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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

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BACKGROUND & AIMS: The risk of metachronous colorectal cancer (CRC) among patients with no adenomas, low-risk adenomas (LRAs), or high-risk adenomas (HRAs), detected at index colonoscopy, is unclear. We performed a systematic review and meta-analysis to compare incidence rates of metachronous CRC and CRC-related mortality after a baseline colonoscopy for each group. **METHODS:** We searched the PubMed, Embase, Google Scholar, and Cochrane databases for studies that reported the incidence of CRC and adenoma characteristics after colonoscopy. The primary outcome was odds of metachronous CRC and CRC-related mortality per 10,000 person-years of follow-up after baseline colonoscopy for all the groups. **RESULTS:** Our final analysis included 12 studies with 510,019 patients (mean age, 59.2 ± 2.6 years; 55% male; mean duration of follow up, 8.5 ± 3.3 years). The incidence of CRC per 10,000 person-years was marginally higher for patients with LRAs compared to those with no adenomas (4.5 vs 3.4; odds ratio [OR], 1.26; 95% CI, 1.06–1.51; I^2=0), but significantly higher for patients with HRAs compared to those with no adenoma (13.8 vs 3.4; odds ratio [OR], 2.92; 95% CI, 2.31–3.69; I^2=0) and patients with HRAs compared to LRAs (13.81 vs 4.5; OR, 2.35; 95% CI, 1.72–3.20; I^2=55%). However, the CRC-related mortality per 10,000 person-years did not differ significantly for patients with LRAs compared to no adenomas (OR, 1.15; 95% CI, 0.76–1.74; I^2=0) but was significantly higher in persons with HRAs compared with LRAs (OR, 2.48; 95% CI, 1.30–4.75; I^2=38%) and no adenomas (OR, 2.69; 95% CI, 1.87–3.87; I^2=0). **CONCLUSIONS:** The results of this systematic review and meta-analysis demonstrate that the risk of metachronous CRC and mortality is significantly higher for patients with HRAs, but this risk is very low in patients with LRAs, comparable to patients with no adenomas. Follow-up of patients with LRAs detected at index colonoscopy should be the same as for persons with no adenomas.

Keywords: Polyp; Risk of Death; Tumor Development; Colon Cancer.

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world.[1] Screening and surveillance colonoscopies have been associated with a reduction in the incidence[2,3] and mortality related to CRC[4,5] through early detection and resection of colorectal adenomas. Colonoscopy is currently a screening tool for the general population in several countries worldwide.[6–8]

Current updated United States Multi-Society Task Force (USMSTF) guidelines[9] categorize colorectal polyps into 3 major groups, based on their characteristics at the time of the index colonoscopy, which includes number, size, and histology. They are classified as (1) low-risk adenoma (LRA), defined as 1 to 2 tubular adenomas <10 mm with low-grade dysplasia, (2) high-risk adenoma (HRA), defined as an advanced adenoma (villous histology, high-grade dysplasia, or ≥10 mm) or ≥3 adenomas, and (3) no adenomas. Surveillance intervals for colonoscopy for these are 3 years in patients with HRA, 7 to 10 years for those with LRA, and 10 years for those with no adenomas.[9]

***Authors share co-first authorship.**

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; HRA, high-risk adenoma; LRA, low-risk adenoma; M-H, Mantel-Haenszel; NA, not mentioned/unable to extract; OR, odds ratio; RR, relative risk; SD, standard deviation; SIR, standardized incidence ratio; SMR, standardized mortality ratio; USMSTF, United States Multi-Society Task Force; ESGE, European Society of Gastrointestinal Endoscopy; UK, United Kingdom; USA, United States of America.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The risk of metachronous colorectal cancer (CRC) among patients with no adenomas, low-risk adenomas, or high-risk adenomas, detected at index colonoscopy, is unclear.

NEW FINDINGS

In a systematic review and meta-analysis, we found the risk of metachronous CRC and mortality to be significantly higher for persons with high-risk adenomas, and the same was low in patients with low-risk adenomas, comparable to persons with no adenomas, at index colonoscopy.

LIMITATIONS

Prospective randomized controlled studies are needed to determine risk of CRC in patients with adenomas.

IMPACT

Follow up of patients with low-risk adenomas detected in an initial colonoscopy should be the same as for persons with no adenomas

The evidence supporting these surveillance recommendations for clinically relevant end points such as cancer and cancer-related deaths among patients who undergo adenoma removal, particularly LRA, is minimal, because most of the evidence was based on the surrogate risk of metachronous advanced neoplasia.[10–13] Although studies have indicated that surveillance after removal of adenomas is associated with a reduction in CRC incidence, some modeling studies report only a marginal benefit of surveillance.[14–16] There is currently a need to optimize the use of surveillance colonoscopy based on well-quantified risk factors and clinically meaningful outcomes, such as the incidence of CRC and mortality, rather than surrogate markers such as adenoma recurrence or incidence of advanced adenomas.

Recently, a few large population-based studies have evaluated metachronous CRC risk in patients with LRAs and HRAs at baseline colonoscopy and compared it with patients with no adenomas.[17–19] We performed a systematic review and meta-analysis of all available studies to compare the incidence of CRC and CRC-related mortality in patients with LRAs, HRAs, and no adenomas at their baseline colonoscopy.

Materials and Methods

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[20]

Search Strategy

A comprehensive electronic literature search was conducted in PubMed/MEDLINE, EMBASE, Google Scholar, and Cochrane databases, and conference proceedings to identify eligible articles from the beginning of indexing for each database to May 15, 2020. The following text words and Medical Subject Heading/Entrée terms (MeSH) were used for the search: "low risk adenoma," "LRA," "high risk adenoma," "HRA," "colorectal cancer," "colon cancer," "CRC," "screening colonoscopy," "surveillance colonoscopy," "incidence," "incidence ratios," "adenoma," "advanced adenoma," "high grade dysplasia," "metachronous," and "mortality." An electronic search summary of the PubMed database is reported in Supplementary Table 1.

