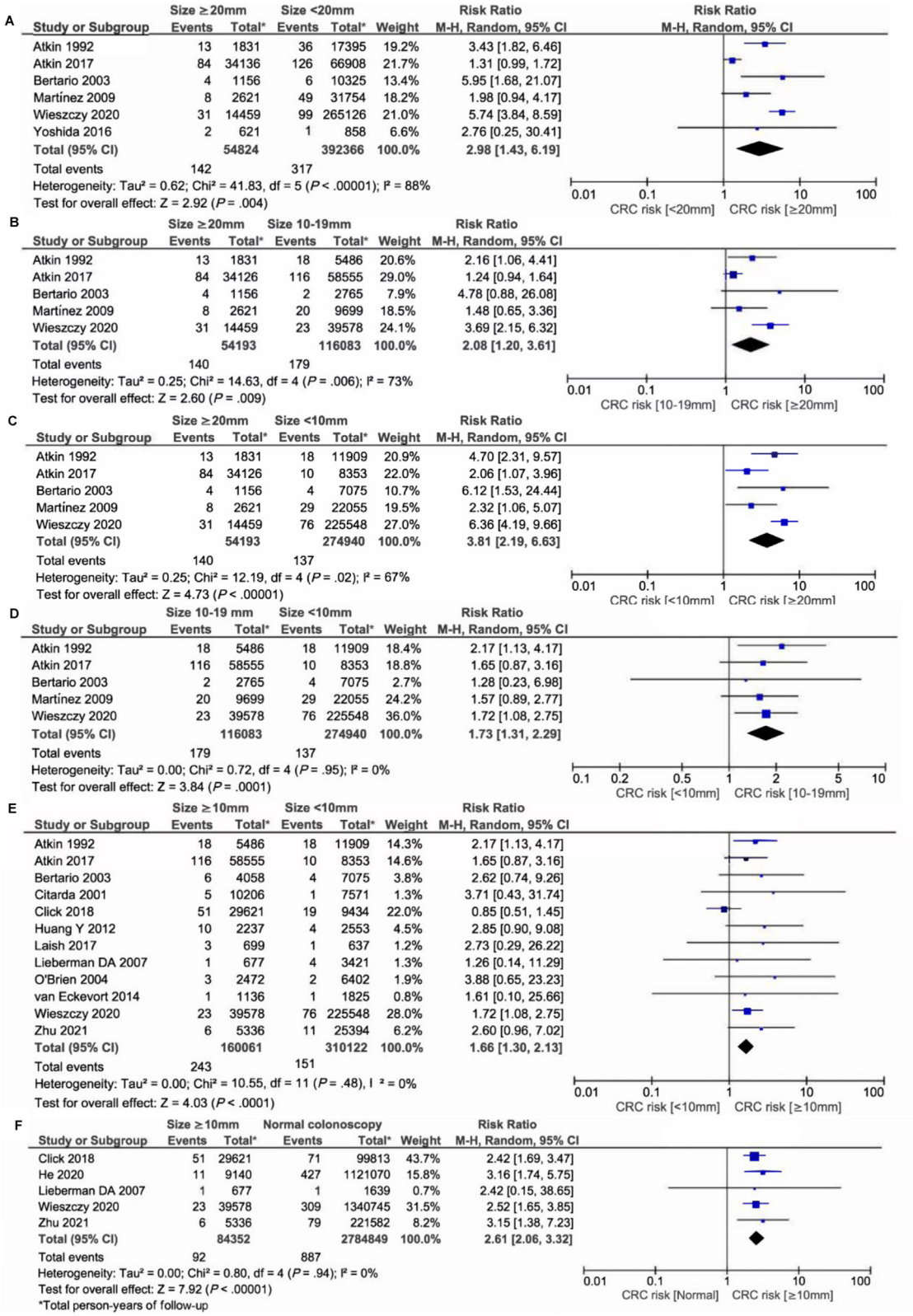
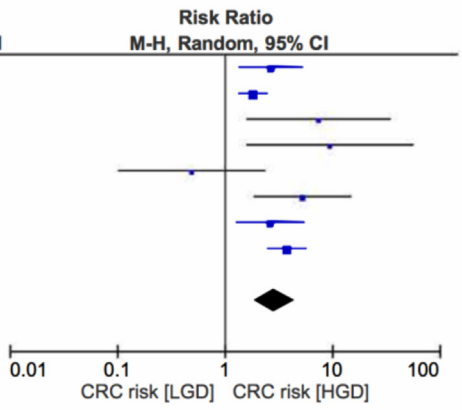


Figure 4. RR for CRC incidence in 1000 person-years comparing adenomas ≥20 mm with <20 mm (*A*); ≥20 mm with 10–19 mm (*B*); ≥20 mm with <10 mm (*C*); 10–19 mm with <10 mm (*D*); ≥10 mm with <10 mm (*E*); and ≥10 mm with normal colonoscopy (*F*).

