Effect of laxative use and laxative type on colorectal cancer risk: A pooling up analysis and evidence synthesis

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Abstract. Colorectal cancer (CRC) is the third most common cancer worldwide and there is a controversy regarding the influence of laxative use on the incidence of CRC. Therefore, the present study aimed to investigate the effects of laxative use and different subtypes of laxatives on the incidence of CRC. To this aim, a comprehensive search of three databases (PubMed, Embase and the Cochrane Library) was conducted on April 12, 2022, using key words that included 'laxative' and 'CRC', which initially retrieved 305 records. Ultimately, 12 studies involving 415,313 patients met all eligibility criteria and were included in a meta-analysis. Subsequently, patients were categorized into the laxative use and non-laxative use groups. Stata 16.0 software was used for all data analyses. The results indicated that laxative use was not significantly associated with CRC risk [odds ratio (OR), 0.95; 95% confidence interval (CI), 0.75-1.20; P=0.65; I^2=94.63%]. In the subgroup analyses, the effects of different laxative types were further examined. Notably, all types of laxatives except for fiber laxatives showed no significant influence on CRC risk (P>0.1). By contrast, fiber laxatives were associated with a reduced risk of CRC (OR, 0.74; 95% CI, 0.59-0.93; P=0.01; I^2=32.15%), suggesting a potential protective effect of this medication. In conclusion, the findings of the present study suggest that the use of laxatives does not increase the risk of CRC. Moreover, the use of fiber laxatives may have a protective effect by reducing CRC incidence.

Introduction

According to recent data from GLOBOCAN, colorectal cancer (CRC) is the third most common cancer (after lung cancer and female breast cancer) and the second leading cause of cancer-related death (after lung cancer). Furthermore, there were 1,926,118 newly diagnosed CRC cases and 903,859 CRC-related deaths in 2022 worldwide (1). Moreover, owing to the greater proportion of older individuals and changes in lifestyle, the incidence of CRC continues to rise (2). Screening and early diagnosis are highly challenging, and improvements could help reduce the morbidity and mortality associated with CRC (3,4). Owing to the large population and limited health care resources in China, colonoscopy is only used as a screening method for high-risk individuals (5-7). In three studies utilizing patient questionnaires, age, family history of cancer, history of smoking, diabetes and frequency of intake of certain foods (such as vegetables, fried food, pickled food and white meat) were noted as being associated with the development of CRC (8-10).

Laxatives are widely used to treat constipation and can be abused in eating disorders (particularly bulimia nervosa and binge-eating disorder), and include stimulant agents, saline and osmotic products (11). However, it has been reported that the prevalence of laxative abuse ranges from 10 to 60% (12), which might lead to disorders of electrolytes and acid-base; these disorders involve the renal and cardiovascular systems and can become life-threatening (13,14). Therefore, more precautions are required to prevent the harm caused by laxative use.

Some laxatives including phenolphthalein laxatives and magnesium laxatives have been reported to significantly increase the incidence of CRC (15-17). However, macrogol and fiber laxatives have been reported to have the opposite effects (18,19). Moreover, other studies have demonstrated that laxative use is not associated with CRC (20-26). Therefore, there is still controversy regarding the influence of laxative use on the incidence of CRC.

Materials and methods

Reporting guidelines. The present study was based on prior established studies (15-26). The findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (27).

Inclusion and exclusion criteria. The inclusion criteria for studies and patients were as follows: i) Patients who had completed any questionnaire including self-reported laxative use; ii) at least one type of laxative was reported; and iii) the