Inclusion/ Exclusion Criteria

Inclusion criteria were (1) studies reporting data on LRA, HRA, and no-adenoma groups in patients undergoing baseline colonoscopy, (2) studies reporting metachronous CRC or CRC-related mortality rates or standardized incidence or mortality ratios compared with a general population, and (3) full-length articles. The exclusion criteria were (1) studies not reporting follow-up duration and (2) abstracts, case reports, and case series.

Data Extraction and Quality Assessment

Data were collected from the retrieved articles and independently reviewed by 2 assessors (A.D. and V.T.). Data extraction was verified for accuracy by a third author (S.S.), and any disagreement was resolved by consensus with the senior author (P.S.). The following details were extracted from each study: first author, study design, age, sex, number of patients, the incidence of metachronous CRC, duration of follow-up, and CRC-related mortality. Study authors were contacted if there was a need for clarification or obtaining more data for analysis. The quality of studies was assessed using the Newcastle-Ottawa scale as poor, fair, or good quality according to the specified recommendations (Supplementary Table 2).

Definitions and Outcomes

In accordance with the USMSTF guidelines, LRA was defined as 1 to 2 tubular adenomas $<$10 mm with low-grade dysplasia, and HRA was defined as the presence of $\geq$3 adenomas or adenomas $\geq$10 mm in size and/or villous features or high-grade dysplasia.[9] Incidence of metachronous CRC was defined as the cumulative occurrence of CRC in patients, after a baseline colonoscopy with no adenoma, LRA, or HRA.

The primary outcomes were (1) incidence of metachronous CRC and CRC-related mortality in LRA, HRA, and no-adenoma groups and (2) comparison of incidence of metachronous CRC and CRC-related mortality per 10,000 person-years between the LRA, HRA, and no-adenoma groups. Secondary outcomes were (1) standardized incidence ratio (SIR) of metachronous CRC in the LRA and HRA group compared with the general population, and (2) standardized mortality ratio (SMR) of metachronous CRC in the LRA and HRA group compared with the general population. Subgroup analyses were performed for studies reporting data on screening/surveillance patients only.

Statistical Analyses

The random-effects model described by DerSimonian and Laird was used for analysis. Incidence per 10,000 person-years of follow-up was calculated using the number of events and the duration of follow-up in each group. Odds ratios (ORs) were obtained by comparison of the pooled rates between the groups, with a P value $<$.05 considered statistically significant. The corresponding forest plots were constructed with the weights of individual studies represented by individual squares. Heterogeneity among studies was assessed using the inconsistency index (I^2 statistic). I^2 values of 0% to 30%, 31% to 60%, 61% to 75%, and 76% to 100% were indicative of low, moderate, substantial, and considerable heterogeneity,

respectively. Publication bias was assessed by funnel plot, and its asymmetry was calculated using Rücker's test.[21] All meta-analytic computations were performed using Open-MetaAnalyst (CEBM, Brown University, Providence, RI) and Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark) statistical software.

Results

The initial literature search resulted in 1634 studies. After the selection criteria were applied, 112 studies were selected and reviewed in detail, and 12 studies were included in the final analysis[10,11,17–19,22–28] (Figure 1). Four studies were from the United States (n =199,145), 1 was a multicenter study from Taiwan and China (n = 4483), and 1 study each was from Korea (n = 2452), Israel (n = 728), the United Kingdom (n =19,806), France (n =5,779), Norway (n=40,826), Denmark (n = 711), and Poland (n =236,089). There were a total of 510,019 patients (no adenoma, n = 366,033; LRA, n = 52,601; HRA, n = 44,780; unable to classify, n = 46,605), with a mean age of 59.2 ± 2.6 years, and 55% were men. The mean duration of follow-up was 8.5 ± 3.3 years (range, 5–14 years) in the no-adenoma group, 8.4 ± 3.3 years (range, 5–14 years) in the LRA group, and 8.8 ± 3.5 years (range, 5–14 years) in the HRA group.

All of these studies were population-based cohort studies, of which 4 were prospective,[22,23,25,26] and 7 were multicenter studies.[11,17–19,26–28] Only 2 studies[24,25] reported the actual number of colonoscopies performed in each group for the duration of follow-up. An overview of the individual studies with their demographic data is provided in Table 1 and Table 2. The quality assessment of studies using the Newcastle-Ottawa scale (Supplementary Table 2) identified 1 study[25] as fair quality and the remaining 11 studies[10,11,17–19,22–24,26,27] as good quality.

Colorectal Cancer Incidence per 10,000 Person-Years

The incidence of CRC per 10,000 person-years was calculated for all studies (using the duration of follow-up and number of CRC cases) that provided data for the no-adenoma (3,003,389 person-years), LRA (380,674 person-years), and HRA (240,708 person-years) groups. The incidence per 10,000 person-years was 3.4 (95% confidence interval [CI], 2.4–4.4) in patients with no adenomas, 4.5 (95% CI, 2.8–6.23) in the LRA group, and 13.81 (95% CI, 8.15–19.47) in the HRA group, respectively. Compared with the no-adenoma group, the OR for CRC incidence per 10,000 person-years was 1.26 (95% CI, 1.06–1.51; $I^2 = 0\%$) for LRA[17–19,22–26] (Figure 2*A*) and 2.92 (95% CI, 2.31–3.69; $I^2 = 40\%$) for HRA[17–19,22–26] (Figure 2*B*). Compared with the LRA group, the OR for CRC incidence per 10,000 person-years in the HRA group was 2.24 (95% CI, 1.53–3.30) (Figure 2*C*).