A

Study or Subgroup	HGD Events	HGD Total*	LGD Events	LGD Total*	Weight	Risk Ratio M-H, Random, 95% CI
Atkin 1992	10	1672	39	17554	15.5%	2.69 [1.35, 5.38]
Atkin 2017	51	15849	139	79243	22.7%	1.83 [1.33, 2.53]
Bertario 2003	2	373	8	11020	5.9%	7.39 [1.57, 34.66]
Citarda 2001	3	2447	2	15330	4.7%	9.40 [1.57, 56.21]
Gimeno-García 2007	3	230	3	112	5.7%	0.49 [0.10, 2.37]
Huang Y 2012	7	769	7	4021	10.2%	5.23 [1.84, 14.86]
Martínez 2009	9	2664	32	25186	14.7%	2.66 [1.27, 5.56]
Wieszczy 2020	26	17293	104	262293	20.6%	3.79 [2.47, 5.83]
Total (95% CI)		**41297**		**414759**	**100.0%**	**2.89 [1.88, 4.44]**
Total events	111		334			

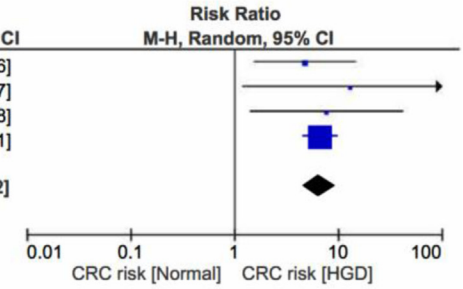
Heterogeneity: Tau² = 0.18; Chi² = 17.52, df = 7 (*P* = .01); I² = 60%
Test for overall effect: Z = 4.85 (*P* < .00001)
*Total person-years of follow-up



B

Study or Subgroup	HGD Events	HGD Total*	Normal colonoscopy Events	Normal colonoscopy Total*	Weight	Risk Ratio M-H, Random, 95% CI
He 2020	3	1660	427	1121070	10.3%	4.74 [1.53, 14.76]
Lieberman DA 2007	2	253	1	1639	2.3%	12.96 [1.18, 142.37]
Matsuda 2009	4	1575	2	6018	4.6%	7.64 [1.40, 41.68]
Wieszczy 2020	26	17293	309	1379608	82.8%	6.71 [4.50, 10.01]
Total (95% CI)		**20781**		**2508335**	**100.0%**	**6.62 [4.60, 9.52]**
Total events	35		739			

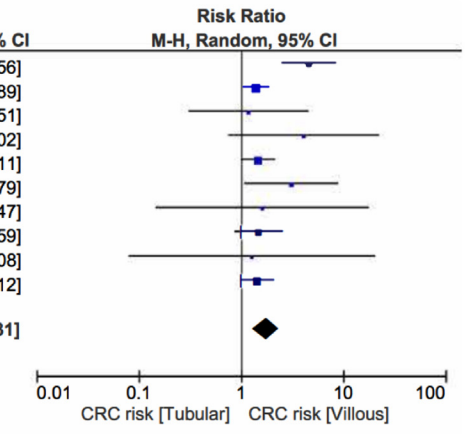
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 3 (*P* = .88); I² = 0%
Test for overall effect: Z = 10.18 (*P* < .00001)
*Total person-years of follow-up



C

Study or Subgroup	Villous component Events	Villous component Total*	Tubular adenoma Events	Tubular adenoma Total*	Weight	Risk Ratio M-H, Random, 95% CI
Atkin 1992	35	6763	14	12463	12.1%	4.61 [2.48, 8.56]
Atkin 2017	123	55456	64	40404	22.2%	1.40 [1.04, 1.89]
Bertario 2003	3	2984	7	8122	3.7%	1.17 [0.30, 4.51]
Citarda 2001	4	5891	2	11886	2.5%	4.04 [0.74, 22.02]
Coleman 2015	97	21508	36	11524	19.2%	1.44 [0.99, 2.11]
Huang Y 2012	8	1455	6	3335	5.6%	3.06 [1.06, 8.79]
Laish 2017	1	637	2	2021	1.3%	1.59 [0.14, 17.47]
Martínez 2009	17	7406	44	28345	13.6%	1.48 [0.85, 2.59]
van Eckevort 2014	1	1321	1	1661	1.0%	1.26 [0.08, 20.08]
Wieszczy 2020	34	55419	96	224166	18.9%	1.43 [0.97, 2.12]
Total (95% CI)		**158840**		**343927**	**100.0%**	**1.75 [1.33, 2.31]**
Total events	323		272			

Heterogeneity: Tau² = 0.07; Chi² = 15.44, df = 9 (*P* = .08); I² = 42%
Test for overall effect: Z = 3.96 (*P* < .0001)
*Total person-years of follow-up



D

Study or Subgroup	Villous component Events	Villous component Total*	Normal colonoscopy Events	Normal colonoscopy Total*	Weight	Risk Ratio M-H, Random, 95% CI
He 2020	25	13730	427	1121070	46.6%	4.78 [3.20, 7.15]
Lieberman DA 2007	1	446	1	1639	2.8%	3.67 [0.23, 58.64]
Wieszczy 2020	34	55419	309	1379608	50.6%	2.74 [1.92, 3.90]
Total (95% CI)		**69595**		**2502317**	**100.0%**	**3.58 [2.24, 5.73]**
Total events	60		737			

Heterogeneity: Tau² = 0.08; Chi² = 4.22, df = 2 (*P* = .12); I² = 53%
Test for overall effect: Z = 5.32 (*P* < .00001)
*Total person-years of follow-up

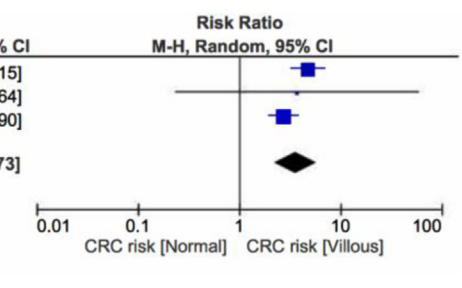


Figure 5. RR for CRC incidence in 1000 person-years in patients with adenomas with HGD compared with adenomas with LGD (*A*) and normal colonoscopy (*B*). RR for CRC incidence in 1000 person-years in patients with villous/tubulo-villous adenomas compared with tubular adenomas (*C*) and normal colonoscopy (*D*).