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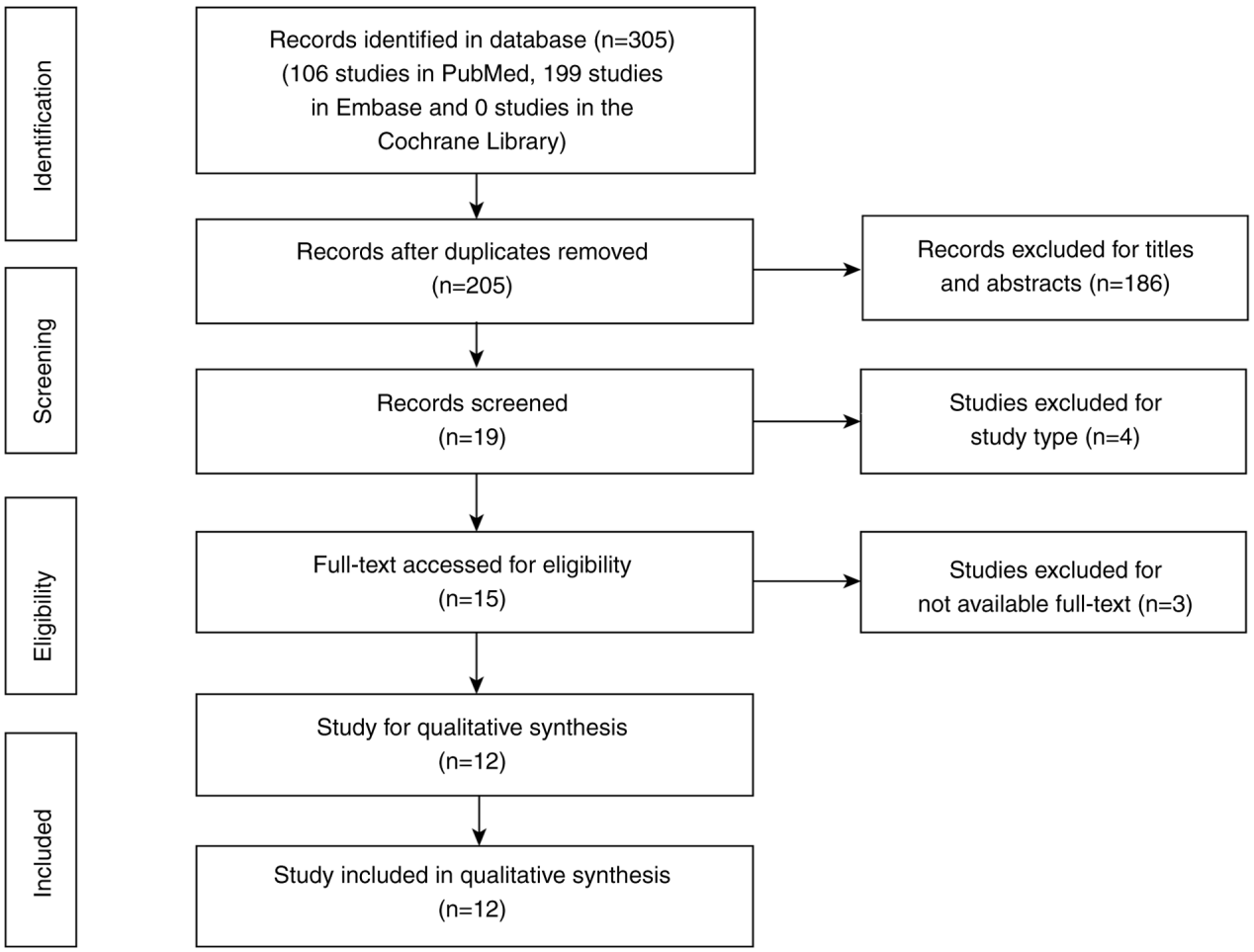

Figure 1. Flowchart of study selection.

