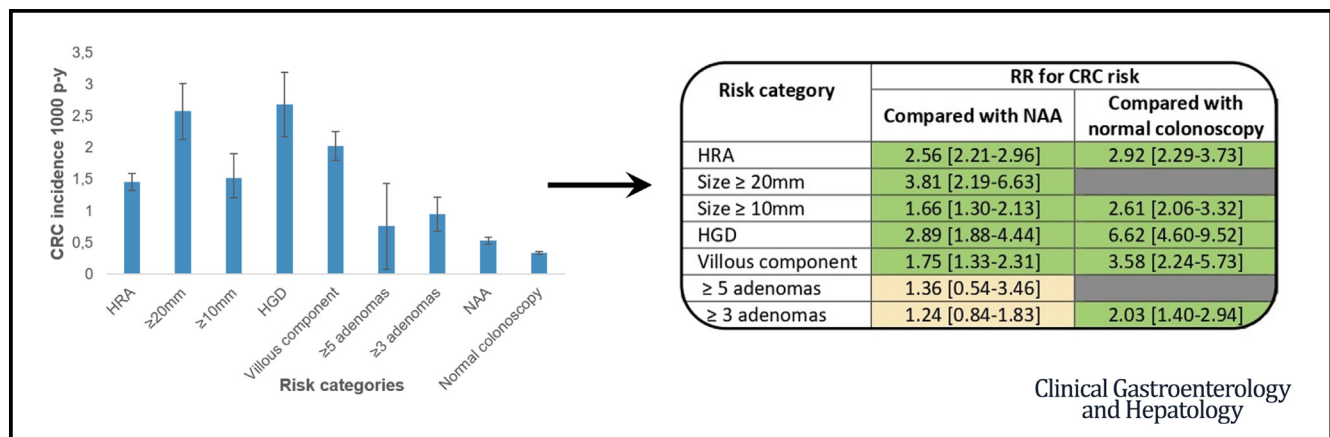


Risk Factors for Metachronous Colorectal Cancer or Advanced Adenomas After Endoscopic Resection of High-risk Adenomas



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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.

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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 ≥ 10 mm, 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 $\geq 25\%$ 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

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.

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}

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.

