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ORIGINAL ARTICLE

Irritable Bowel Syndrome Is Not Associated with an Increased Risk of Polyps and Colorectal Cancer: A Systematic Review and Meta-Analysis

Theodoros Vichos[1] · Ali Rezaie[2,3] · Petros Vichos[4] · Brooks Cash[5] · Mark Pimentel[2,3]

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Abstract

Objectives Colorectal cancer (CRC) is the third most common malignancy in the US. Several factors are associated with increased/decreased CRC risk and often linked to adenomatous colorectal polyps (CRP). Recent studies suggest a lower risk of neoplastic lesions among irritable bowel syndrome (IBS) patients. We aimed to systematically assess the occurrence of CRC and CRP in IBS patients.

Methods Searches of the Medline, Cochrane, and EMBASE databases were performed, blindly and independently, by two investigators. Studies of CRC or CRP incidence in IBS patients (diagnosed by Rome or other symptom-based criteria) were eligible for inclusion. CRC and CRP effect estimates were pooled in meta-analyses using random models.

Results Of 4941 non-duplicate studies, 14 were included, comprising 654,764 IBS patients and 2,277,195 controls in 8 cohort studies, and 26,641 IBS patients and 87,803 controls in 6 cross-sectional studies. Pooled analysis revealed a significantly decreased prevalence of CRP in IBS subjects vs. controls, with a pooled odds ratio (OR) of 0.29 (95% CI (0.15, 0.54)). There was significant heterogeneity between studies ($I^2 = 96\%$, $p < 0.01$). This finding persisted when studies which did not report pre-cancerous polyps separately were excluded (OR 0.23, 95% CI (0.15, 0.35), $I^2 = 85\%$, $p < 0.01$). CRC prevalence was lower in IBS subjects, but this did not reach statistical significance (OR 0.40, 95% CI (0.09, 1.77]).

Conclusion Our analyses reveal a decreased incidence of colorectal polyps in IBS, although CRC did not reach significance. Mechanistic studies with detailed genotypic analysis and clinical phenotyping are needed to better elucidate the potentially protective effect of IBS on CRC development.

Keywords Irritable bowel syndrome · Colorectal neoplasia · Meta-analysis

Introduction

Colorectal cancer (CRC) is the third most common type of cancer and the second most common cause of cancer-related mortality, with an annual incidence of over 19 new cases per 100,000 people [1] and costs of up to $50,000 per patient [2]. Multiple distinct histologic subtypes of CRC exist, each possibly having a different pathophysiologic mechanism [3]. While most forms of CRC are thought to arise from preexisting adenomatous polyps [3], not all polyps are precancerous and not all adenomas carry equivalent risk of CRC, with characteristics such as size and histological features determining the probability of neoplastic transformation.

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain related to defecation or stool changes [4]. Its global prevalence is also high, around 4% based on the contemporary Rome IV criteria [5],

✉ Mark Pimentel
pimentelm@cshs.org

1 Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

2 Medically Associated Science and Technology (MAST) Program, Cedars-Sinai, 770 N. San Vicente Blvd, Suite G271, West Hollywood, CA, USA

3 Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars-Sinai, Los Angeles, CA, USA

4 Medical School, University of Cyprus, Nicosia, Cyprus

5 University of Texas Health Science Center at Houston, Houston, TX, USA

decreasing life quality and increasing patients' health-related expenses [6]. While chronic gastrointestinal disorders, like inflammatory bowel disease (IBD), are known to increase the risk of CRC [7], the intestinal homeostasis dysregulation of IBS is only now being investigated [8, 9]. Moreover, the role of intestinal dysbiosis, immune dysregulation, and motility disturbances seen in IBS in colonic mucosal cell neoplastic proliferation is still unclear. A decreased prevalence of colorectal polyps (CRP) has been observed in patients with IBS [10], possibly suggesting evidence of an anti-neoplastic process. Unfortunately, since the relationship between IBS and colorectal neoplasia development is unclear, IBS patients cannot be counseled in an evidence-based manner.

To our knowledge, the prevalence of CRC and CRP in IBS has not been assessed in a systematic review. Therefore, we conducted a systematic review and meta-analysis to define the rates of CRC and CRP in IBS patients.

Methods

The following meta-analysis was conducted following the MOOSE guidelines [11]. The complete MOOSE checklist can be found in the Supplemental Information (Supplemental Table 1).