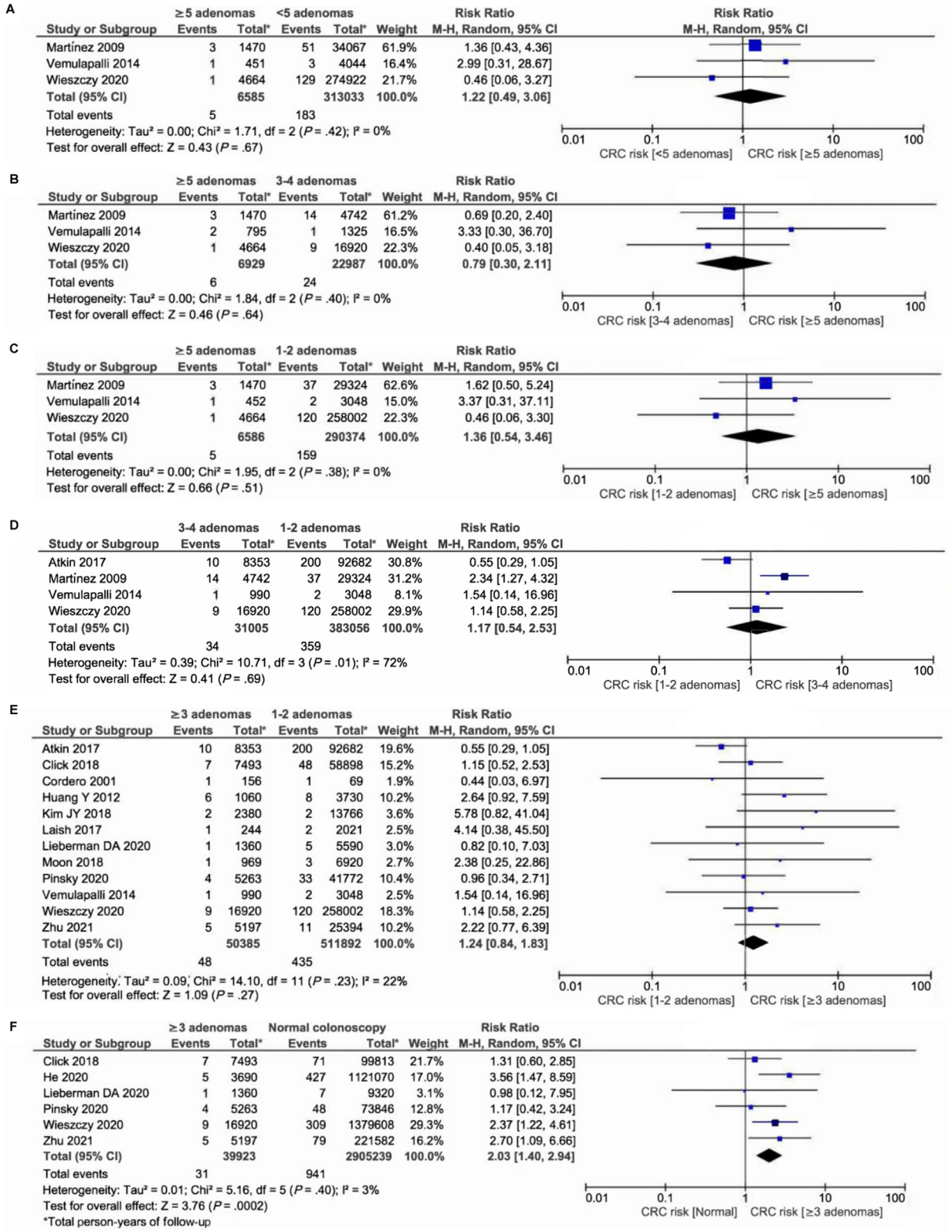


Figure 6. RR for CRC incidence in 1000 person-years comparing ≥5 adenomas with <5 adenomas (*A*); ≥5 adenomas with 3–4 adenomas (*B*); ≥5 adenomas with <3 adenomas (*C*); 3–4 adenomas with <3 adenomas (*D*); ≥3 adenomas with <3 adenomas (*E*); ≥3 adenomas with normal colonoscopy (*F*).

patients with ≥3 adenomas with respect to <3 adenomas (RR, 1.24; 95% CI, 0.84–1.83; I^2 = 22%); However we did find a significant increase in CRC risk when comparing patients with ≥3 adenomas vs normal colonoscopy (RR, 2.03; 95% CI, 1.40–2.94) (Figure 6). The risk for metachronous AA was higher in patients with ≥5 adenomas compared with <5 adenomas (RR, 2.89; 95% CI, 1.44–5.77; I^2 = 0%), and in ≥3 adenomas compared with 1 to 2 adenomas (RR, 2.26; 95% CI, 1.70–3.02; I^2 = 75%) (Supplementary Figure 6).

