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A systematic review and meta-analysis investigating the association between constipation and colorectal cancer

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Abstract

Introduction: Colorectal cancer (CRC) ranks as the third most prevalent diagnosed tumor worldwide. While the association between constipation and certain tumors has been established, our study aims to examine the relationship between constipation and colorectal tumors.
Materials and Methods: This study employed a systematic review and meta-analysis following the PRISMA reporting guidelines. Searches were conducted without time restrictions until November 4, 2023, across various databases, including PubMed, Scopus, Web of Science, Cochrane, and the Google Scholar search engine. Data analysis was performed using STATA 14, and statistical significance was indicated by $P<0.05$.
Results: This meta-analysis included 18 studies (9 cohort studies and 9 case-control studies) with a total sample size of 1,462,496 individuals. Overall, no significant association was found between constipation and colorectal tumors (OR: 1.09, 95% CI: 0.91–1.31), colon tumor (OR: 1.09, 95% CI: 0.89–1.34), and rectal tumor (OR: 0.95, 95% CI: 0.69–1.32). Subgroup analysis, however, revealed no statistically significant association between constipation and colorectal tumors (OR: 0.93, 95% CI: 0.76–1.14), colon tumors (OR: 0.92, 95% CI: 0.75–1.13), and rectal tumor (OR: 0.92, 95% CI: 0.65–1.21) in cohort studies. In case-control studies, constipation was associated with an increased risk of colorectal tumors (OR: 1.78, 95% CI: 1.12–2.83) and colon tumors (OR: 2.32, 95% CI: 1.58–3.42), while the association between constipation and rectal tumor in case-control studies was (OR: 1.40 (95% CI: 0.62, 2.89).
Conclusion: In case-control studies, constipation emerged as a risk factor for colorectal and colon tumors, raising concerns given the high prevalence of constipation globally.
Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023481321) and Research Registry (UIN: reviewregistry1741) website.

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Introduction

In 2020, colorectal cancer (CRC) was identified as the third most common tumor and the second leading cause of cancer-related mortality worldwide (1). Globally, one in every 10 individuals is diagnosed with colorectal tumor (1). This cancer has evolved into a major health concern, with factors such as processed meat or red meat consumption, alcohol intake, smoking, and obesity, among others, recognized as colorectal tumor-related factors (2-5).

Constipation is a common gastrointestinal disorder and a prevalent symptom in cancer patients. This condition, characterized by infrequent bowel movements, hardened stools, or difficulty in bowel evacuation, may occur independently or secondarily with other diseases (6). Chronic constipation affects approximately 15% of adults worldwide (7). Its prevalence steadily increases after the age of 50 years, the recommended age for colonoscopy screening for colorectal lesions (7). Chronic constipation symptoms negatively impact patients' quality of life and may impose a significant social and economic burden (8,9).

Key point

There is no significant association between constipation and rectal tumor in both cohort and case-control studies. No significant association was observed in cohort studies regarding colorectal and colon tumors. However, constipation significantly increased the risk of colon and colorectal tumors in case-control studies.

It remains unclear whether constipation increases the risk of colorectal tumor or not. One hypothetical causal relationship between constipation and an elevated risk of colorectal tumor suggests that prolonged bowel transit times increase the contact duration between the colonic mucosa and carcinogenic substances in the lumen, such as bile acids (10). Given the varying results of previous studies in this field (11,12), the objective of our study is to investigate the association between constipation and colorectal tumor using a systematic review and meta-analysis approach.

Materials and Methods

Study design

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13), and its protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) and Research Registry websites.