A subgroup analysis was performed for 5 studies[18,19,22,23,26] that included patients who underwent screening/surveillance only and reported data on those with no adenomas (1,544,898 person-years), LRAs (227,972 person-years), and HRAs (126,873 person-years). For this analysis, the cumulative CRC incidence per 10,000 person-years was 2.21 (95% CI, 1.75–2.67) in the no-adenoma group, 2.75 (95% CI, 1.81–4.80) in the LRA group, and 6.60 (95% CI, 5.19–8.02) in the HRA group. The OR of CRC incidence among these groups was 1.32 (95% CI, 1.02–1.71; $I^2 = 0\%$) comparing LRA and no-adenoma groups (Figure 3*A*), 2.91 (95% CI, 2.30–3.69; $I^2 = 0\%$) comparing HRA and no-adenoma groups (Figure 3*B*), and 2.19 (95% CI, 1.59–3.00; $I^2 = 0\%$) comparing HRA and LRA groups, respectively (Figure 3*C*). There was no evidence of publication bias for any of the groups compared by the funnel plot (Supplementary Figure 1) and its asymmetry assessed by Rücker's test ($P = .747$).

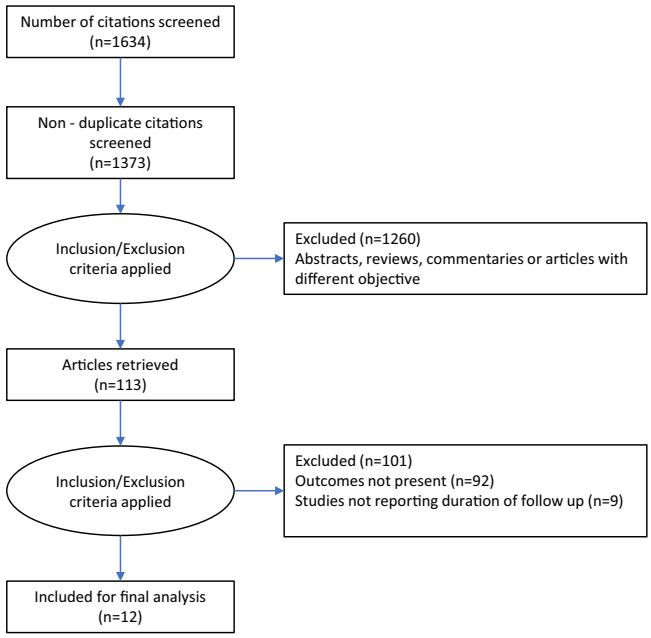

Figure 1. Flowchart for study selection process.

Colorectal Cancer-Related Mortality

Three studies[18,19,25] reported information on CRC-related mortality for all 3 groups. The pooled CRC-related mortality per 10,000 person-years was 0.71 (95% CI, 0.59–0.83), 0.78 (95% CI, 0.28–1.28), and 2.07 (95% CI, 1.26–2.88) in the no-adenoma (1,848,079 person-years), LRA (337,083 person-years), and HRA (206,658 person-years) groups, respectively. The OR for CRC-related mortality comparing the LRA and no-adenoma groups was 1.15 (95% CI, 0.76–1.74; $I^2 = 0\%$) (Figure 4*A*) showing no statistically significant difference. On the other hand, the OR for CRC-related mortality comparing the HRA and no-adenoma groups was 2.69 (95% CI, 1.87–3.87; $I^2 = 0\%$) (Figure 4*B*) and HRA and LRA groups was 2.48 (95% CI, 1.30–4.75; $I^2 = 38\%$), demonstrating a statistically significant difference (Figure 4*C*).

Standardized Incidence and Mortality Ratios Compared With the General Population

There were 5 studies[10,11,19,27,28] providing data on CRC incidence and mortality between the LRA, HRA groups, and the general population. Bjerrum et al[28] compared CRC incidence between the LRA and HRA groups and a

Table 1. Characteristics of the Included Studies

Study	Country	Study design	Multicenter experience	Indication for index colonoscopy	Bowel preparation	LRA/HRA definition
Chiu et al, 2015[22]	China	Prospective	No	Screening and surveillance	Good preparation colonoscopy in >90% of patients	USMSTF
Chung et al, 2011[23]	South Korea	Prospective	No	Screening and surveillance	Graded as good or excellent preparation in 82%	USMSTF
Laish et al, 2015[24]	Israel	Retrospective	No	Screening, surveillance and diagnostic	Bowl preparation was good to excellent in 72% of patients and fair in 28%	USMSTF
Click et al, 2018[25]	USA	Prospective	No	Screening, surveillance, and diagnostic	Unclear	USMSTF
Lieberman et al, 2020[26]	USA	Prospective	Yes	Screening and surveillance	If inadequate or poor preparation, repeat examination performed in 1 year and those outcomes included	USMSTF
Lee et al, 2020[18]	USA	Retrospective	Yes	Screening, surveillance, and diagnostic	Adequate preparation in 100% of patients	USMSTF
He et al, 2020[17]	USA	Retrospective	Yes	Screening, surveillance, and diagnostic	No information on bowel preparation	USMSTF
Wieszczy et al, 2020[19]	Poland	Retrospective	Yes	Screening and surveillance	Excluded patients with inadequate or poor bowel preparation	USMSTF
Cross et al, 2020[27]	UK	Retrospective	Yes	Screening and diagnostic	Good or excellent preparation in 33.5%, satisfactory bowel preparation in 16.1%, poor bowel preparation in 4.6%, and unknown in 44.8% of patients	2002 UK guidelines
Bjerrum et al, 2020[28]	Denmark	Retrospective	Yes	Diagnostic	No information on bowel preparation	ESGE definition. Data obtained similar to USMSTF definition
Cottet et al, 2011[10]	France	Retrospective	No	Screening, surveillance, and diagnostic	No information on bowel preparation	Advanced adenomas defined as per USMSTF definition. Information on number of adenomas not given within the nonadvanced adenomas
Løberg et al, 2014[11]	Norway	Retrospective	Yes	Unclear	No information on bowel preparation	Norwegian guidelines

ESGE, European Society of Gastrointestinal Endoscopy; UK, United Kingdom; USA, United States of America.