Search Strategy and Selection Criteria

A thorough search of Medline, Cochrane, and EMBASE (from inception to February 14th, 2022) indexed articles was conducted independently and blindly by two independent investigators, TV and PV. Eligibility criteria were defined a priori (see Table 1). These required studies to be clinical trials, cross-sectional, case–control or cohort studies and to assess the incidence or prevalence of CRC or CRP in patients diagnosed with IBS. Case reports, case series, and reviews were excluded. IBS was required to be diagnosed using a version of the Rome or other symptom-based criteria. CRC was expected to be diagnosed using pathology, while colonoscopy was sufficient to diagnose CRP. If the study investigators did not perform colonoscopy and/or biopsy, but the diagnosis was already established, made by another physician, then the study was considered eligible. Non-English studies were not included. There were no exclusion criteria for abstracts, unpublished studies, population size, or follow-up. For the database search, two search strategies were constructed to identify articles related to IBS and articles related to colonic neoplasia and then combined with the Boolean operator "AND". The search terms combined using the Boolean operator "OR" to identify studies related to IBS included: irritable bowel syndrome (both as a medical subject heading (MeSH)/emtree and a free text term) and IBS, spastic colon, functional adj5 bowel, Manning, "Rome 1," "Rome I," "Rome 2," "Rome II," "Rome 3," "Rome III," "Rome 4," "Rome IV" (all as free text terms). To identify studies related to colorectal adenoma or carcinoma, the search terms that were combined, again using the Boolean operator "OR," included: colonic neoplasms, colonic polyps (both as MeSH/emtree and free text terms), organic colon* lesion* (as a free text term) and the combination of free text terms referring to neoplasia (polyp*, adenoma*, cancer, carcinoma, neoplasm*, tumor* combined with the "OR" Boolean operator) with free text terms related to the colon (colorectal, colorectum, colon*, rectal, rectum combined with the "OR" Boolean operator) with the "AND" Boolean operator.

Subsequently, studies titles and abstracts were reviewed based on the above-mentioned criteria. If a decision could still not be made, then the full text of the article was examined. Eligible studies' reference lists were subsequently uploaded in the Mendeley citation manager, version 1.19.8, to identify duplicates. These articles were screened, using the same methodology, for potentially relevant papers, as were the references of additional eligible studies ("snowball method") [12]. Finally, we conducted an inquiry via mail in studies with potential overlap [13–17] and missing data [13–16, 18–23].

Table 1 Inclusion and exclusion criteria

Included	Clinical trials, cross-sectional, case–control or cohort studies assessing the incidence or prevalence of CRC or CRP in patients diagnosed with IBS
	IBS diagnosed using some edition of Rome, or other symptom-based criteria
	CRC diagnosed using pathology, if colonoscopy and/or biopsy not performed, diagnosis established beforehand by another physician
	CRP diagnosed using colonoscopy, if colonoscopy and/or biopsy not performed, diagnosis established beforehand by another physician
Excluded	Case reports, case series, reviews
	Non-English studies

CRC colorectal carcinoma, *CRP* colorectal polyps, *IBS* irritable bowel syndrome

Data Abstraction and Study Quality Assessment

Data regarding study characteristics (first author, year of publication, journal, country, means of patient recruitment, recruitment period, study design), population characteristics (eligibility and exclusion criteria, means of IBS, CRC and CRP diagnosis, sex, mean age and average follow-up, IBS and control population sizes) and effect estimates (cases of CRC and CRP in IBS and control groups, as well as person-years for cohort studies) were identified and inserted in a predefined spreadsheet. Two reviewers, TV and PV, independently conducted the data abstraction process. When missing, the average follow-up of cohort studies was calculated by dividing the person-years contributed by the IBS group by the number of its participants [20, 23]. In one study where data were given in age and follow-up strata [23], the cases of CRC, population, and person-years in the IBS and control groups were calculated by summing all the subgroups. When pre-neoplastic and non-neoplastic polyps were reported separately [10, 24, 25], only pre-neoplastic polyps were used. Finally, when colon and rectal cancer were reported separately [20, 24], they were combined.

Quality assessment of included studies was conducted by two reviewers, TV and PV, using the Newcastle–Ottawa scale [26] for cohort studies and the NIH study quality assessment tool (SQAT) [27] for cross-sectional studies. Quality assessors were blinded to each other, and any differences in assessments were resolved by discussion between the raters. The compete assessment strategy is available in the Supplementary Information (Supplemental Methods).

Statistical Analysis

The risk ratio (RR), extracted from cohort studies, and odds ratio (OR), extracted from cross-sectional studies, of CRC and CRP were pooled. CRP RR was not pooled due to the limited number of studies examining it. When overlap between the populations of two studies was confirmed [13–16, 18, 23], the study with the bigger sample size was included [13, 23]. Sources of heterogeneity were explored using sensitivity analyses for the calculation of CRP and CRC OR using high quality studies exclusively. A sensitivity analysis of pre-neoplastic polyp OR was also performed. Due to statistically significant heterogeneity between the studies, random effect models were used in all analyses.

Statistical significance was set at $p < 0.05$. Also, inter-study heterogeneity was assessed using the I^2 statistics and Cochran Q statistic with the significance level set at $p < 0.10$ [28]. No other sensitivity or meta-regression analyses could be performed due to the limited number of studies in each analysis. Finally, publication bias was not assessed due to the small number of study arms in each meta-analysis.

All analyses were performed using Review Manager version 5.4.