Search strategy

A comprehensive search was performed using the Google Scholar search engine and databases, including Scopus, PubMed, Web of Science, and Cochrane, without time restrictions up to November 4, 2023. Medical Subject Headings (MeSH) and their equivalents, namely constipation, colonic inertia, dyschezia, colorectal neoplasms, colorectal tumor, and colorectal cancer, were utilized for resource retrieval. These keywords were combined using Boolean operators (AND, OR), and advanced search techniques were employed. Manual searches were also conducted by reviewing the bibliographies of eligible studies. The search strategy for PubMed was as follows: (Constipation [Title/Abstract] OR Colonic Inertia [Title/Abstract] OR Dyschezia[Title/Abstract]) AND (Colorectal Neoplasms[Title/Abstract] OR Colorectal Tumor[Title/Abstract] OR Colorectal Cancer[Title/Abstract])

Inclusion criteria

This study evaluated cohort and case-control studies that examined the association between constipation and colorectal tumor.

PICO component

- Population: Studies investigating the relationship between constipation and colorectal tumor.
- Intervention: In cohort studies, individuals with colorectal tumor, with or without constipation, were assessed. In case-control studies, individuals with constipation, with or without colorectal tumor, were examined.
- Comparison: The comparison group was similar to the target group in terms of age and gender.
- Outcomes: The odds ratio of the association between constipation and colorectal, colon, and rectal tumors.

Exclusion criteria

Cross-sectional studies, duplicate studies, studies with incomplete data, studies with unavailable full-text, review studies, low-quality studies, editorials, and studies that presented the association between constipation and colorectal tumor in a descriptive manner were excluded.

Quality assessment

As all the reviewed studies were either cohort or case-control studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (14) was used for quality assessment. This checklist consists of 22 questions, and the cut-off score in this study was 14. It should be noted that the minimum and maximum scores are 0 and 44, respectively. Two researchers evaluated discrepancies in responding to the questions and, through consultation, reached a consensus on a common response.

Data extraction

Data extraction from the reviewed studies was independently conducted by two researchers. The designed data extraction checklist included the first author's name, study type, sample size, patient age, year, country, and odds ratio of the association between constipation and colorectal, colon, and rectal tumors, along with its 95% confidence interval. A third researcher reviewed the extracted data from the two previous researchers and resolved any discrepancies.

Statistical analysis

The extracted data from the reviewed studies were based on the indicators of OR (odds ratio), RR (relative risk), and HR (hazard ratio). To combine the studies, the logarithm of these indicators was used in each study. The I^2 statistic was employed to assess heterogeneity, with three categories based on I^2 values (less than 25% indicating low heterogeneity, between 25% and 75% indicating moderate heterogeneity, and more than 75% indicating high heterogeneity) (15). Given the substantial heterogeneity among the studies (I^2 = 96.1%) in this study, a random-effects model was used. Data analysis was performed using STATA 14 software, and a significance level of $P<0.05$ was considered for the tests.

Results

A total of 1549 studies were retrieved from the mentioned databases. After reviewing the titles, 584 duplicate studies were removed. The abstracts of the remaining studies were reviewed, and 66 studies for which we did not have access to the full text were excluded. Out of the remaining 899 studies, 231 studies were excluded due to incomplete data required for the analysis. In the next stage, 668 studies were examined, with 650 studies being excluded based on other exclusion criteria, leaving 18 studies for systematic review and meta-analysis (Figure 1).

In this meta-analysis, 18 studies (nine cohort studies and 9 case-control studies) were included, with a total sample size of 1 462 496 individuals. The information from the eligible studies is presented in Table 1.

Figure 2 demonstrates that, overall, there is no statistically significant association between constipation and colorectal tumor (OR: 1.09, 95% CI: 0.91, 1.31). However, in case-control studies, constipation was associated with an increased risk of colorectal tumor (OR: 1.78, 95% CI: 1.12, 2.83). In contrast, in cohort studies, no significant association was observed between constipation and colorectal tumor (OR: 0.93, 95% CI: 0.76, 1.14) (Figure 3).

In Figure 4, across all studies, no significant association was found between constipation and colon tumor (OR: 1.09, 95% CI: 0.89, 1.34). However, subgroup analysis revealed that in case-control studies, constipation increased the risk of colon tumor (OR: 2.32, 95% CI: 1.58, 3.42), while in cohort studies, no association was observed (OR: 0.92, 95% CI: 0.75, 1.13) (Figure 5).