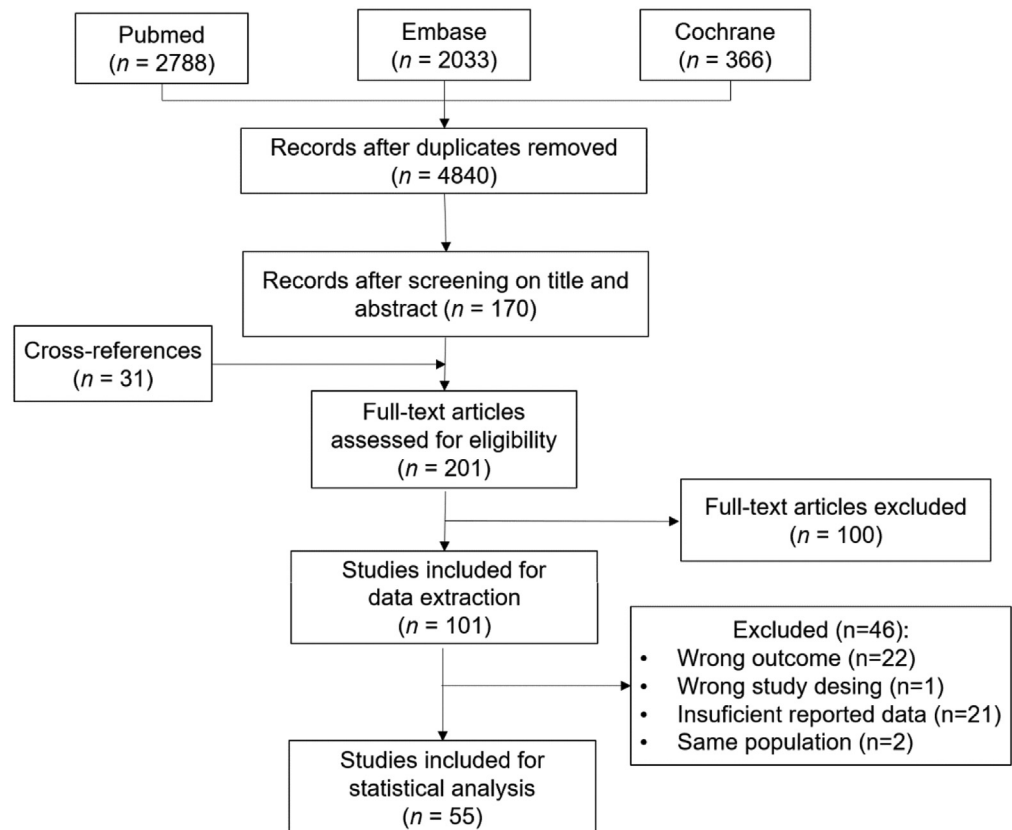


Figure 1. Flow diagram of study selection.

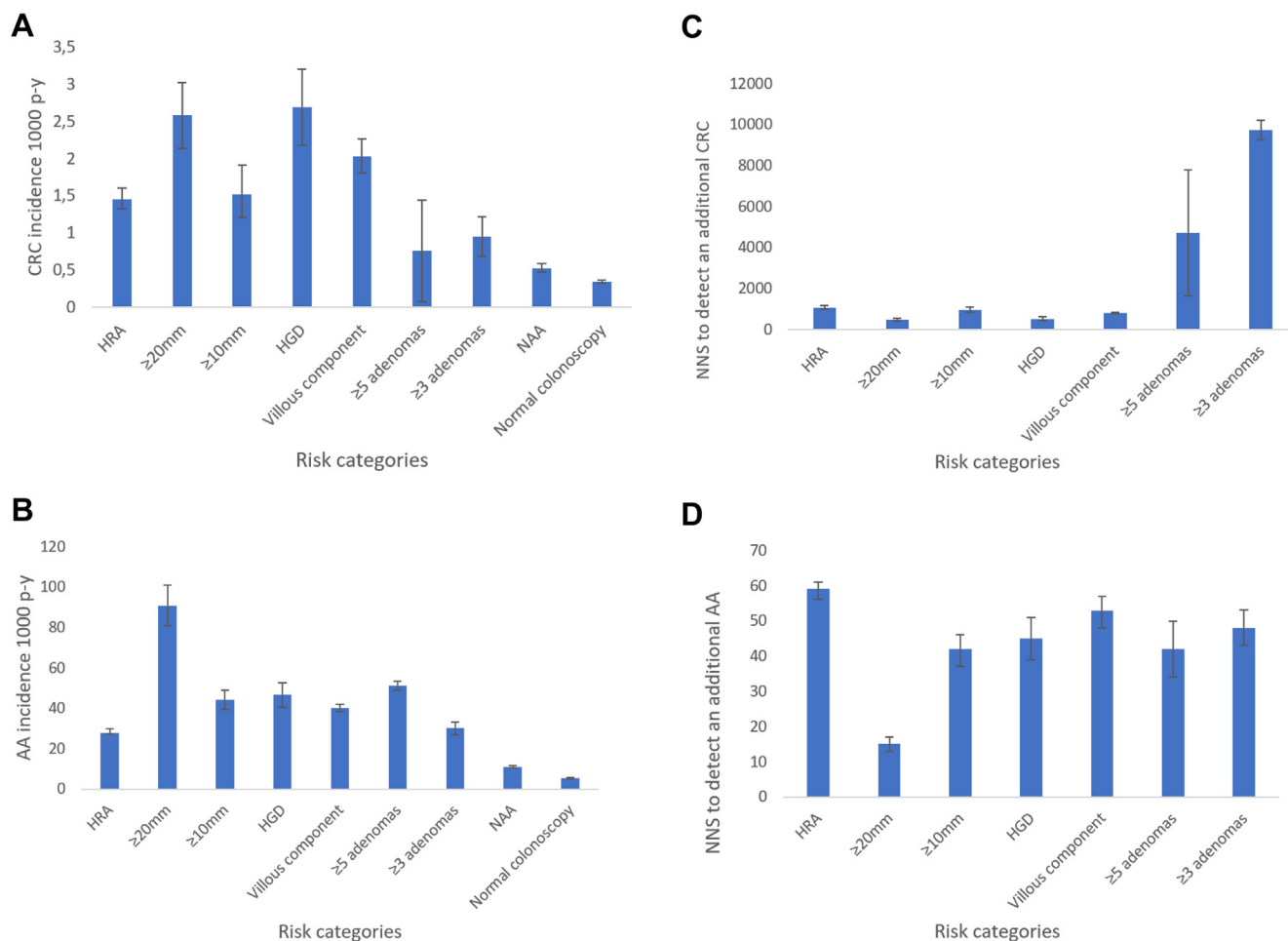


Figure 2. CRC (A) and AA (B) incidence per 1000 person-years in each high-risk category and in the population with NAA and normal colonoscopy. NNS to detect one additional CRC (C) or AA (D) for each HRA characteristic compared with NAA.