Sensitivity Analysis

In studies that included a colonoscopy quality assessment (Supplementary Figures 7–10) and in studies with a follow-up time longer than 5 years (mean follow-up time, 8.5 ± 2.1 years) (Supplementary Figures 11–14) patients with HRA, adenomas ≥10 mm, HGD, or villous component continued having significantly higher CRC risk compared with patients with NAA, whereas multiplicity only increased the risk when comparing ≥3 adenomas vs normal colonoscopy.

Finally, in studies with patient enrolment from 2005 onwards, patients with HRA or adenomas ≥10 mm had a significantly higher CRC risk compared with patients with NAA. However, villous component did not seem to significantly increase CRC risk compared with tubular adenomas (RR, 1.44; 95% CI, 0.98–2.11; I^2 = 0%). (Supplementary Figures 15–18).

Discussion

This systematic review and meta-analysis synthesizes all the available evidence on which high-risk adenoma characteristics at baseline colonoscopy best predict the risk of metachronous CRC or AA, in an attempt to provide evidence to help standardize post-polypectomy surveillance. Our results suggest that patients with baseline adenomas ≥20 mm or HGD have the highest risk of metachronous CRC or AA, whereas patients with adenomas ≥10 mm or villous component have also a significant increase of CRC risk. However, according to our results, multiplicity is not convincingly associated with a higher CRC risk over a mean follow-up period of 5.4 years.

Recent individual studies have highlighted specific risk features of adenomas for the development of CRC, such as size ≥20 mm or HGD.[17,18] Our pooled results suggest that these features confer the highest risk for CRC incidence (approximately 3-fold risk when compared with NAA). Adenoma size of 10 to 19 mm vs <10 mm was associated with a 1.7-fold higher risk of subsequent CRC. Although the evidence is growing that a larger adenoma size is a powerful predictor of metachronous CRC risk, polyp size is not measured precisely by endoscopists,[74] and size at pathology may not reflect in vivo size. Therefore, more studies are needed to address what adenoma size cutoff identifies high enough risk of metachronous CRC to warrant surveillance.

Our results suggest that villous histology confers an increased risk of CRC. The level of risk associated with a villous component has been controversial, with studies supporting villous component as a risk factor,[75-77] but large recent publications reporting opposing evidence[17,18]; the latter forming the basis for the new recommendations of the European Society of Gastrointestinal Endoscopy guidelines.[12] Because villous histology has a high inter-observer variability, uncertainties remain. Consequently, more studies are needed to assess the independent risk of CRC conferred by villous histology in small adenomas without HGD.

With the arrival of high-definition colonoscopy, detection of multiple polyps is increasingly common, and it may become even more common with the incorporation of artificial intelligence detection systems. Three new large studies have addressed the role of adenoma multiplicity on post-polypectomy CRC risk, showing that the number of NAA was not associated with a higher risk of CRC incidence or mortality compared with patients with normal colonoscopy[30] or with the general population.[17,18] Also, a recent systematic review and meta-analysis shows that patients with 3 to 4 NAA or ≥3 NAA have a significatively higher risk of metachronous advanced neoplasia than patients with 1 to 2 NAA, without finding statistically significant differences in metachronous CRC risk.[78] Similarly, our pooled estimates reflect a significantly elevated risk of metachronous AA but not a convincingly increased risk of CRC after removal of multiple adenomas. The role of surveillance is to reduce CRC incidence and mortality,[19] not only to detect AA. Therefore, the associations between the number of small adenomas and varying risks of future CRC and AA should inform indications for surveillance. However, given that some of our analysis may be underpowered with a low number of events, RR for CRC were above 1 for multiple categories, mean follow-up in the pooled studies was only 5.4 years, and the significant association between multiplicity and metachronous AA risk, it remains possible that adenoma multiplicity may be associated with a substantially higher metachronous CRC risk in the intermediate long term (eg, 5–10 years).

Our meta-analysis highlights that even with adenoma removal in a high-quality colonoscopy setting and subsequent endoscopic surveillance, patients with high-risk adenomas remain at increased risk for metachronous CRC and CRC mortality. These results are in line with a recent meta-analysis by Duvvuri et al,[79] who reported an almost 3-fold increase in risk for CRC and CRC mortality in patients with baseline HRA compared with those with normal colonoscopy. Does this represent a failure to reduce CRC risk in this high-risk population? Or would the risk have been substantially higher without intervention? Previous retrospective studies[17,30,80] have suggested that surveillance significantly reduces the risk of CRC in this population, even achieving risk levels

comparable to those of the general population in specific subgroups. However, their observational design, with a possible selection bias in who underwent surveillance, prevents us from proving a causal association between surveillance and CRC incidence reduction. Our estimates reflect a relatively high NNS to detect 1 additional CRC when compared with people with normal colonoscopy or NAA at baseline. However, NNS for detecting additional AA are substantially lower. These results are relevant to establish the true yield and benefit of surveillance, with the best scenario in terms of CRC prevention being a program resulting in low CRC incidence, combined with high AA detection and removal.[19] Our results on incidence of CRC, RR, and NNS can inform the role of surveillance for specific baseline adenoma characteristics.