Table 2. Summary of Studies With Definitions, Mean Duration of Follow-up, and Incidence Colorectal Cancer Cases

Study	Age, mean (SD), *y*	Male sex, %	No adenoma			LRA			HRA		
			Total number of patients	Mean follow-up duration, mo	Number of patients with metachronous CRC	Total number of patients	Mean follow-up duration, *mo*	Number of patients with metachronous CRC	Total number of patients	Mean follow-up duration, *mo*	Number of patients with metachronous CRC
Chiu[22]	58.6 (7)	62.9	3257	60	3	921	60	0	305	60	0
Chung[23]	56.7 (8.8)	65.6	1242	56.4	0	671	54	0	539	52.8	1
Laish[24]	NA	51.64	318	105.6	6	158	98.4	5	252	76.8	3
Click[25]	NA	NA	7985	180	71	4496	180	48	2882	180	56
Lieberman[26]	NA	96.8	932	120	7	559	120	5	401	120	6
Lee[18]	61.2 (7.1)	47.6	45881	91.2	117	10978	88.8	37	7563	87.6	60
He[17]	57 (10)	17	112107	120	427	2908	120	10	2453	120	39
Wiesczcy[19]	56	37.8	194311	85.2	309	26536	85.2	58	15242	85.2	72
Cross[27]	64	56	NA	NA	NA	5235	111.6	195	14571	105.6	330
Bjerrum[28]	63.1	66	NA	NA	NA	139	120	3	572	120	19
Cottet[10]	61.5 (12.9)	58.4	NA	NA	NA	All adenomas: 5779	92.4	CRC in all groups: 87	All adenomas: 5779	92.4	CRC in all groups: 87
Løberg[11]	NA	50.8	All patients: 40,826 All adenomas: 45,755	92.4	NA	All patients: 40,826 All adenomas: 45,755	92.4	CRC in all adenoma 1group: 1273	All patients: 40,826 All adenomas: 45,755	92.4	CRC in all adenoma group: 1273

NA, not mentioned/unable to extract; SD, standard definition.

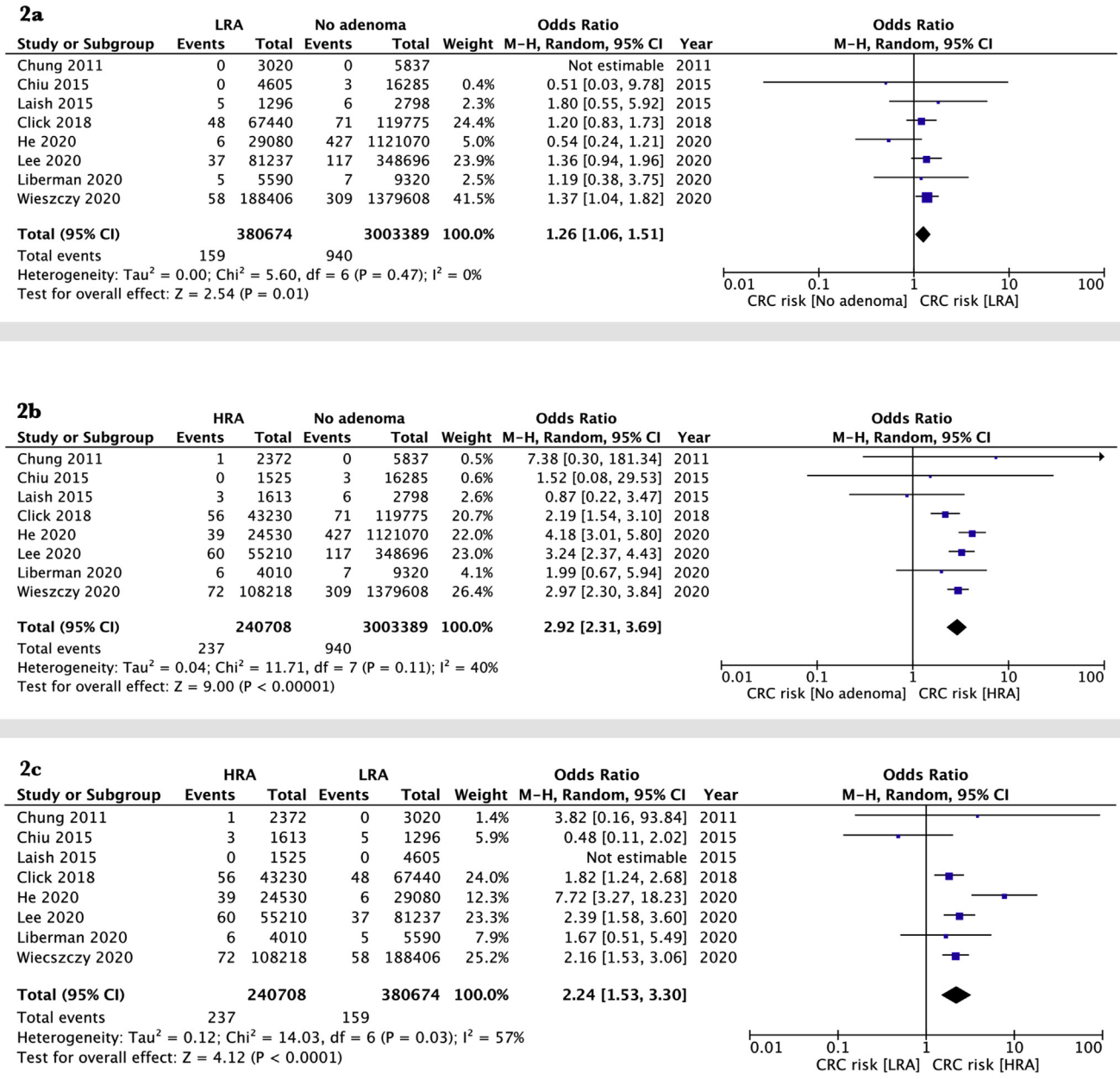

Figure 2. ORs for CRC incidence in 10,000 person-years comparing (*A*) the LRA vs the no-adenoma group, (*B*) the HRA vs no–adenoma group, and (*C*) the LRA vs HRA group. The size of the *solid squares* denotes the mean difference, the *horizontal lines* represent the 95% CIs, the *diamond* denotes the weighted mean difference, and the *lateral tips* of the diamond indicate the associated CIs. M-H, Mantel- Haenszel.