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.

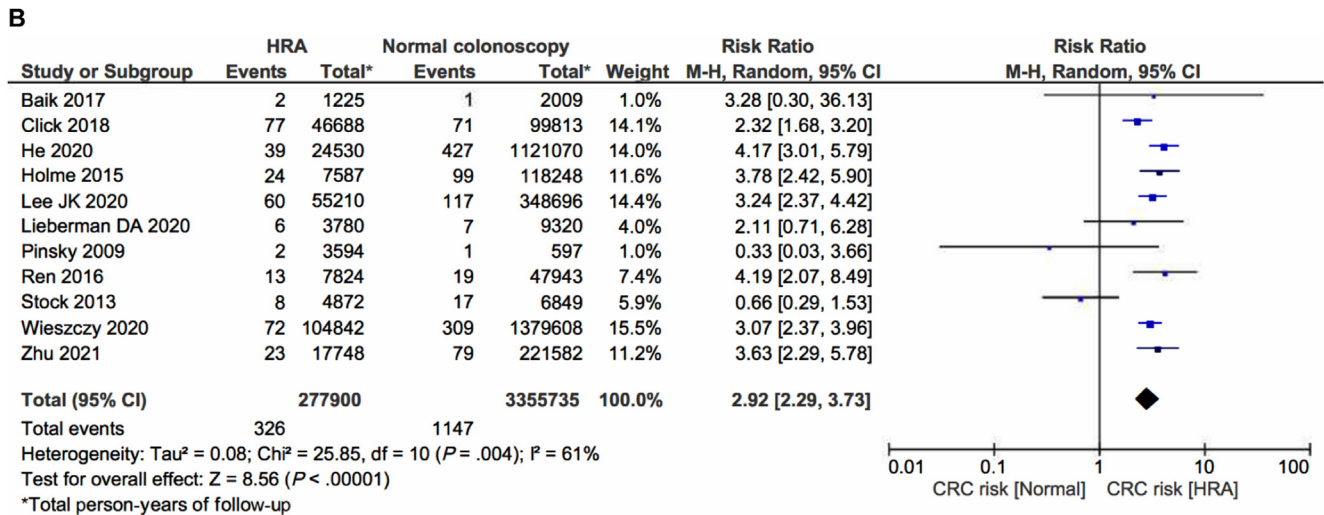
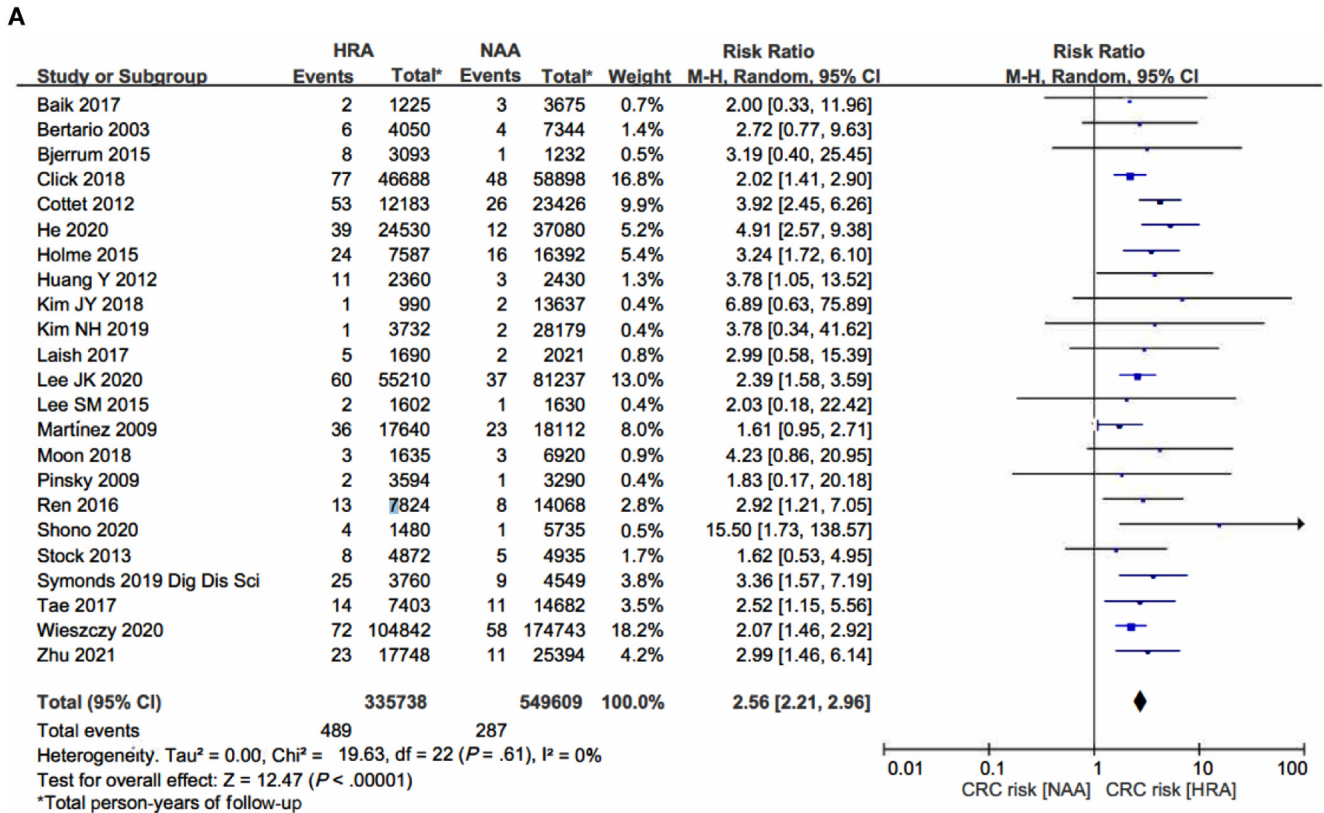