Our meta-analysis has several strengths. We focused on specific high-risk characteristics to establish which ones substantially increase metachronous CRC incidence, expanding on the results of a recently published meta-analysis[79] by analyzing the risk added by each specific adenoma risk attribute. Our data and nomenclature are in line with recent recommendations for studies about surveillance.[19] Our expansive search aimed to cover all available evidence, resulting in pooled data from more than 900,000 patients with a mean follow-up of 5.4 years. We focused on clinically relevant outcomes, including CRC incidence or CRC mortality. We extracted raw data from each study, used person-years of follow-up for our analysis, and assured comparable adenoma nomenclature and study groups. Finally, we have included risk analysis of metachronous CRC and AA, showing the bidirectionality of both endpoints for some risk factors.

Our study has limitations. First, most available studies are observational studies, 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. 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. This is particularly important in adenomas $\geq$20 mm, where incomplete resection and local recurrence is known to be more frequent, and therefore. it would have been interesting to know if post-polypectomy surveillance was adequately performed. For some analyses, especially those addressing CRC mortality or comparing with normal colonoscopy, there were few available studies. Also, we were unable to account for correlation between different risk factors, to assess the isolated effect of each feature independently of the others, or to quantify the impact in risk of having multiple risk characteristics. 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. Finally, we did not consider clinical characteristics of the patient such as age or obesity that have proven to be risk factors for metachronous lesions,[81] nor emerging factors that might inform surveillance recommendations in the future, including quality indicators of the endoscopists[82] or molecular markers as predictors of risk.[83]

In summary, our results show that metachronous CRC risk is the highest in patients with baseline adenomas of size $\geq$20 mm or HGD and also significantly high for adenomas of $\geq$10 mm or with a villous component. This supports an indication for surveillance in these patients. On the other hand, multiplicity does not seem to be associated with a substantially elevated CRC risk over the next 5 years, making it possible that patients with multiple NAA may not benefit from near-term endoscopic surveillance. More studies are required to evaluate the optimal cutoff in adenoma size requiring surveillance (eg, 10 vs 20 mm threshold), the isolated effect of each risk feature independently of the others (for instance, the independent risk conferred by a villous component in small adenomas), the optimal management of patients with a large number of NAA, and whether surveillance intervals should differ by specific high-risk feature. Our results can inform guidelines and clinical decisions on which baseline adenoma characteristics are associated with elevated risks of metachronous CRC and AA, thus warranting surveillance.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.12.005.

References

1. World Health Organization. Globocan. Accessed May 30, 2021. Available at: www.globocan.iacr.fr.
2. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–1981.
3. Nagtegaal I, Odze R, Klimstra D, et al. WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020; 76:182–188.
4. Mangas-Sanjuan C, Jover R, Cubiella J, et al. Endoscopic surveillance after colonic polyps and colorrectal cancer resection. 2018 update. Gastroenterol Hepatol 2019;42:188–201.
5. Nusko G, Mansmann U, Kirchner T, et al. Risk related surveillance following colorectal polypectomy. Gut 2002;51:424–428.
6. Noshirwani KC, van Stolk RU, Rybicki LA, et al. Adenoma size and number are predictive of adenoma recurrence: implications for surveillance colonoscopy. Gastrointest Endosc 2000; 51:433–437.
7. van Stolk RU, Beck GJ, Baron JA, et al. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. The Polyp Prevention Study Group. Gastroenterology 1998;115:13–18.