In Figure 6, across all studies, no significant association was found between constipation and rectal cancer (OR: 0.95, 95% CI: 0.69, 1.32). However, when studies were stratified by study type, both case-control (OR: 1.40, 95% CI: 0.62, 2.89) and cohort studies (OR: 0.92, 95% CI: 0.65, 1.21) confirmed these results (Figure 7).

The funnel plot for publication bias showed no

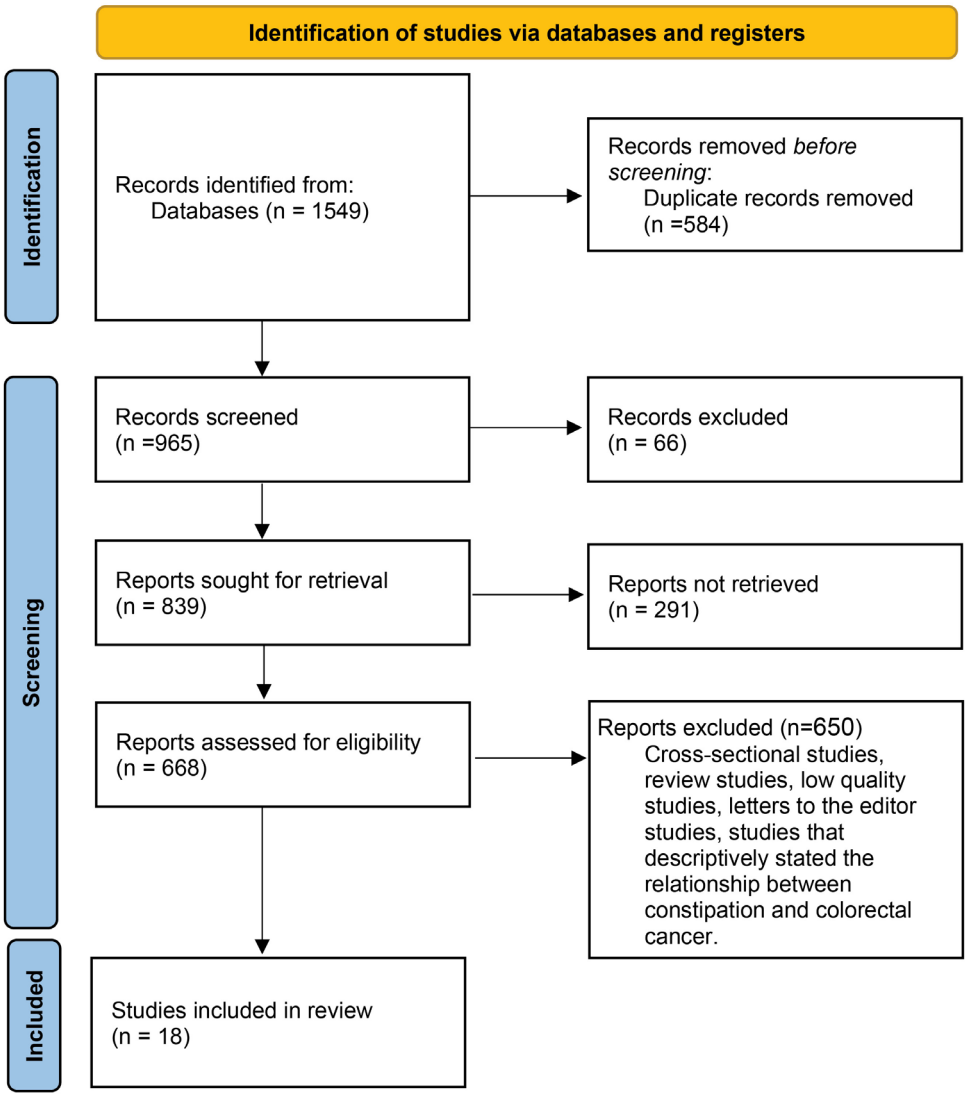

Figure 1. The flow chart of study selection.