Figure 3. RR for CRC incidence in 1000 person-years in the HRA group compared with the NAA group (A) and the normal colonoscopy group (B).

Seventeen studies stratified the risk of metachronous 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; I² = 42%) compared with tubular adenomas, and 3.58 (95% CI, 2.24–5.73; I² = 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; I² = 0%); nor in

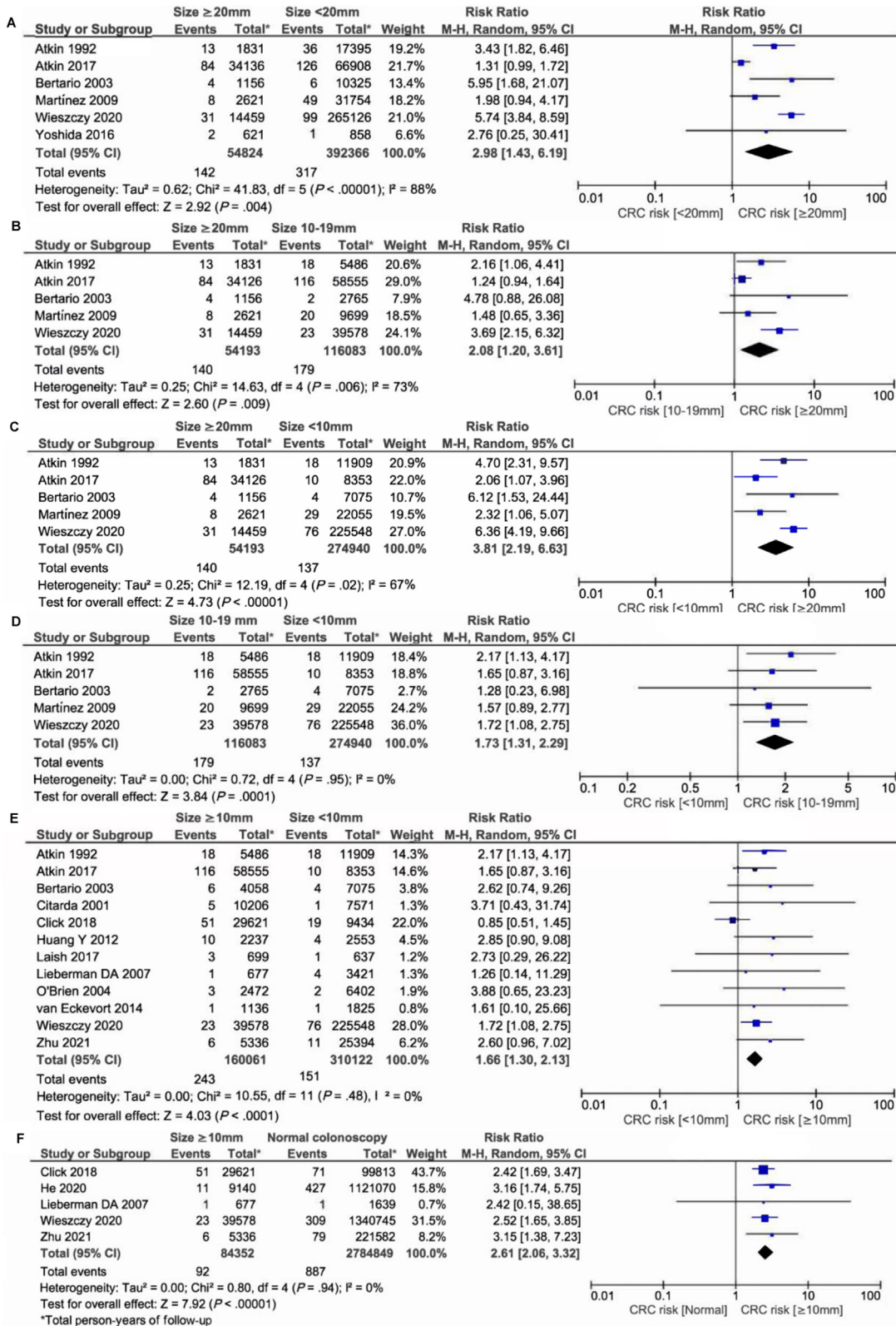
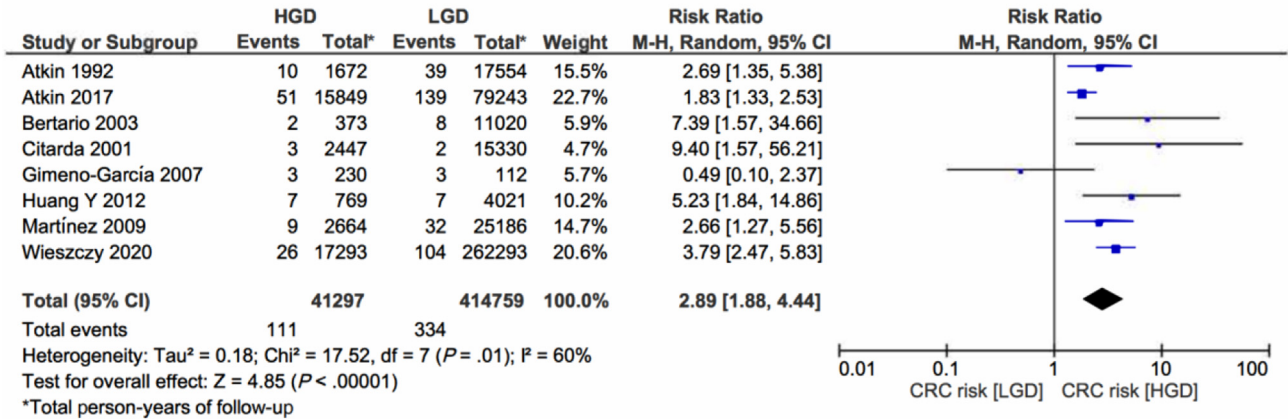
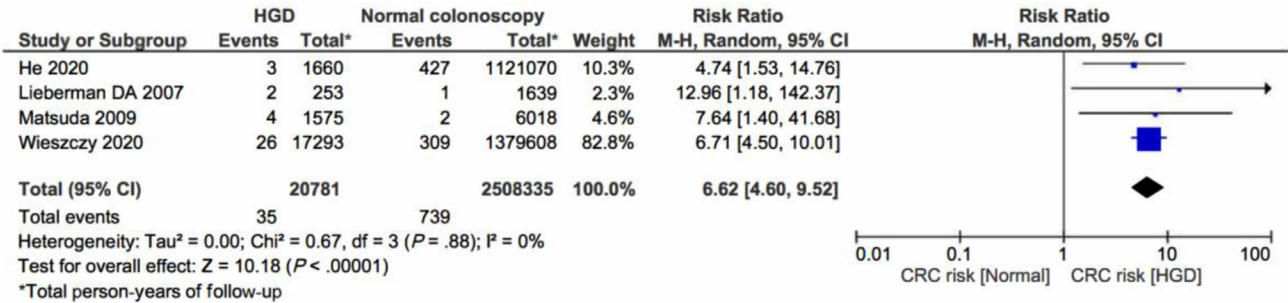