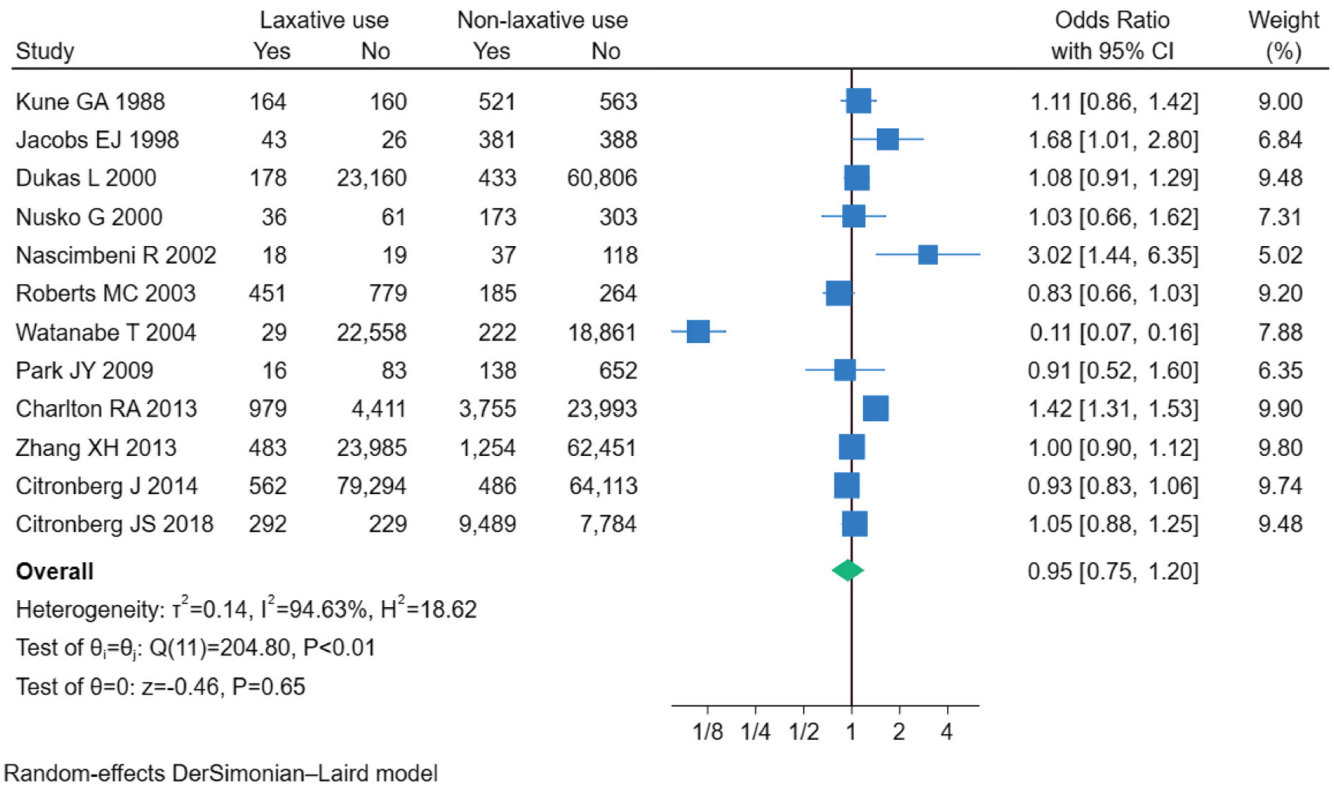

Figure 2. Incidence of colorectal cancer between the laxative use and the non-laxative use groups. CI, confidence interval.

Table I. Baseline characteristics of the included studies.

First author/s, year	Country	Study date	No. of patients	Study type	Laxative type	Conclusion	NOS	(Refs.)
Kune *et al*, 1988	Australia	1980-1981	1,442	Case-control	NR	Laxative use was unlikely to be an etiological factor in the development of CRC.	8	(20)
Jacobs and White, 1998	United States	1985-1989	838	Case-control	Phenolphthalein, fiber, magnesium and other commercial laxatives	All types of commercial laxatives, except for fiber laxatives, seemed to be associated with increased risk of CRC.	7	(15)
Dukas *et al*, 2000	United States	1984-1996	84,577	Cohort	Softeners, bulk agents and suppositories	The findings did not support an association between laxative use and the risk of CRC.	7	(21)
Nusko *et al*, 2000	Germany	1993-1996	554	Case-control	Anthranoid laxative	Anthranoid laxative use was not associated with any significant risk of developing colorectal adenoma or carcinoma.	7	(22)
Nascimbeni *et al*, 2002	Italy	1997-1999	192	Case-control	Anthranoid-containing laxatives were defined as herbal drugs containing senna, cascara, frangula, aloe and rheum, or as laxative drugs containing danthrone and purified sennosides.	The findings did not support the hypothesis of a cause-effect relationship of CRC with laxative use.	6	(23)
Roberts *et al*, 2003	United States	1996-2000	1,691	Case-control	Phenolphthalein, fiber, magnesium, other commercial and non-commercial or unknown laxatives.	There was no association between laxative use and colon cancer.	7	(24)
Watanabe *et al*, 2004	Japan	1990-1997	41,670	Cohort	NR	Laxative use increased the risk of colon cancer.	9	(16)
Park *et al*, 2009	United Kingdom	1993-1997	889	Cohort	NR	Laxative use was not associated with CRC risk.	8	(25)
Charlton *et al*, 2013	United Kingdom	2000-2009	33,138	Case-control	All stimulant, osmotic and. bulk laxatives, fecal softeners and bowel cleansing preparations	A reduced CRC risk associated with macrogol use was observed after accounting for the lead time for CRC.	7	(18)
Zhang *et al*, 2013	United States	1982-2010	88,173	Cohort	Softeners, bulking agents and suppositories.	Laxative use seemed to not be associated with CRC risk.	9	(26)
Citronberg *et al*, 2014	New Zealand	2000-2010	144,455	Cohort	Fiber-based (Metamucil, Citrucel, FiberCon or Fiberall) and non-fiber (Ex-lax, Correctol or milk of magnesia) laxatives	The risk of CRC increased with non-fiber laxative use and decreased with fiber laxative use.	9	(19)

Table I. Continued.