Table 1. Specifications of articles which entered into the meta-analysis process

Author, year of publication	Country	Type of study	Number of patients	Mean age (y)	The number of people in the target group	Mean age in the target group (year)	The number of people in the control group	Mean age in the control group (year)	During the study period
Staller K, 2022(11)	Sweden	Case-control	244480	NR	41299	71.8	203181	71.8	Between July 2007 and December 2016
Sundboll J, 2019(12)	Denmark	Cohort	175901	54	NR	NR	NR	NR	1978–2013
Yang SC, 2019(16)	China	Cohort	510134	52	NR	NR	NR	NR	2004-2016
Khan NA, 2015(17)	Pakistan	Case-control	222	NR	74	41.47	148	41.47	From October 2011 to July 2015
Citronberg J, 2014(18)	USA	Cohort	8352	50-76	63	50-76	NR	NR	(2000–2002) until 2008
Guerin A, 2014(19)	USA	Cohort	115416	NR	28854	61.9	86562	61.9	1999-2011
Tayyem RF, 2013(20)	Jordan	Case-control	503	NR	232	53.3	271	51.8	Between January 2010 and December 2012
Zhang X, 2013 (W)(21)	USA	Cohort	88173	40-75	NR	NR	NR	NR	1982–2010
Zhang X, 2013 (M)(21)	USA	Cohort	23722	40-75	NR	NR	NR	NR	2000-2010
Tashiro N, 2011(22)	Japan	Case-control	832	NR	141	20-74	691	20-74	From September 2000 to December 2003
Simons CC, 2010(23)	Netherlands	Cohort	58279	55-69	NR	NR	NR	NR	1986–1999
Promthet SS, 2010(24)	Thailand	Case-control	260	NR	130		130		2002–2006
Hamilton W, 2009(25)	UK	Case-control	43791	NR	5477	>30	38314	>30	Between January 2001 and July 2006
Kojima M, 2004 (M)(26)	Japan	Cohort	25731	40–79	NR	NR	NR	NR	1988-1990
Kojima M, 2004 (W)(26)	Japan	Cohort	37198	40–79	NR	NR	NR	NR	1988-1990
Watanabe T, 2004(27)	Japan	Cohort	41670	40-64	NR	NR	NR	NR	Between June and August 1990
Roberts MC, 2003(28)	USA	Case-control	1691	NR	643	63.7	1048	66.1	Between October 1996 and September 2000
Dukas L, 2000(29)	USA	Cohort	84577	30-55	611	NR	NR	NR	1984 through 1996
Jacobs EJ, 1998(30)	USA	Case-control	838	NR	424	30-62	414	30-62	1985-1989
Kotake K, 1995(31)	Japan	Case-control	726	NR	363	63.3	363	63.3	1992 to 1994

NR: Not reported.

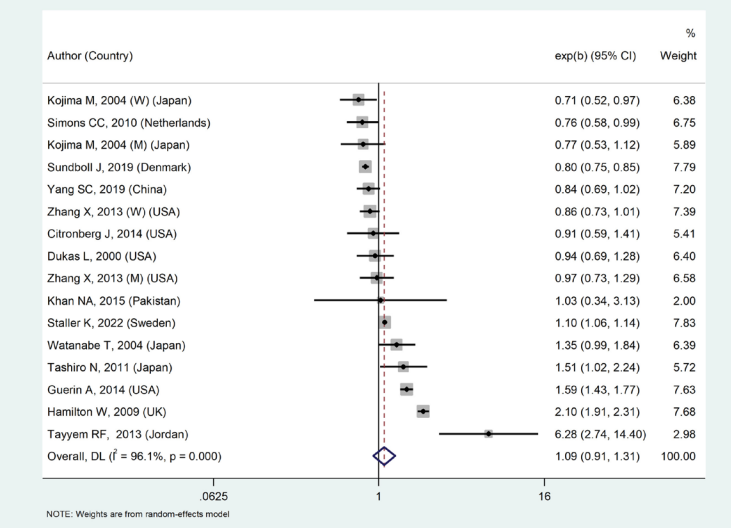

Figure 2. Forest plot showing the association between constipation and colorectal cancer.