Figure 4. RR for CRC incidence in 1000 person-years comparing adenomas ≥20 mm with <20 mm (A); ≥20 mm with 10–19 mm (B); ≥20 mm with <10 mm (C); 10–19 mm with <10 mm (D); ≥10 mm with <10 mm (E); and ≥10 mm with normal colonoscopy (F).

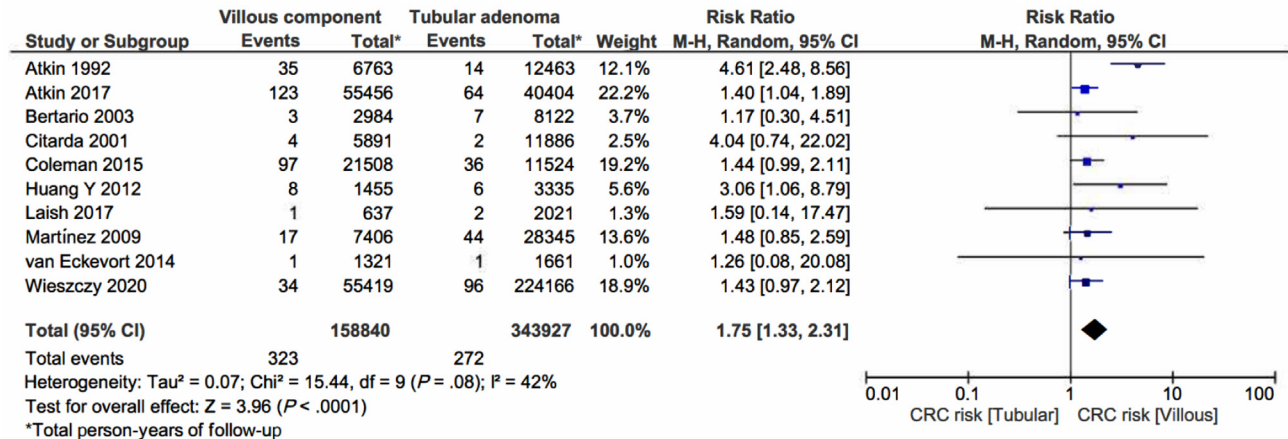
A



B



C



D

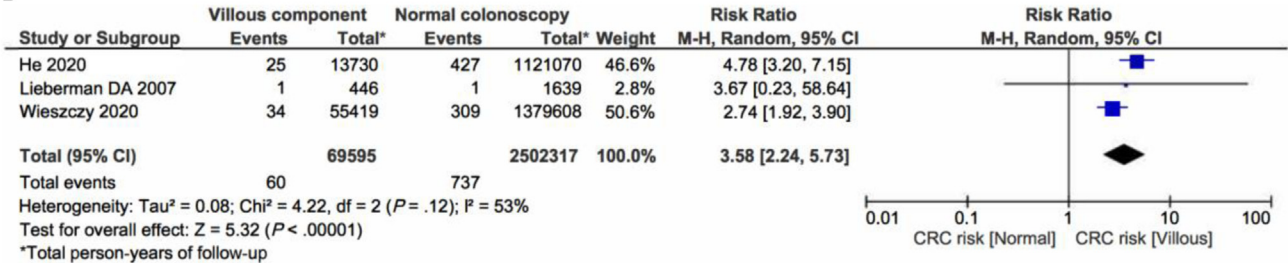


Figure 5. RR for CRC incidence in 1000 person-years in patients with adenomas with HGD compared with adenomas with LGD (A) and normal colonoscopy (B). RR for CRC incidence in 1000 person-years in patients with villous/tubulo-villous adenomas compared with tubular adenomas (C) and normal colonoscopy (D).