contemporaneous matched general population cohort that did not undergo a screening colonoscopy within 2 years before the study start date. They reported a CRC incidence of 220 per 100,000 person-years in the LRA group, 347 per 100,000 person-years in the HRA group, and 244 per 100,000 person-years in the general population group, with an adjusted hazard ratio of 0.77 (95% CI, 0.25–2.39) for the LRA group and 1.15 (95% CI, 0.74–1.81) for the HRA group compared with the general population.[28]

The "general population" reported in other studies calculated the expected rates from population statistics. The expected cases of CRC and mortality were calculated in the general population by estimating the number of sex- and 5-year age-group–specific person observed-years of CRC and mortality multiplied by the corresponding incidence and mortality in the general population of the national databases of the respective countries. Three studies[11,19,27] provided data on the observed incidence of CRC for the LRA group

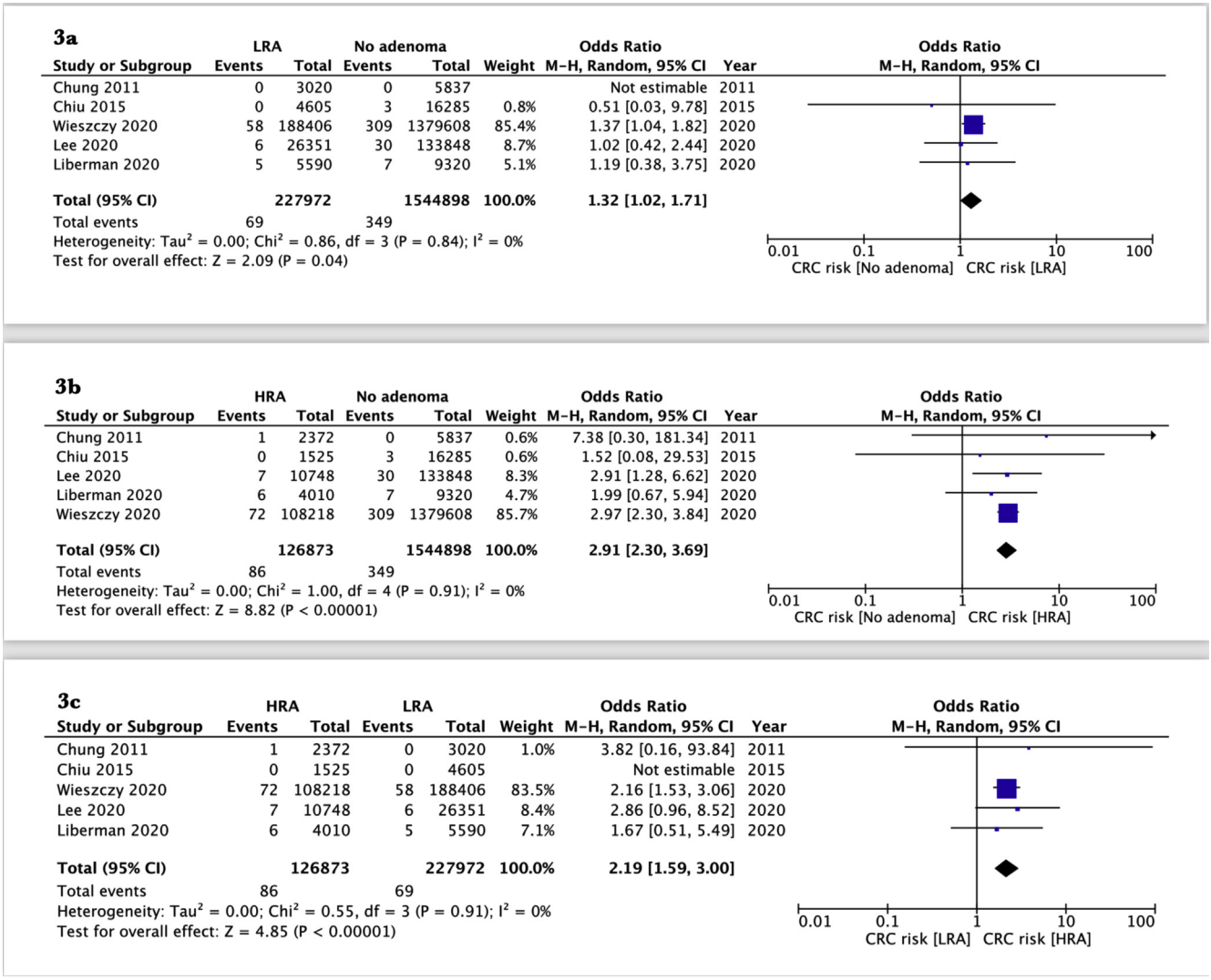

Figure 3. OR for CRC incidence per 10,000 person-years (*A*) LRA vs no-adenoma group, (*B*) HRA vs no–adenoma group, and (*C*) LRA vs HRA group for screening and surveillance population only. The size of the *solid squares* denotes the mean difference, the *horizontal lines* represent the 95% CIs, the *diamond* denotes the weighted mean difference, and the *lateral tips* of the diamond indicate the associated CIs. M-H, Mantel- Haenszel.

(n = 44,173) and 2 studies[19,27] for the HRA group (n = 32,619) and the expected CRC incidence in the general population. An SIR was calculated using the observed and expected CRC incidence. The pooled SIR for CRC in the LRA group, compared with the general population, was 0.45 (95% CI, 0.27–0.76) (Supplementary Figure 2). A sensitivity analysis was performed for the 2 studies[19,27] (n = 40,937) that used the USMSTF definitions. Compared with the general population, the pooled SIR for CRC was 0.35 (95% CI, 0.27–0.45) in the LRA group and 0.79 (95% CI, 0.55–1.13) in the HRA group.