First author/s, year	Country	Study date	No. of patients	Study type	Laxative type	Conclusion	NOS	(Refs.)
Citronberg *et al*, 2018	United States	1997-2008	17,694	Case-control	Fiber (Metamucil, Citrucel, Fibercon, Serutan and psyllium) and non-fiber (Ex-Lax, Correctol, Dulcolax, Senokot, Colace, castor oil, cod liver oil, mineral oil, milk of magnesia, lactulose and Epsom salts) laxatives.	Individuals who reported using non-fiber-based laxatives regularly were at a significantly increased risk for CRC compared with those who reported no laxative use. No statistically significant associations were observed between fiber-based laxative use and CRC.	9	(17)

NR, not reported; NOS, Newcastle-Ottawa Scale; CRC, colorectal cancer.

Figure 3. Funnel plot of all types of laxatives. CI, confidence interval.

incidence of CRC was reported. The exclusion criteria were as follows: i) The type of study was case reports, reviews, meta-analysis, letters to the editor, comments or conference abstracts/proceedings (due to typically limited peer review and incomplete datasets); ii) only had pediatric populations; and iii) data were insufficient including missing core variables, incomplete metrics or non-extractable data.

Search strategy and study selection. A comprehensive search strategy was developed to identify relevant studies, which included terms such as 'laxative' and 'CRC'. For laxative, the additional search terms were 'cathartics' OR 'laxative'. For CRC, the additional search terms were 'colorectal cancer' OR 'colon cancer' OR 'rectal cancer' OR 'colorectal neoplasm' OR 'colon neoplasm' OR 'rectal neoplasm' OR 'colorectal tumor' OR 'colon tumor' OR 'rectal tumor'. The search scope was limited to the title, abstract or key words, and only studies published in English were included. The search strategy was implemented by two independent authors across three databases including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and the Cochrane Central Register of Controlled Trials (https://www.cochranelibrary.com/central). After removing duplicated studies, the titles and abstracts were screened to identify potentially relevant studies. Then, full texts were reviewed to determine eligible studies based on the inclusion and exclusion criteria. Additionally, the reference lists of included studies were examined to identify additional relevant articles. In cases of disagreement between the two authors, a group discussion with a third individual was consulted to reach a consensus.

Data collection. Data extraction was performed independently by two authors at the same time. The study characteristic data extracted were as follows: The first author, publication year, country where the study was conducted, study period, sample size, study type, laxative subtype, and conclusion. Patients who used laxatives were categorized into the laxative use group, and those who had no history of laxative use were categorized into the non-laxative use group. The incidence of CRC in each group was recorded. To ensure accuracy and completeness, the extracted data were cross-checked by both authors, and any discrepancies were resolved through discussion.