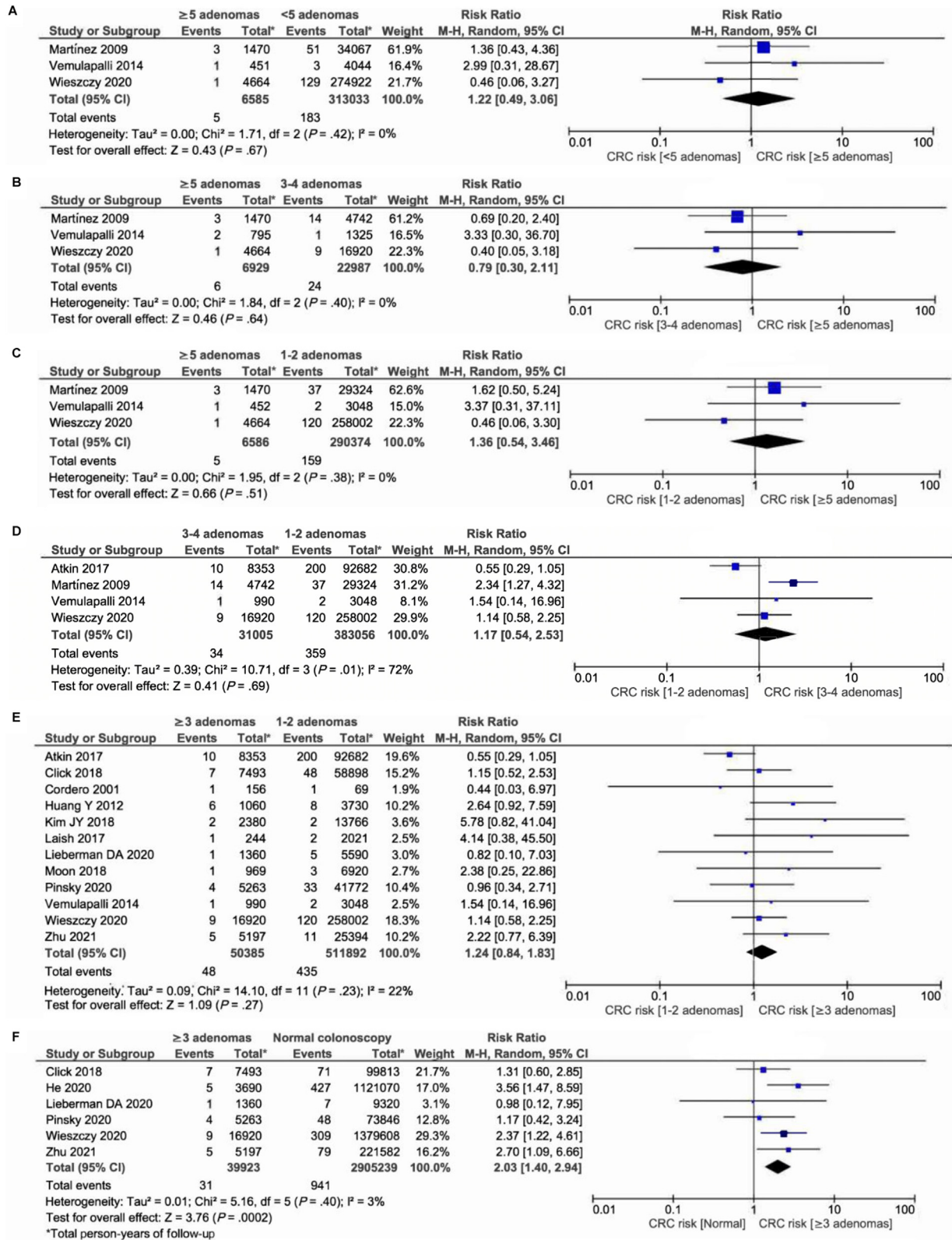


Figure 6. RR for CRC incidence in 1000 person-years comparing ≥5 adenomas with <5 adenomas (A); ≥5 adenomas with 3–4 adenomas (B); ≥5 adenomas with <3 adenomas (C); 3–4 adenomas with <3 adenomas (D); ≥3 adenomas with <3 adenomas (E); ≥3 adenomas with normal colonoscopy (F).

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 colonoscopy³⁰ 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 significantly 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-analysis⁷⁹ 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 ≥ 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 endoscopists⁸² 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 ≥ 20 mm or HGD and also significantly high for adenomas of ≥ 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>.

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Conflicts of interest

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