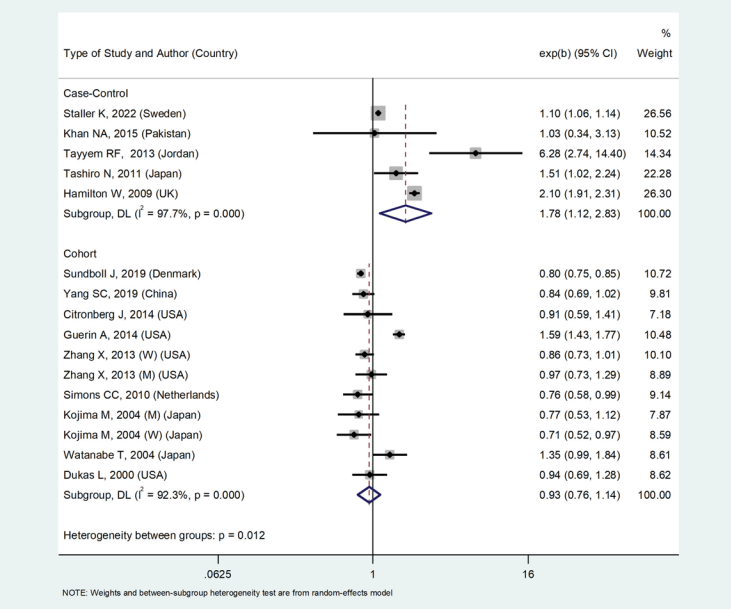

Figure 3. Forest plot showing the association between constipation and colorectal cancer by type of study.

significant asymmetry ($P=0.860$), indicating that the search for sources was comprehensive and unbiased. Indeed, studies considering constipation as a risk factor for colorectal tumor and studies believing there is no association between constipation and colorectal tumor both had equal chances of being published and were investigated in our search (Figure 8).

Discussion

The results of this meta-analysis indicate that, overall, there was no statistically significant association between constipation and colorectal, colon, and rectal tumors in both cohort and case-control studies. However, in case-control studies, constipation was associated with an increased risk of colorectal and colon tumors, indicating constipation as a risk factor for these tumors. However, no significant association was found between constipation and rectal tumor in case-control studies.

In the study by Shen et al, which aimed to investigate the association between bowel movements and the risk of colorectal tumor, the results showed that having bowel movements less than once a day, compared to once a day, had no significant association with the risk of colorectal tumor (RR=1.00, 95% CI: 0.87–1.16) (32). Similarly, in the cohort study by Yang in 2019, conducted on 510,134 individuals in China, researchers found no significant association between constipation and colorectal tumor (HR=0.84, 95% CI: 0.69–1.02) (16). Our meta-analysis also revealed no association between constipation and colorectal tumor when combining the results of all studies.

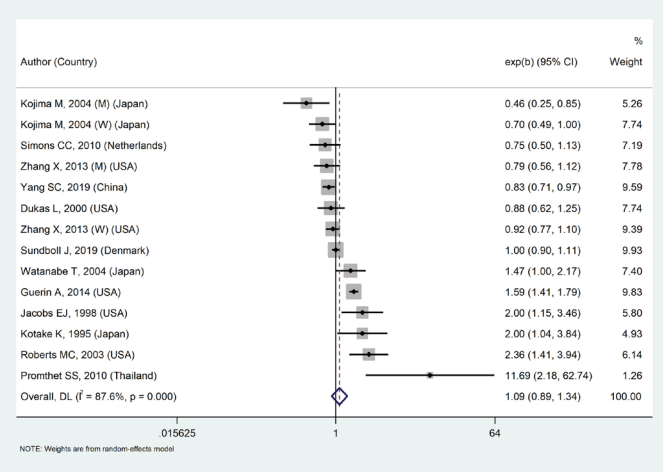

Figure 4. Forest plot showing the association between constipation and colon cancer.