Results

Search Results

The literature search results are summarized in Fig. 1. The database search yielded 4941 non-duplicate studies; 19 were considered potentially eligible after the title and abstract were examined. After examination of the full-text article, 14 [10, 13–25] were included and 5 [29–33] were excluded for cause. There was overlap between two studies. One study [13–16], confirmed through e-mail communication, was drawn from the same database (Longitudinal health insurance database of the Taiwan national health insurance/National Health Insurance research database) at the same period (2003, 2000–2010, 1999–2004, and 2000–2010). The other cohort [18, 34] was also drawn from the same database (Clinical practice Research datalink/General Practice Research Database) during the same periods (1994 and 1989–2012), and the overlap was acknowledged in the latter study [34].

Characteristics of Included Studies

The descriptive characteristics of included studies are provided in Table 2. Seven studies were conducted in Asia [13–16, 21, 22, 24], five in Europe [17, 18, 20, 23, 25], and two in the US [10, 19]. Of 14 studies, 8 were cohort studies [13–18, 20, 23] and 6 were cross-sectional studies [10, 19, 21, 22, 24, 25]. Overall, 654,764 IBS patients in cohort studies contributed over 2,430,743 person-years and 2,277,195 controls contributed 8,703,717 person-years; with mean follow-up ranging from 1.67 to 12.2 years. Furthermore, 26,642 IBS patients and 87,803 controls participated in the cross-sectional studies. Participants were recruited between 1977 and 2016, generally excluding patients with a previous cancer diagnosis, organic disease, and alarm features. For cohort studies, IBS diagnoses were ascertained from large databases with codes assigned by physicians. For cross-sectional studies, Rome or other accepted criteria were used in all studies, except for one [25] which was drawn from a database with disease coding. In cohort studies, CRP and CRC diagnoses were derived from database codes, except for one study utilizing immunochemical fecal occult blood test followed by colonoscopy [14]. In cross-sectional studies, colonic neoplasia diagnoses were supported by colonoscopy or biopsy, apart from the aforementioned study [25]. Finally, only three cross-sectional studies [10, 24, 25] separately reported pre-neoplastic CRP.