8. Martinez ME, Sampliner R, Marshall JR, et al. Adenoma characteristics as risk factors for recurrence of advanced adenomas. Gastroenterology 2001;120:1077–1083.
9. Hassan C, Quintero E, Dumonceau JM, et al. European Society of Gastrointestinal Endoscopy. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842–851.
10. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020;158:1131–1153.e5.
11. Atkin WS, Valori R, Kuipers EJ, et al; International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Colonoscopic surveillance following adenoma removal. Endoscopy 2012;44(Suppl 3):SE151–SE163.
12. Hassan C, Antonelli G, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2020. Endoscopy 2020; 52:687–700.
13. Rutter MD, East J, Rees CJ, et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. Gut 2020; 69:201–223.
14. Lieberman DA, Holub J, Eisen G, et al. Utilization of colonoscopy in the United States: results from a national consortium. Gastrointest Endosc 2005;62:875–883.
15. Mangas-Sanjuan C, Santana E, Cubiella J, et al. , QUALISCOPIA Study Investigators. Variation in colonoscopy performance measures according to procedure indication. Clin Gastroenterol Hepatol 2020;18:1216–1223.e2.
16. Jover R, Bretthauer M, Dekker E, et al. Rationale and design of the European Polyp Surveillance (EPoS) trials. Endoscopy 2016; 48:571–578.
17. Atkin W, Wooldrage K, Brenner A, et al. Adenoma surveillance and colorectal cancer incidence: a retrospective, multicentre, cohort study. Lancet Oncol 2017;18:823–834.
18. Wieszczy P, Kaminski MF, Franczyk R, et al. Colorectal cancer incidence and mortality after removal of adenomas during screening colonoscopies. Gastroenterology 2020;158:875–883.e5.
19. Rutter MD, Bretthauer M, Hassan C, et al. WEO Surveillance Working Group. Principles for evaluation of surveillance after removal of colorectal polyps: recommendations from the World Endoscopy Organization. Gastroenterology 2020; 158:1529–1533.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
21. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med 2013; 158:280–286.
22. Anderson JC, Butterly LF, Robinson CM, et al. Risk of metachronous high-risk adenomas and large serrated polyps in individuals with serrated polyps on index colonoscopy: data from the New Hampshire Colonoscopy Registry. Gastroenterology 2018;154:117–127.e2.
23. Atkin W, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658–662.
24. Baik SJ, Park H, Park JJ, et al. Advanced colonic neoplasia at follow-up colonoscopy according to risk components and adenoma location at index colonoscopy: a retrospective study of 1,974 asymptomatic Koreans. Gut Liver 2017;11:667–673.
25. Bertario L, Russo A, Sala P, et al. Predictors of metachronous colorectal neoplasms in sporadic adenoma patients. Int J Cancer 2003;105:82–87.
26. Bjerrum A, Milter MC, Andersen O, et al. Risk stratification and detection of new colorectal neoplasms after colorectal cancer screening with faecal occult blood test: experiences from a Danish screening cohort. Eur J Gastroenterol Hepatol 2015; 27:1433–1437.
27. Bonithon-Kopp C, Piard F, Fenger C, et al; European Cancer Prevention Organisation Study Group. Colorectal adenoma characteristics, as predictors of recurrence. Dis Colon Rectum 2004;47:323–333.
28. Chung SJ, Kim YS, Yang SY, et al. Five-year risk for advanced colorectal neoplasia after initial colonoscopy according to the baseline risk stratification: a prospective study in 2452 asymptomatic Koreans. Gut 2011;60:1537–1543.
29. Citarda F, Tomaselli G, Capocaccia R, et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48(6):812–815.
30. Click B, Pinsky PF, Hickey T, et al. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. JAMA 2018;319:2021–2031.
31. Coleman HG, Loughrey MB, Murray LJ, et al. Colorectal cancer risk following adenoma removal: A large prospective population-based cohort study. Cancer Epidemiol Biomarkers Prev 2015; 24:1373–1380.
32. Cordero C, Leo E, Cayuela A, et al. Utilidad de la colonoscopia precoz para el tratamiento de adenomas que pasan desapercibidos en la primera exploración. Rev Esp Enferm Dig 2001; 93:519–523.
33. Cottet V, Jooste V, Fournel I, et al. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. Gut 2012;61:1180–1186.
34. Couso LM, Lubrano P, Castelluccio S, et al. Polipectomía endoscópica de adenomas colorrectales: seguimiento de los pacientes con el objeto de evaluar el intervalo entre las videocolonoscopías de control. Acta Gastroenterol Latinoam 2014; 44:216–222.
35. Gimeno-García AZ, Ramírez F, Gonzalo V, et al. Displasia de alto grado como factor de riesgo de neoplasia colorrectal avanzada metacrónica, en pacientes con adenomas avanzados. Gastroenterol Hepatol 2007;30:207–211.
36. He X, Hang D, Wu K, et al. Long-term risk of colorectal cancer after removal of conventional adenomas and serrated polyps. Gastroenterology 2020;158:852–861.e4.
37. Holme Ø, Bretthauer M, Eide TJ, et al. Long-term risk of colorectal cancer in individuals with serrated polyps. Gut 2015; 64:929–936.
38. Huang Y, Gong W, Su B, et al. Risk and cause of interval colorectal cancer after colonoscopic polypectomy. Digestion 2012;86:148–154.
39. Huang Y, Gong W, Su B, et al. Recurrence and surveillance of colorectal adenoma after polypectomy in a southern Chinese population. J Gastroenterol 2010;45:838–845.
40. Jang HW, Park SJ, Hong SP, et al. Risk factors for recurrent high-risk polyps after the removal of high-risk polyps at initial colonoscopy. Yonsei Med J 2015;56:1559–1565.