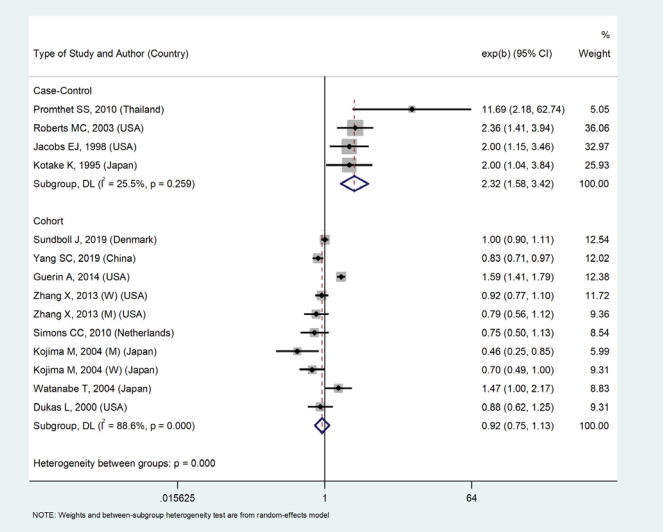

Figure 5. Forest plot showing the association between constipation and colon cancer by type of study

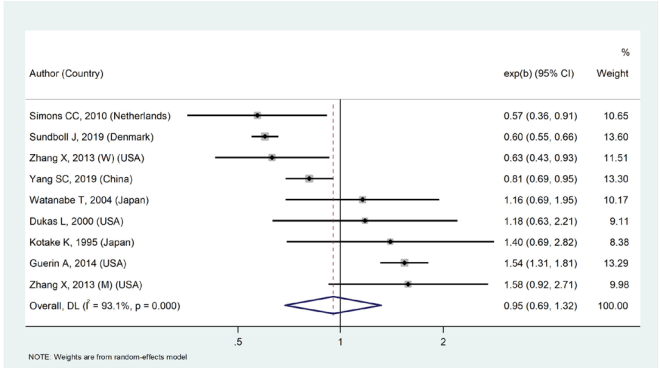

Figure 6. Forest plot showing the association between constipation and rectal cancer.

In a cohort study conducted in the United States, Guerin and colleagues concluded that constipation increased the risk of colorectal (RR=1.59, 95% CI: 1.43–1.78), colon (RR=1.59, 95% CI: 1.41–1.79), and rectal (RR=1.54, 95% CI: 1.31–1.81) tumors (19). However, the results of this study did not align with our findings, as our investigation of cohort studies showed no significant association between constipation and colorectal, colon, or rectal tumors. Differences in sample size and the age groups of patients in these two studies could be contributing factors

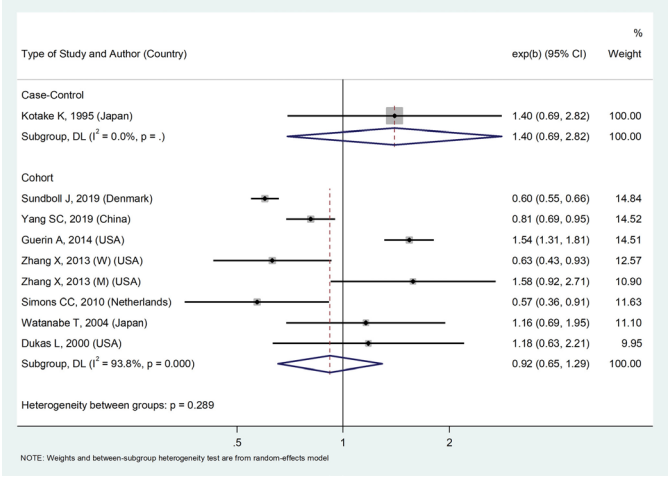

Figure 7. Forest plot showing the association between constipation and rectal cancer by type of study.

to the discrepancy in results.