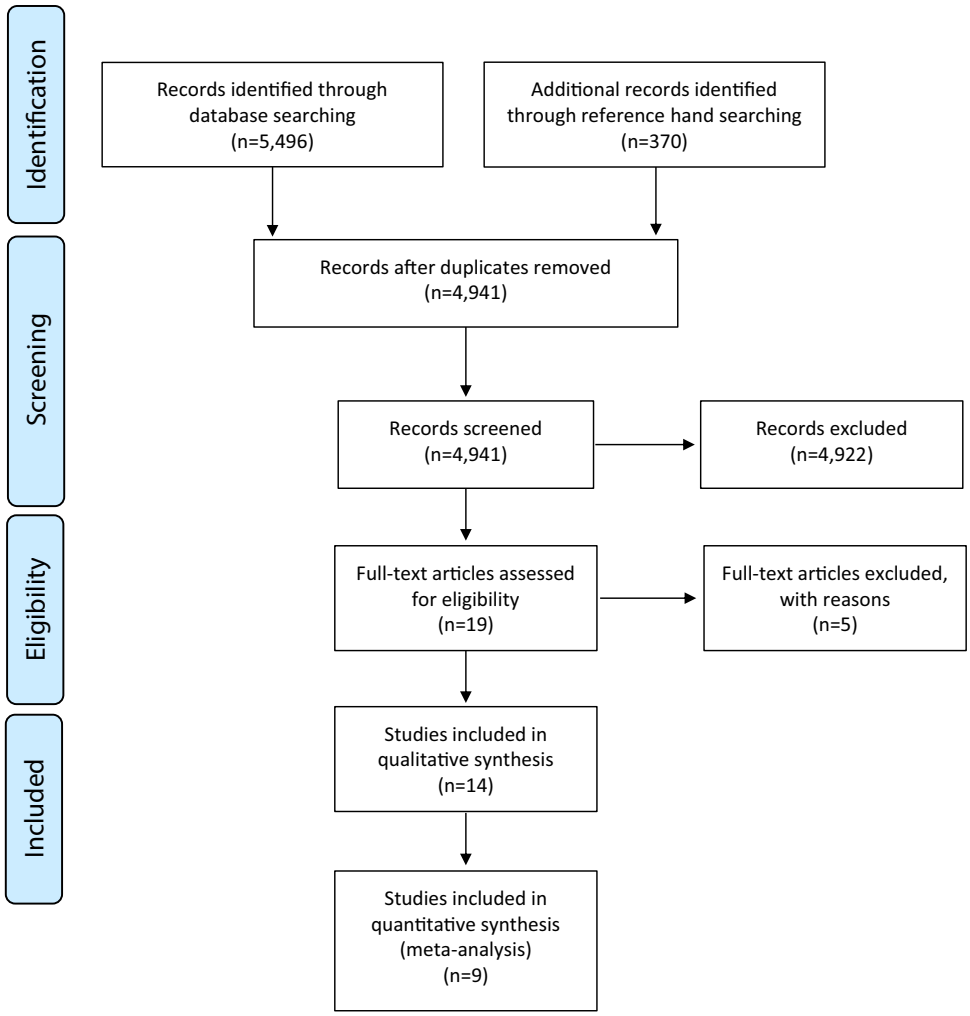

Fig. 1 Study selection diagram

Quality of Studies

Overall, satisfactory quality was recorded in cohort studies (Table 3), with mixed quality demonstrated in cross-sectional studies (Table 4). Only two cohort studies lost more than one point in the NOS [18, 23]; however, only one was included in the quantitative synthesis [23]. The most common quality measures deficiencies were no description of participant follow-up percentage, followed by insufficient follow-up duration. However, all studies demonstrated appropriate ascertainment of exposure and outcome evaluation (Table 3). Regarding cross-sectional studies, all but two were rated as "Fair" or "Good" in quality. The remaining two [19, 22] were of "Poor" quality (Table 4). Common methodological errors were no calculation of the sample size needed to reach statistical significance, and no correction for potential confounders in the statistical analysis. The majority of studies had satisfactory descriptions of study populations and adequate assessments of exposure and outcomes.

Synthesis of Results

Pooled analysis of cross-sectional studies showed a significantly decreased prevalence of CRP in IBS patients compared to controls (Fig. 2). Five studies contributed to a pooled OR of 0.29 (95% CI 0.15–0.54) for CRP [10, 19, 22, 24, 25]; however, there was significant heterogeneity between the studies ($I^2 = 96\%$, $p < 0.01$). This finding persisted in a sensitivity analysis excluding the two studies not reporting pre-cancerous polyps separately (Fig. 3), which were also the studies rated as "Poor" using the NIH Study quality assessment tool [19, 22] (OR 0.23; 95% CI 0.15–0.33; $I^2 = 85\%$, $p < 0.01$). Pooling CRC data between the five studies [10, 19, 21, 24, 25] did not show a significant decrease in CRC prevalence among IBS patients, with a pooled OR of 0.40 (95% CI 0.09–1.77) (Fig. 4). Similarly,

Table 2 Characteristics of included studies

Study	Wu (2022)	Staller (2021)	Pan (2016)	Hu (2015)	Chang (2015)	Hsiao (2014)	Canavan (2014)
Age (mean/SD)	56.21/8.11	44.7/17.0	49.5/15.8	Median 50.89	60.9/12.2	44.6/19.7	42.9
CRC diagnosis	NCR	SNOMED	ICD-9: 153, 154	Registry for Catastrophic Illness	IFOBT, colonoscopy, NCR	ICD-9: 153, 154	GP diagnosis
Polyp diagnosis	N/A	SNOMED (pre-neoplastic reported)	N/A	N/A	IFOBT, colonoscopy	Colonoscopy	N/A
IBS diagnosis	ICD-10	ICD-9: 564B, ICD-10: K58	ICD-9: 564.1	ICD-9-CM: 561.4	ICD-9: 564.0, 564.1	ICD-9: 564.1	GP diagnosis
Population description	Ex: Prior cancer, IBD, CD diagnosis, missing baseline questionnaires and anthropometric information, withdrawal from UK Biobank	In: Colonoscopy with biopsy < 6 months from IBS diagnosis Ex: Biopsy from surgery, diagnosis of CD, MC, CRP or CRC until − 7 days from biopsy	In: 2 diagnoses of IBS in 2003 Ex: IBS before 2003, 1 IBS diagnosis, organic disease	Ex: Prior malignancies, < 3 doctor visits, altered diagnosis within 3 months after first IBS diagnosis, < 20 years old	Ex: Colonic neoplasia, IBS diagnosis before screening for colorectal neoplasia	Ex: Cancer, missing information on age or sex	In: age 18–75 Ex: Prior CD, IBD, CRC diagnosis
Mean follow-up (years)	12.2	N/A	10	Median 4.56	7.92	5.74	1.67
Number of participants	22,338 cases 427,257 controls	21,944 cases 81,101 controls	1225 cases 4900 controls	29,838 cases	9160 cases 30,224 controls	91,746 cases 183,492 controls	442,437 cases 1,631,136 controls
Design	Cohort	Cross-sectional	Cohort	Cohort	Cohort	Cohort	Cohort
Study Period	2006–2010	1987–2016	2003	2000–2010	1999–2004	2000–2010	1989–2012
Patient recruitment	UK Biobank	ESPRESSO study, 28 Swedish centers	LHID of the NHIRD	NHIRD	NHIRD	LHID of the NHIRD	CPRD
Country	UK	Sweden	Taiwan	Taiwan	Taiwan	Taiwan	UK
Study	Hilmi (2013)	Ishihara (2012)	Gu (2011)	Nørgaard (2011)	Chey (2010)	Akhtar (2006)	García-Rodríguez (2000)
Age (mean/SD)	Median 51	57.9	34.1/7.8	Median 47	41.1/ 12.9	Range 19–91	Missing
CRC diagnosis	N/A	Biopsy	Biopsy	ICD-10: C18, C19, C20	N/A	Biopsy	GP diagnosis
Polyp diagnosis	Colonoscopy	N/A	Colonoscopy with biopsy (pre-neoplastic reported)	N/A	Colonoscopy with biopsy (pre-neoplastic reported)	Colonoscopy	Modified Oxmiss codes
IBS diagnosis	Rome III criteria	Rome III criteria	Rome III criteria	I ICD-8: 564.19 ICD-10: K58.0, K58.9	Rome II criteria	Rome I, Rome II, Manning criteria	Modified Oxmiss codes