41. Kim JY, Kim TJ, Baek SY, et al. Risk of metachronous advanced neoplasia in patients with multiple diminutive adenomas. Am J Gastroenterol 2018;113:1855–1861.
42. Kim NH, Jung YS, Park JH, et al. Risk of developing metachronous advanced colorectal neoplasia after resection of low-risk diminutive versus small adenomas. Gastrointest Endosc 2019;91:622–630.
43. Laish I, Seregeev I, Naftali T, et al. Surveillance after positive colonoscopy based on adenoma characteristics. Dig Liver Dis 2017;49:1115–1120.
44. Laiyemo AO, Murphy G, Albert PS, et al. Postpolypectomy colonoscopy surveillance guidelines: Predictive accuracy for advanced adenoma at 4 years. Ann Intern Med 2008; 148:419–426.
45. Lee JK, Jensen CD, Levin TR, et al. Long-term risk of colorectal cancer and related death after adenoma removal in a large, community-based population. Gastroenterology 2020; 158:884–894.e5.
46. Lee SM, Kim JH, Sung IK, et al. The risk of metachronous advanced colorectal neoplasia rises in parallel with an increasing number of high-risk findings at baseline. Gut Liver 2015;9:741–749.
47. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133:1077–1085.
48. Lieberman D, Sullivan BA, Hauser ER, et al. Baseline colonoscopy findings associated with 10-year outcomes in a screening cohort undergoing colonoscopy surveillance. Gastroenterology 2020;158:862–874.e8.
49. Lorenzo-Zúñiga V, Moreno De Vega V, Domènech E, et al. High-definition colonoscopy and risk factors for recurrence of advanced adenomas in patients with a personal history of polyps. Eur J Gastroenterol Hepatol 2011;23:425–430.
50. Macaron C, Vu HT, Lopez R, et al. Risk of metachronous polyps in individuals with serrated polyps. Dis Colon Rectum 2015; 58:762–768.
51. Martínez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009;136:832–841.
52. Matsuda T, Fujii T, Sano Y, et al. Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol 2009; 39:435–442.
53. Moon CM, Jung SA, Eun CS, et al. The effect of small or diminutive adenomas at baseline colonoscopy on the risk of developing metachronous advanced colorectal neoplasia: KASID multicenter study. Dig Liver Dis 2018; 50:847–852.
54. O'Brien MJ, Winawer SJ, Zauber AG, et al; National Polyp Study Workgroup. Flat adenomas in the National Polyp Study: is there increased risk for high-grade dysplasia initially or during surveillance? Clin Gastroenterol Hepatol 2004;2:905–911.
55. Park SK, Song YS, Jung YS, et al. Do surveillance intervals in patients with more than five adenomas at index colonoscopy be shorter than those in patients with three to four adenomas? A Korean Association for the Study of Intestinal Disease study. J Gastroenterol Hepatol 2017;32:1026–1031.
56. Pereyra L, Zamora R, Gómez EJ, et al. Risk of metachronous advanced neoplastic lesions in patients with sporadic sessile serrated adenomas undergoing colonoscopic surveillance. Am J Gastroenterol 2016;111:871–878.
57. Pinsky PF, Schoen RE, Weissfeld JL, et al. The yield of surveillance colonoscopy by adenoma history and time to examination. Clin Gastroenterol Hepatol 2009;7:86–92.
58. Pohl H, Robertson DJ, Mott LA, et al. Association between adenoma location and risk of recurrence. Gastrointest Endosc 2016;84:709–716.
59. Ren J, Kirkness CS, Kim M, et al. Long-term risk of colorectal cancer by gender after positive colonoscopy: population-based cohort study. Curr Med Res Opin 2016;32:1367–1374.
60. Stock C, Hoffmeister M, Birkner B, et al. Performance of additional colonoscopies and yield of neoplasms within 3 years after screening colonoscopy: a historical cohort study. Endoscopy 2013;45:537–546.
61. Symonds E, Anwar S, Young G, et al. Sessile serrated polyps with synchronous conventional adenomas increase risk of future advanced neoplasia. Dig Dis Sci 2019;64:1680–1685.
62. Symonds EL, Cole SR, Lau SY, et al. The significance of the small adenoma: a longitudinal study of surveillance colonoscopy in an Australian population. Eur J Gastroenterol Hepatol 2019;31:563–569.
63. Tae CH, Moon CM, Kim SE, et al. Risk factors of nonadherence to colonoscopy surveillance after polypectomy and its impact on clinical outcomes: a KASID multicenter study. J Gastroenterol 2017;52:809–817.
64. van Enckevort CCG, de Graaf APJ, Hollema H, et al. Predictors of colorectal neoplasia after polypectomy: based on initial and consecutive findings. Neth J Med 2014;72:139–145.
65. Vemulapalli KC, Rex DK. Risk of advanced lesions at first follow-up colonoscopy in high-risk groups as defined by the United Kingdom post-polypectomy surveillance guideline: data from a single U.S. Center. Gastrointest Endosc 2014;80:299–306.
66. Yoshida N, Naito Y, Siah KTH, et al. High incidence of metachronous advanced adenoma and cancer after endoscopic resection of colon polyps ≥20 mm in size. Dig Endosc 2016; 28:194–202.
67. Chang J, Chien CH, Chen SW, et al. Long term outcomes of colon polyps with high grade dysplasia following endoscopic resection. BMC Gastroenterol 2020;20:376.
68. Park SK, Yang HJ, Jung YS, et al. Risk of advanced colorectal neoplasm by the proposed combined United States and United Kingdom risk stratification guidelines. Gastrointest Endosc 2018;87:800–808.
69. Pinsky PF, Schoen RE. Contribution of surveillance colonoscopy to colorectal cancer prevention. Clin Gastroenterol Hepatol 2020;18:2937–2944.
70. Shono T, Oyama S, Oda Y, et al; Kumamoto Colon Cancer Study Group. Risk stratification of advanced colorectal neoplasia after baseline colonoscopy: cohort study of 17 Japanese community practices. Dig Endosc 2020;32:106–113.
71. Waldmann E, Kammerlander A, Gessl I, et al. Association of adenoma detection rate and adenoma characteristics with colorectal cancer mortality after screening colonoscopy. Clin Gastroenterol Hepatol 2021;19:1890–1898.
72. Zhang Q, Shen Y, Xu J, et al. Clear colonoscopy as a surveillance tool in the prediction and reduction of advanced neoplasms: a randomized controlled trial. Surg Endosc 2021; 35:4501–4510.
73. Zhu Y, Huang Y, Hu Y, et al. Long-term risk of colorectal cancer after removal of adenomas during screening colonoscopies in a large community-based population in China. Int J Cancer 2022; 150:594–602.