In a case-control study conducted in Sweden, Staller and colleagues demonstrated that constipation was a risk factor for colorectal tumor (OR=1.10, 95% CI: 1.06–1.14) (11). Our meta-analysis also indicated that, in case-control studies, constipation is a risk factor for colorectal tumor. Conversely, a study in Pakistan in 2015 by Khan and colleagues in a case-control study showed no significant association between constipation and colorectal tumor (OR=1.03, 95% CI: 0.34–3.13) (17).

In a previous meta-analysis by Sonnenberg and Müller investigating constipation and cathartics as risk factors for colorectal tumor based on case-control studies, researchers concluded that constipation increased the risk of colorectal tumor (OR: 1.48, 95% CI: 1.32, 1.66) (33). According to the results of the meta-analysis by Power et al, investigating the association between constipation and colorectal tumor and searching databases such as Embase, Embase classic, and Medline, no significant association was found in cohort studies (OR=0.80; 95% CI: 0.61–1.04). However, in case-control studies, constipation increased the risk of colorectal tumor (OR=1.68; 95% CI: 1.29–2.18) (34). The results of these studies were consistent with our findings. It is worth noting that our study is more recent than the Sonnenberg and Müller study, and in addition to case-control studies, it also includes cohort studies. Compared to the Power study, our study searched for more databases, and studies published in the last 10 years, which were not present in the Power study, were included in the current meta-analysis.

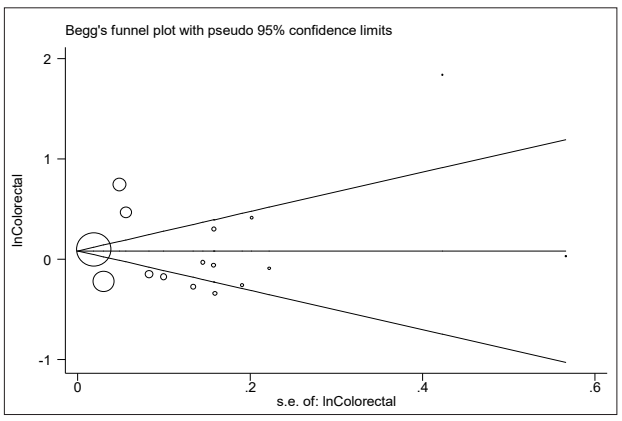

Figure 8. Publication bias.

Conclusion

Overall, we concluded that there is no significant association between constipation and rectal tumor in both cohort and case-control studies. Regarding colorectal and colon tumors, no significant association was observed in cohort studies. However, constipation significantly increased the risk of colon and colorectal tumors in case-control studies, with the risk for colon tumor being notably higher than that for colorectal tumor. Considering the high prevalence of constipation and colorectal tumor globally and the direct association between these two conditions, it seems necessary to implement appropriate health measures for the prevention and control of constipation. This approach may help to some extent in preventing the increased likelihood of developing colorectal and colon tumors.

Study limitations

The age groups specified in the studies that met the criteria were such that analyzing based on age was not possible. The studies investigating the relationship between constipation and colorectal tumor did not present the data separately for women and men, preventing subgroup analysis based on gender. The intensity of constipation was not examined in the studies investigating the relationship between constipation and colorectal tumor, so no analytical assessment based on the association between the severity of constipation and the risk of colorectal tumor was performed. In the context of the relationship between constipation and rectal tumor, only one eligible

case-control study was available, suggesting the need for further studies in this area.

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Authors' contribution

Conceptualization: Elham Mohammadzadeh and Razieh Bagheri Shahzadeh Aliakbari.
Data curation: Farzin Banei and Babak Gholamine.
Formal analysis: Atieh Nouralishahi.
Investigation: Elahe Zaremoghadam and Shahrzad Ghaffariyan.
Methodology: Atieh Nouralishahi and Amin Khameneh.
Project management: Elahe Zaremoghadam.
Resources: Alireza Baghaei and Elham Mohammadzadeh.
Supervision: Elham Mohammadzadeh.
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Visualization: Babak Gholamine.
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Writing—reviewing and editing: Elahe Zaremoghadam, Razieh Bagheri Shahzadeh Aliakbari, and Shahrzad Ghaffariyan.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD42023481321) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1741). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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