Similarly, only 2 studies[11,19] provided data on mortality in the LRA (n = 49,985) and HRA (n = 32,619) groups, using the observed deaths, compared with the general population, using the expected deaths. The pooled SMRs were 0.42 (95% CI, 0.13–1.36) and 0.64 (95% CI, 0.19–2.16) for the LRA and HRA groups, respectively, compared with general population.

Discussion

The results of this systematic review and meta-analysis demonstrate that patients with LRA or no adenoma have a very low risk of CRC incidence, ranging between 3.4 and 4.5 per 10,000 patient-years and that there was no difference in CRC mortality between the 2 groups. On the other hand, patients with HRA at baseline colonoscopy had both a significantly higher incidence of CRC and mortality compared with both the LRA and no-adenoma groups.

In a CRC prevention program, surveillance colonoscopy can be an expensive component, so the use of a cost-effective strategy is critical.[29] Studies have demonstrated that there is an overuse of surveillance colonoscopy after detection and removal of LRA but underuse within the HRA group.[30–32] Hence, differentiating high-risk groups requiring intensive surveillance from low-risk patients is crucial. The growing emphasis on high-quality colonoscopy and

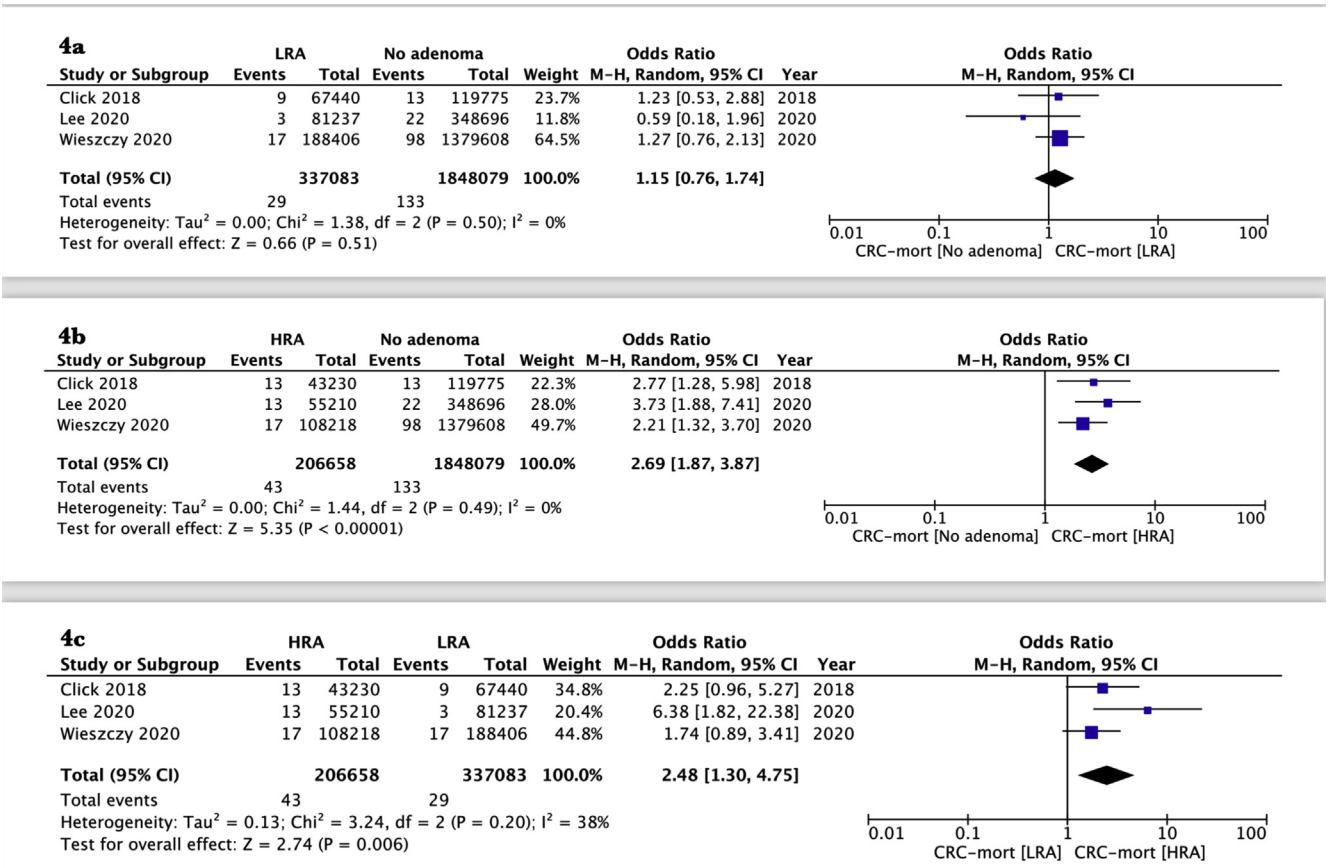

Figure 4. OR for CRC-related mortality in 10,000 person-years comparing the (*A*) LRA vs no–adenoma group, (*B*) HRA vs no-adenoma group, and (*C*) LRA vs HRA groups. The size of the *solid squares* denotes the mean difference, the *horizontal lines* represent the 95% CIs, the *diamond* denotes the weighted mean difference, and the *lateral tips* of the diamond indicate the associated CIs. M-H, Mantel-Haenszel.

improved bowel preparation has increased the number of LRAs diagnosed at colonoscopy.[33] Because the exact risk of CRC and mortality from these LRAs is unknown, there are concerns related to the excessive use of available resources in this group.[34] This leads to the need for a better understanding of CRC incidence and mortality associated with LRA and HRA to guide optimal surveillance intervals.

Although there are multiple guidelines with some differences in the nomenclature for polyps,[35,36] for consistency, we have used the USMSTF-defined criteria for all reported outcomes[9] because most of the studies have used that definition. The updated USMSTF guidelines from 2020 recommend a surveillance interval of 7 to 10 years for patients with LRA.