74. Chaptini L, Chaaya A, Depalma F, et al. Variation in polyp size estimation among endoscopist and impact on surveillance intervals. Gastrointest Endosc 2014;80:652–659.
75. Good NM, Macrae FA, Young GP, et al. Ideal colonoscopic surveillance intervals to reduce incidence of advanced adenoma and colorectal cancer. J Gastroenterol Hepatol 2015; 30:1147–1154.
76. Van Heijningen EM, Lansdorp-Vogelaar I, Kuipers EJ, et al. Features of adenoma and colonoscopy associated with recurrent colorectal neoplasia based on a large community-based study. Gastroenterology 2013;144:1410–1418.
77. Fairley KJ, Li J, Komar M, et al. Predicting the risk of recurrent adenoma and incident colorectal cancer based on findings of the baseline colonoscopy. Clin Transl Gastroenterol 2014;5:e64.
78. Park S, Jeon SR, Kim HG, et al. Risk of metachronous colorectal advanced neoplasia and cancer in patients with 3-4 non-advanced adenomas at index colonoscopy: a systematic review and meta-analysis. Am J Gastroenterol 2022;117:588–602.
79. Duvvuri A, Chandrasekar VT, Srinivasan S, et al. Risk of colorectal cancer and cancer related mortality after detection of low-risk or high-risk adenomas, compared with no adenoma, at index colonoscopy: a systematic review and meta-analysis. Gastroenterology 2021;160:1986–1996.e3.
80. Cross A, Robbins AJ, Pack K, et al. Long-term colorectal cancer incidence after adenoma removal and the effects of surveillance on incidence: a multicentre, retrospective, cohort study. Gut 2020;69:1645–1658.
81. Park CH, Jung YS, Kim NH, et al. Optimization of the surveillance strategy in patients with colorectal adenomas: a combination of clinical parameters and index colonoscopy findings. J Gastroenterol Hepatol 2021;36:974–982.
82. Mangas-Sanjuan C, Zapater P, Cubiella J, et al. COLONPREV study investigators. Importance of endoscopist quality-metrics for findings at surveillance colonoscopy: the detection-surveillance paradox. United European Gaastroenterol J 2018;6:622–629.
83. Murcia O, Martínez-Roca A, Juárez M, et al. Effect of somatic methylation in colonic polyps on risk of developing metachronous advanced colorectal lesions. Cancers (Basel) 2021;13:246.

Correspondence:
Dr Rodrigo Jover Martínez, Servicio de Medicina Digestiva, Hospital General Universitario Dr Balmis, C/ Pintor Baeza, 12, 03010, Alicante, Spain; e-mail: rodrigojover@gmail.com; tel: +34 965933468.

Acknowledgments
The authors thank and acknowledge Mrs Carmen Sánchez-Ardila for optimizing their literature search.

CRediT Authorship Contributions

Sandra Baile-Maxía (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Project administration: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

Carolina Mangas Sanjuán (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – review & editing: Supporting)

Uri Ladabaum (Conceptualization: Equal; Methodology: Equal; Supervision: Equal; Writing – review & editing: Equal)

Cesare Hassan (Conceptualization: Equal; Methodology: Equal; Supervision: Supporting; Writing – review & editing: Equal)

Matthew D Rutter (Conceptualization: Supporting; Methodology: Supporting; Supervision: Supporting; Writing – review & editing: Equal)

Michael Bretthauer (Conceptualization: Supporting; Methodology: Supporting; Supervision: Supporting; Writing – review & editing: Equal)

Lucía Medina Prado (Conceptualization: Supporting; Data curation: Supporting; Writing – review & editing: Supporting)

Noelia Sala Miquel (Conceptualization: Supporting; Data curation: Supporting; Writing – review & editing: Supporting)

Óscar Murcia Pomares (Conceptualization: Supporting; Data curation: Supporting; Funding acquisition: Equal; Writing – review & editing: Supporting)

Pedro Zapater (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Equal)

Rodrigo Jover (Conceptualization: Lead; Methodology: Lead; Supervision: Lead; Writing – review & editing: Equal)

Conflicts of interest
These authors disclose the following: Rodrigo Jover has received research grants from MSD, and has participated as an advisor to MSD, Norgine, Alpha-Sigma, and GISupply. Matthew D. Rutter has no conflicts of interest since start of 2020 (Advisor for Norgine in 2019). The remaining authors disclose no conflicts.

Funding
This work was supported by the Instituto de Salud Carlos III (PI17/01756, PI20/01527), Fundación de Investigación Biomédica de la Comunidad Valenciana–Instituto de Investigación Sanitaria y Biomédica de Alicante Foundation (UGP-190276). Oscar Murcia received a Rio-Hortega grant from the Instituto de Salud Carlos III (CM18/00058). Asociación para la Investigación en Gastroenterología de la Provincia de Alicante (AIGPA), a private association that promotes research in gastrointestinal diseases in Alicante, also supported the logistical aspects of the study, but declares no conflict of interest.