Table 2 (continued)

Study	Hilmi (2013)	Ishihara (2012)	Gu (2011)	Nørgaard (2011)	Chey (2010)	Akhtar (2006)	García-Rodríguez (2000)
Population description	Ex: Prior GI surgery, significant loss of weight, bloody stool, metabolic disorders (thyrotoxicosis, corticosteroid use in the past month), recent GI infection	Ex: Emergency cases with a lot of melena	Ex: Alarm features, family history of CRC, onset of symptoms after 50 years of age	Ex: Cancer before IBS diagnosis	Ex: Old IBS diagnosis, IBS-C, alarm features, pregnant/breastfeeding, first degree relative with CRC, prior CD, IBD, disease causing GI symptoms, colonoscopy, GI surgery	–	In: age 20–79, 2 years on same GP Ex: pregnant, cancer diagnosis before 1994, IBD, alcoholism, PUD, GERD, pancreatitis, cholecystitis, antispasmodics/acid-suppressants
Mean follow-up (years)	N/A	N/A	N/A	8.8	N/A	N/A	3
Number of participants	74 cases 46 controls	203 cases 3975 controls	3332 cases 1588 controls	57,851 cases	466 cases 451 controls	622 cases 642 controls	169 cases 186 controls
Design	Cross-sectional	Cross-sectional	Cross-sectional	Cohort	Cross-sectional	Cross-sectional	Cohort
Study Period	2010–2011	March-June 2009	2000–2009	1977–2008	August 2003–August 2008	1989–2003	1994
Patient recruitment	University of Malaya Medical Center, Endoscopy Unit	17 centers in Japan	Nanfang Hospital, Southern Medical University	Danish National Registry of Patients	Naval Medical Centers of Bethesda & Portsmouth, University of Michigan Ann Arbor	LA community hospital	CPRD
Country	Malaysia	Japan	China	Denmark	US	US	UK

LHID longitudinal health insurance database, *NHID* national health insurance database, *CDRD* clinical practice research datalink, *IBS* irritable bowel syndrome, *IBS-C* irritable bowel syndrome - constipation subtype, *IBD* inflammatory bowel disease, *CD* celiac disease, *MC* microscopic colitis, *CRP* colorectal polyp, *CRC* colorectal carcinoma, *GI* gastrointestinal, *GP* general practitioner, *PUD* peptic ulcer disease, *GERD* gastroesophageal reflux disease, *N/A* not applicable, *In* inclusion criteria (always including IBS diagnosis), *Ex* exclusion criteria, *IFOBT* immunochemical fecal occult blood test, *ICD* international classification of disease, *SNOMED* systematized nomenclature of medicine codes, *Alarm features* fever, weight loss, GI bleeding, anemia

Table 3 The Newcastle–Ottawa Scale for assessing the quality of cohort studies

Study		Wu (2022)	Pan (2016)	Hu (2015)	Chang (2015)	Hsiao (2014)	Canavan (2014)	Nørgaard (2011)
Outcome	Adequacy of follow up of cohorts	d	d	d	d	d	d	a
	Was follow-up long enough for outcomes to occur	a	a	a	a	a	b	a
	Assessment of outcome	b	b	b	a	b	b	b
Comparability	Comparability of cohorts on the basis of the design or analysis	b	b	b	b	b	b	b
		a	a	a	a	a	a	a
Selection	Demonstration that outcome of interest was not present at start of study	a	a	a	a	a	a	a
	Ascertainment of exposure	a	a	a	a	a	a	a
	Selection of the non-exposed cohort	a	a	a	a	a	a	a
	Representativeness of the exposed cohort	b	b	b	b	b	b	b
NOS score		8/9	8/9	8/9	8/9	8/9	9/9	7/9

The letters a-e denote different things in the different categories

significant heterogeneity between the studies ($I^2 = 96\%$, $p < 0.01$) was observed. Sensitivity analyses excluding studies rated as "Poor" using the NIH Study quality assessment tool [19] resulted in similar estimates (OR 0.30; 95% CI 0.07–1.28) but failed to resolve the inter-study heterogeneity ($I^2 = 90\%$, $p < 0.01$). Finally, pooling data from four cohort studies [13, 17, 20, 23] did not show a significant difference in CRC incidence between IBS patients and controls (RR 1.31; 95% CI 0.75–2.26; Fig. 5). Additionally, there was significant heterogeneity between the studies ($I^2 = 99\%$, $p < 0.01$).