The evidence for this recommendation is primarily based on 2 meta-analyses. Hassan et al[37] included in their analysis 7 studies with 11,387 patients (4079 LRA patients) and 2 to 5 years of follow-up after a baseline colonoscopy. The pooled rate of metachronous advanced neoplasia was significantly higher in the LRA group compared with the no-adenoma group (3.6% vs 1.6%), with an RR of 1.8 (95% CI, 1.3–2.6). In the second meta-analysis, Dubé et al[38] (10,139 total patients and 3340 LRA patients) found the cumulative rate of advanced adenomas at 5 years was not significantly different in patients with LRA and no-adenoma groups at 4.9% (95% CI, 3.18%–6.97%) vs 3.3% (95% CI, 1.85–5.10%).

Our meta-analysis has a significantly higher number of patients in the LRA (n = 52,601) and HRA (n = 44,780) groups, and also, we estimated the risk of metachronous CRC and mortality (rather than advanced adenomas), both objective and clinically important outcomes. For LRA patients, although the current recommendations from the task force is that of a surveillance colonoscopy in 7 to 10 years,[9] in practice, clinicians often use more frequent surveillance (ie, ≤5 years) in this low-risk group.[30,32,39,40]

Our meta-analysis shows that the incidence of metachronous CRC in the LRA group and the no-adenoma group was very low and comparable with overlapping CIs. Similarly, the CRC-related mortality per 10,000 person-years was also comparable in both groups. Also, as expected, the HRA group had a significantly higher CRC incidence and CRC-related mortality compared with the other 2 groups (no adenoma and LRA). Furthermore, we also analyzed CRC incidence and mortality in the LRA group compared with the general population, with the SIR being lower and SMR being comparable, confirming that it is indeed a low-risk group.

Our meta-analysis has several strengths. Our analysis included >500,000 patients, which is significantly higher than the previously published meta-analyses. We calculated the metachronous CRC risk rather than metachronous advanced adenoma risk as reported in prior studies. We also reported the risk of CRC-related mortality, SIR, and SMR comparing the LRA and HRA groups with the general population, data that have not been previously reported.

To estimate outcomes like CRC incidence and mortality, longitudinal studies with a long duration of follow-up are required, and the mean duration of follow-up in our analysis is close to 10 years, providing a meaningful longitudinal follow-up for comparison between the groups. We also used person-years of follow-up for our analysis to negate the effect of variable follow-up duration in published studies.

Our meta-analysis includes data from several large cohort studies published recently,[17–19,26] which have not been included in any prior analyses, including the recent USMSTF recommendations.

Finally, there was no heterogeneity in most of our primary and secondary outcomes, which makes our result estimates more robust.

However, this study has some limitations. All studies included in this meta-analysis were prospective or retrospective in nature, and no randomized controlled trials were available. The lack of data from randomized controlled trials can introduce potential bias. Using CRC incidence as an outcome measure can be subject to lead time and overdiagnosis bias. Hence, we also used CRC-related mortality as a primary outcome, which is a more unbiased outcome.

Loss of patient follow-up is a known factor in cohort studies that could have influenced the outcomes, but we still had a robust patient population with follow-up for the analyzed outcomes.

It is also likely that the patients in the LRA and HRA groups underwent more colonoscopies compared with the no-adenoma group, leading to a comparability bias. The exact effect of the number of colonoscopies performed and their outcomes could not be analyzed because most of the studies did not report individual colonoscopy-level data (Supplementary Table 3). However, the mean duration of follow-up was similar in all groups with equivalent timing of the last colonoscopy, thus reducing the significance of such a bias.

Finally, there could be another potential bias, the healthy screenee bias, in which the patient sample may not be the exact representation of the general population. We attempted to minimize this by comparing the 3 study groups with the general population.

Conclusion

The results of this systematic review and meta-analysis demonstrate that the risk of metachronous CRC and mortality is very low in patients with LRAs, comparable to individuals with no adenomas. We recommend that the interval for follow-up colonoscopy should be the same in patients with LRAs or no adenomas but that the HRA group should have a more frequent surveillance interval for CRC surveillance compared with these groups. Future studies should evaluate whether surveillance intervals could be lengthened beyond 10 years in the no-adenoma and LRA groups after an initial high-quality index colonoscopy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.01.214.