Discussion

This systematic review and meta-analysis summarizes the results of eight cohort studies examining the association between CRC and IBS, and six cross-sectional studies examining the relationship between CRP and IBS. All cohort studies drew their populations from large national databases and focused on middle-aged patients. For cross-sectional studies, populations represented middle-aged adults, most consecutively recruited in endoscopy centers around the world. Pooled analysis showed a significantly decreased prevalence of CRP in IBS patients. CRC prevalence was also decreased in IBS patients, but the result did not reach statistical significance.

IBS is the most well-recognized functional disorder of the gastrointestinal tract, is one of the most common disorders encountered in primary and specialty care, and occurs in all age categories [5]. According to the Rome criteria, IBS symptoms must include abdominal pain and/or discomfort that are associated with changes in stool form (diarrhea, constipation, or both) and/or frequency. Although IBS can have a dramatic effect on health-related quality of life, evidence-based practice guidelines purport a low risk for luminal pathology, including IBD and CRC, in patients with typical IBS symptoms and no alarm features. Recently published American College of Gastroenterology guidelines on the management of IBS suggest, due to this low risk, that colonoscopy is unnecessary under 45 years of age in the absence of alarm features such as weight loss and blood in the stool [35]. However, patients often fear the possibility of cancer and there have been few studies to support a guidance on the risk of CRC in IBS patients. This is due in part to the non-specific nature of IBS symptoms (which can be similar to CRC), the lack of adoption of a symptom-based, positive diagnostic approach to IBS (the tradition of IBS being a diagnosis of exclusion), and a lack of validated diagnostic biomarkers for IBS. The same guidelines argue for avoiding the diagnosis-of-exclusion approach to IBS and adopting a positive diagnostic approach [35]. Nonetheless, having a more complete understanding of the risks for CRC in IBS could help clinicians counsel patients in clinical practice.

Given the potential for similar symptoms in patients with CRC and IBS, understanding the risk of both CRC and CRP in IBS is an important question. Independent studies have suggested a reduced prevalence of CRP in IBS. However, in the absence of further evidence, Chey et al. [10] proposed that in their study, the finding of lower CRP in IBS might have been the result of stricter exclusion criteria for IBS cases vs. controls as well as differing mean ages of included patients. In the current study, pooling of a number of studies suggests a significantly decreased CRP prevalence in IBS patients compared to controls. This finding persisted in a sensitivity analysis of pre-cancerous polyps. A decreased

Table 4 The NIH Study Quality assessment tool for cross-sectional studies

Study	Staller (2021)	Hilmi (2013)	Ishihara (2012)	Gu (2011)	Chey (2010)	Akhtar (2006)
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes
Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA
Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	No
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No	No	No
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	No	No	No	No	No
Was a sample size justification, power description, or variance and effect estimates provided?	Yes	No	No	No	Yes	No
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	No	Yes	Yes	No	No
Was the participation rate of eligible persons at least 50%?	Yes	NR	Yes	Yes	NR	NA
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Quality (G,F,P)	G	P	F	F	F	P

NR not reported, *NA* not applicable

CRP prevalence might imply a reduction in the incidence of CRC in IBS; however, no significant reduction in colorectal cancer was found based upon this pooled analysis. Of the five cross-sectional CRP studies identified, only two [24, 25] selected cases and controls using the same exclusion criteria. This argument is further supported by the previously highlighted poor definition of controls in cross-sectional studies [36]. Nevertheless, since this finding persisted in the two studies using the same exclusion criteria for cases and controls, it increases the confidence in a lower CRP rate in IBS patients.

In addition to the lower prevalence of CRP in IBS, the current study also found a lower rate of CRC in IBS, although this did not reach statistical significance. The finding of a decreased CRP prevalence likely supports a protective relationship between IBS and CRC since CRP are widely accepted as the primary precursors to CRC. The lack of significance may be due to large heterogeneity among CRC trials. Some of this heterogeneity could be attributed to misdiagnosis [13, 20] or surveillance bias [13]. Regarding misdiagnosis, primary care providers usually diagnose and manage IBS patients, while extensive workup and subspecialty consultation are often not necessary [24]. Cohorts in this review included patients diagnosed with IBS from 1977 to 2012. The latest Rome criteria (Rome IV) were published in 2016, with previous editions in 2006, 1999–2000, and 1994 [37]. Thus, these patients may have been diagnosed using various

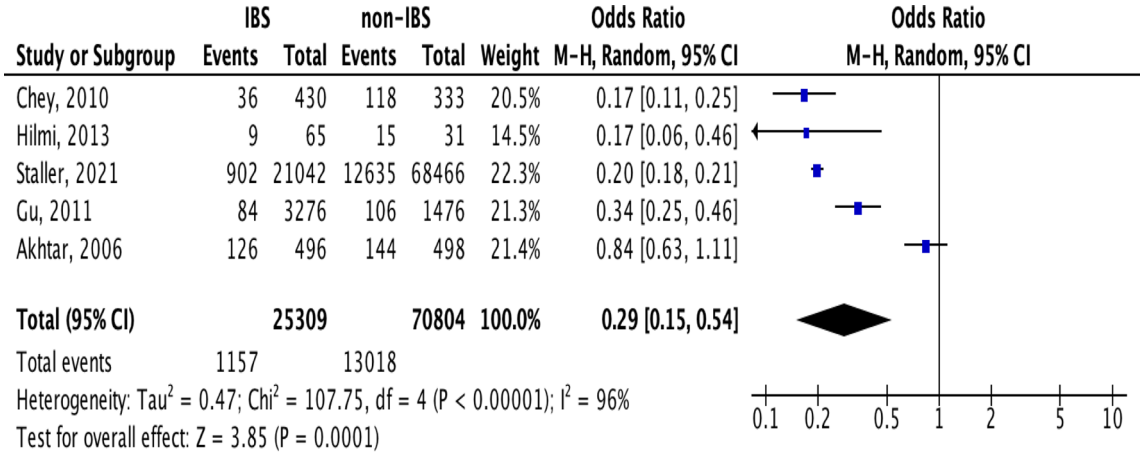

Fig. 2 Pooling of odds ratios of colorectal polyps from cross-sectional studies

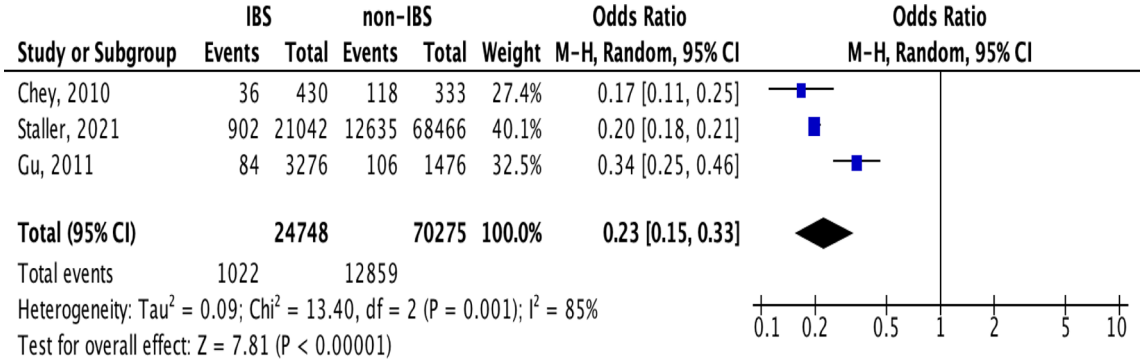

Fig. 3 Sensitivity analysis of pre-cancerous colorectal polyps from cross-sectional studies

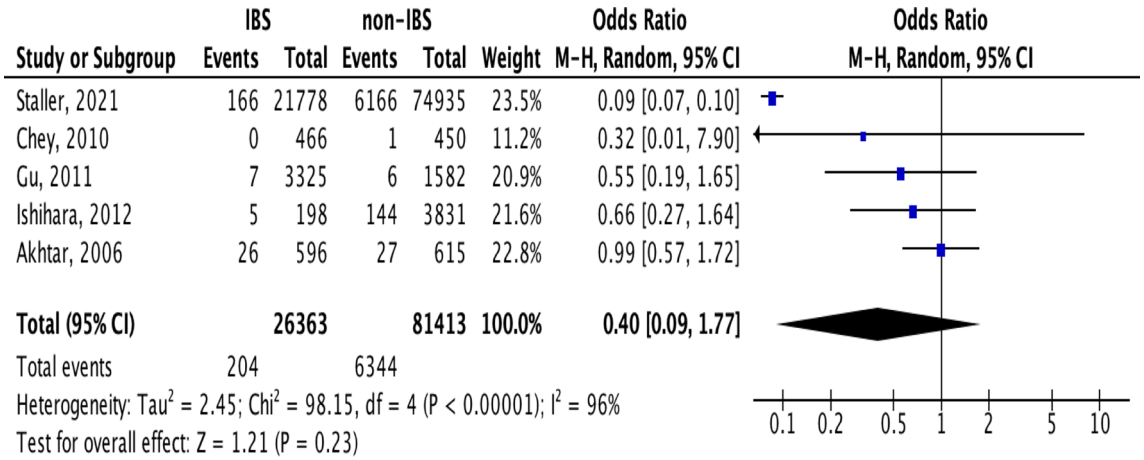

Fig. 4 Pooling of odds ratios of colorectal cancer from cross-sectional studies

criteria [38], with IBS-D being confused with IBD or chronic functional diarrhea, especially in young adults, and IBS-C being mistaken for chronic functional constipation, especially in older patients [21]. Surveillance bias could also be present, since IBS patients are more likely to be referred for colonoscopy than healthy individuals—one study found that 28.7% of colonoscopy referrals in people < 50 are due to suspected IBS [33]. This increased