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Conflicts of interest
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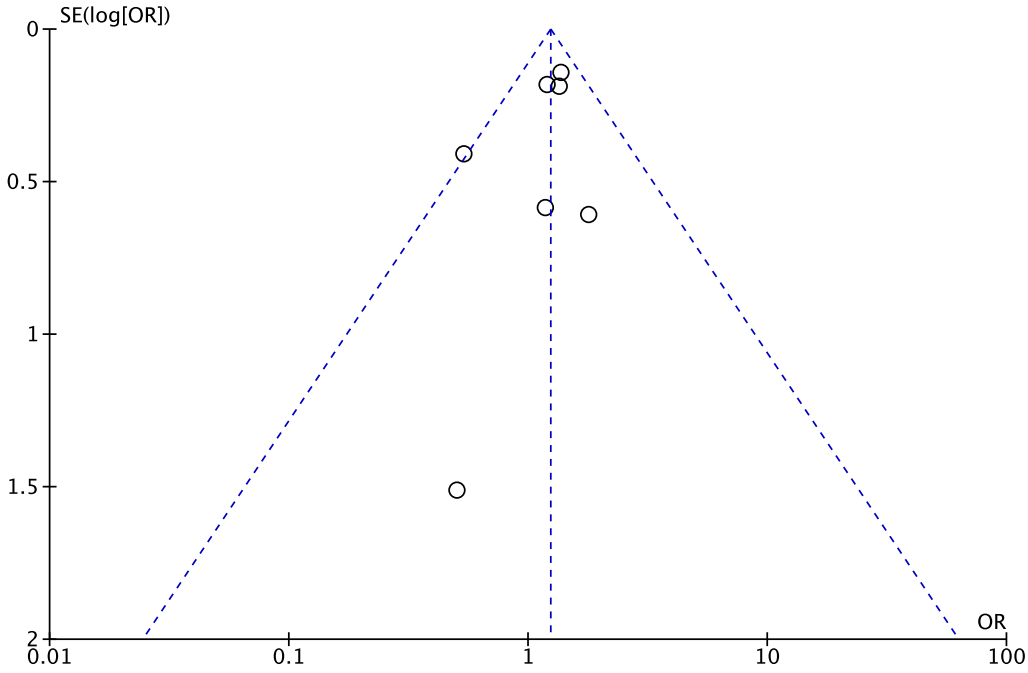
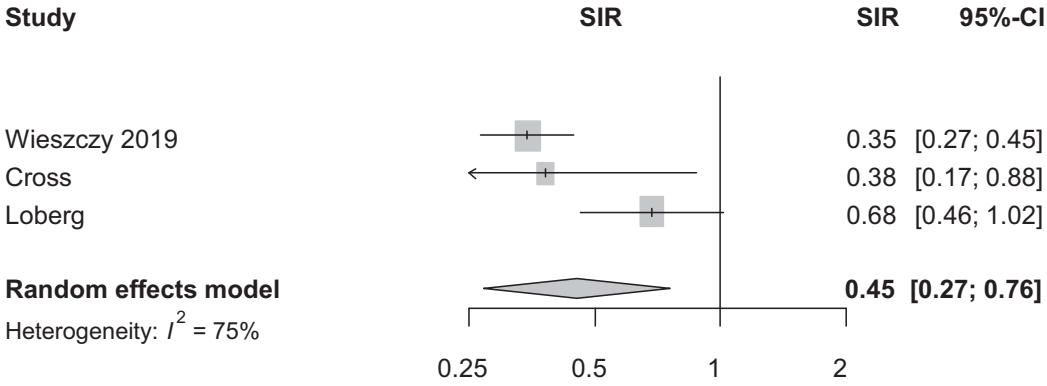


Supplementary Figure 1. Funnel plot assessing publication bias for studies comparing LRA and no adenoma. SE, standard error.



Supplementary Figure 2. SIR of CRC in LRA group compared with the general population.

Supplementary Table 1. PubMed Search Strategy

Search	Query	Items found
# 5	(adenoma or low risk adenoma or LRA) AND (high risk adenoma or HRA or advanced adenoma or high grade dysplasia) AND (colonoscopy or screening colonoscopy or surveillance colonoscopy)) AND (colorectal cancer or colon cancer or rectal cancer) AND (incidence or incidence ratios)	1360
#4	(adenoma or low risk adenoma or LRA) AND (high risk adenoma or HRA or advanced adenoma or high grade dysplasia) AND (colonoscopy or screening colonoscopy or surveillance colonoscopy)) AND (colorectal cancer or colon cancer or rectal cancer)	2880
# 3	(adenoma or low risk adenoma or LRA) AND (high risk adenoma or HRA or advanced adenoma or high grade dysplasia) AND (colonoscopy or screening colonoscopy or surveillance colonoscopy))	3024
# 2	(high risk adenoma or HRA or advanced adenoma or high grade dysplasia)	18,704
# 1	(adenoma or low risk adenoma or LRA)	132,944

Supplementary Table 2. Newcastle Ottawa Scale for Quality Assessment of Studies

Study	Selection[a]				Comparability	Outcomes		Quality
	Representativeness	Nonexposed cohort	Ascertainment of exposure	Outcome not present at start		Assessment	Follow-up	
Chiu, 2015[22]	*	–	*	*	**	*	*	Good
Chung, 2011[23]	*	–	*	*	*	*	*	Good
Cottet, 2011[10]	*	*	*	*	–	*	*	Good
Laish, 2015[24]	*	–	*	*	*	*	*	Good
Click, 2018[25]	–	–	*	*	*	*	*	Fair
Lieberman, 2020[26]	*	–	*	*	*	*	*	Good
Lee, 2020[18]	*	–	*	*	*	*	*	Good
He, 2020[17]	*	–	*	*	*	*	*	Good
Wieszczy, 2020[19]	*	–	*	*	**	*	*	Good
Løberg, 2014[11]	*	*	*	*	*	*	*	Good
Cross, 2020[27]	*	–	*	*	*	*	*	Good

[a]Ensuring that cohort was reflective of the intended group. Used USMSTF definition. Exclusion of individuals with a family history of colorectal carcinoma (higher risk), mention of quality of bowel preparation: 1 star if at least 2 factors were addressed; 2 stars if all factors were addressed.

Supplementary Table 3. Details of Surveillance Intervals and Number of Colonoscopies Performed

Study	Follow-up colonoscopy performed Yes/No/NA			Follow-up interval, *y*			Number of surveillance colonoscopies		
	No adenoma	LRA	HRA	No adenoma	LRA	HRA	No adenoma	LRA	HRA
Chiu et al, 2015[22]	Yes	Yes	Yes	10	5	3	NA	NA	NA
Chung et al, 2011[23]	Yes	Yes	Yes	5	3–5	3 and 5	1	1–2	1–2
Laish et al, 2015[24]	Yes	Yes	Yes	10	5	3	2	2	2
Click et al, 2018[25]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Lieberman et al, 2020[26]	Yes	Yes	Yes	5 or per provider	2–5 or per provider	2 and 5	NA	NA	NA
Lee et al, 2020[18]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
He et al, 2020[17]	Yes	Yes	Yes	NA	NA	NA	NA	NA	NA
Wieszczy et al, 2020[19]	Yes	Yes	Yes	10	5–10	3	NA	NA	NA
Cross et al, 2020[27]	NA	Yes	Yes	NA	NA	NA	NA	1–3	1–3
Bjerrum et al, 2020[28]	NA	Yes	Yes	NA	NA	NA	NA	1–4	1–4
Cottet et al, 2011[10]	NA	NA	Yes	NA	NA	NA	NA	NA	NA
Løberg et al, 2014[11]	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, not mentioned/unable to extract.