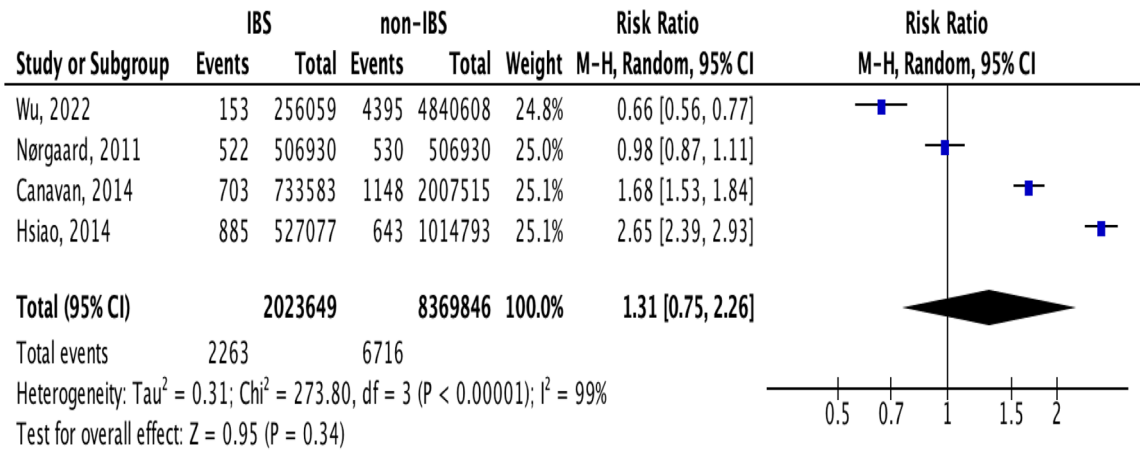

Fig. 5 Pooling of risk ratios of colorectal cancer from cohort studies

monitoring in IBS patients could lead to a falsely elevated risk of detecting and removing colonic lesions, thus lowering the risk of CRC development [23].

The cohort studies used to examine CRC incidence drew their populations from large national databases, and as such, accurately represent IBS patients' management in primary care settings rather than specialized ones [39]. However, one study contributed more than 80% of the included population [25]. To lessen the impact of this study, the random effect model was used to create the pooled effect estimate. This large study reported significantly decreased CRP prevalence in IBS patients [25], similar to our pooled estimate, but also reported significantly decreased CRC prevalence. This was a striking result for CRC in a very large study, but when pooled with the other CRC studies this observation did not drive statistical significance. All of the other studies included also had ORs suggesting decreased CRC prevalence in IBS patients, but none reached significance due to small population sizes contributing to larger variance. The random effect model used (due to substantial inter-study heterogeneity) attributed comparable weights to all study arms, despite lesser variance in the larger study.

This study has several limitations that could partially explain the inter-study heterogeneity observed. The main limitation concerns the variability of the IBS diagnosis. Several different criteria were used for diagnostic purposes, but none used the latest Rome IV criteria or recently developed biomarkers. The absence of a robust IBS diagnostic method, with periodic updates of symptom-based IBS diagnostic criteria, is a major source of heterogeneity. The number of the included studies was small, which limited our ability to perform sensitivity or stratified analysis to account for known risk factors for CRC and CRP. Additionally, all cohort studies were conducted through anonymous databases, rendering them prone to confounding [13], and one cross-sectional study did not include any IBS-C patients [10], with constipation being a common presenting symptom of CRC [21]. While most cohort studies had adequate quality, cross-sectional studies had poor or fair quality, in addition to their inherent limitation in inferring causality. Sensitivity analysis with exclusion of poor-quality studies did not significantly change the findings. Lastly, the mean follow-up in the included studies was insufficient to determine CRC risk.

In conclusion, this systematic review and meta-analysis suggests that there is a decreased prevalence of CRP in IBS. There was also a numerically reduced incidence of CRC that while notable, did not reach statistical significance. Further studies are needed to determine if there truly is a reduced rate of CRC in IBS. However, this study should be at least reassuring to clinicians that there is no suggested increased risk of pre-neoplastic or neoplastic colon disease. Colonoscopy is not indicated in individuals known to have IBS unless there are red flag symptoms, and such individuals might be expected to have a higher incidence of polyps or CRC. Therefore, the fact that we did not find an increased prevalence of CRP or CRC in IBS patients may be particularly reassuring. Our findings further support recent ACG clinical IBS guidelines suggesting that that colonoscopy should not be performed in IBS patients with no alarm features without other indication for CRC screening.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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