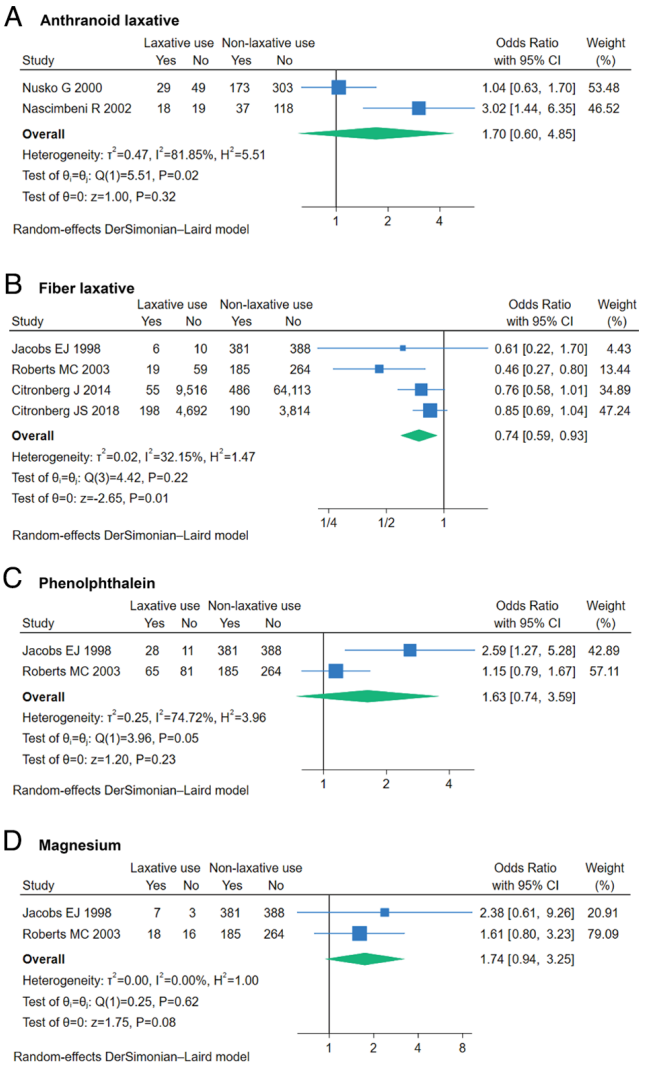

Figure 4. Incidence of colorectal cancer between the laxative use and the non-laxative use groups for different laxative types including (A) anthranoid, (B) fiber, (C) phenolphthalein and (D) magnesium laxatives. CI, confidence interval.

Quality assessment. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) score (28). Then, two independent authors assigned ratings based on the following criteria: 9 points indicated high quality, 7-8 points indicated median quality and <7 points indicated low quality. Any discrepancies in scoring were resolved through discussion or consultation with a third individual.

Statistical analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to compare the incidence of CRC between the laxative use and the non-laxative use groups. Heterogeneity was assessed using the I^2 statistic and the χ^2 test (29,30). According to the Cochrane handbook, an I^2<30% was considered non-important, an I^2 range of 30-60% was considered moderate and an I^2>60% was considered substantial (30). The random-effect model was applied as the default model, and P<0.05 indicated a statistically significant difference. Publication bias was evaluated using funnel plot. All statistical analyses were performed using Stata V18.0 (StataCorp LP).

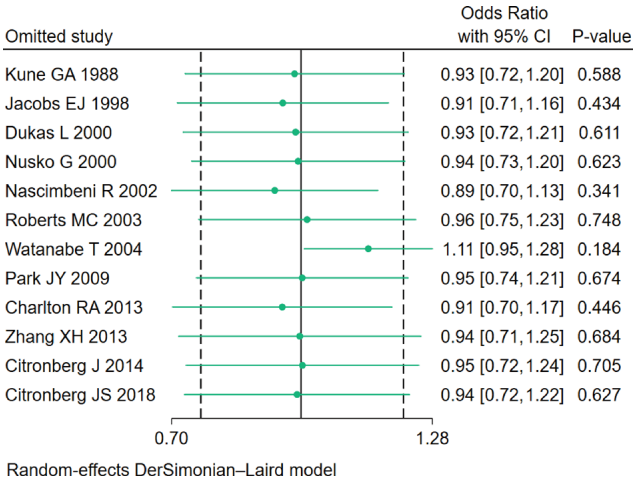

Figure 5. Sensitivity analysis. CI, confidence interval.

Results

Study selection. Following the initial search, 305 studies were identified (106 studies in PubMed, 199 studies in Embase and 0 studies in the Cochrane Library). After removing duplicates, 205 studies remained. Screening of the titles and abstracts identified 19 studies with potentially relevant content. Finally, 12 observational studies with sufficient data were included in the pooled analysis after full-text review (Fig. 1). Additionally, the reference lists of these studies were screened, but no further eligible studies were identified.

Baseline characteristics. The 12 included studies were published between 1988 and 2019, spanning a period of 30 years. These studies were conducted in seven countries, with 5 studies originating from the United States. Among the included studies, 7 were case-control studies and the remaining 5 were cohort studies. The primary laxative types investigated included anthraquinone, fiber, phenolphthalein and magnesium laxatives. Detailed information on the laxative types and the conclusions of each study are shown in Table I.

History of laxative use and the risk of CRC. The results from the 12 included studies indicated that a history of laxative use was not significantly associated with the incidence of CRC (OR, 0.95; 95% CI, 0.75-1.20; P=0.65; I^2=94.63%; Fig. 2) To assess potential publication bias, a funnel plot was generated (Fig. 3). Visual inspection of the funnel plot revealed asymmetry, suggesting the possibility of publication bias.

History of different laxative type use and the risk of CRC. In total, 4 studies reported data on fiber laxatives. Pooled analysis revealed that fiber laxative use was associated with a reduced risk of CRC (OR, 0.74; 95% CI, 0.59-0.93; P=0.01; I^2=32.15%; Fig. 4B). Additionally, 3 other types of laxatives were each reported in 2 studies. However, anthranoid, phenolphthalein and magnesium laxatives showed no significant association with CRC risk (Fig. 4A, C and D).

Sensitivity analysis. To evaluate the robustness of the study findings, a sensitivity analysis was performed by sequentially

excluding each study and re-running the pooled analysis. The results remained consistent across all iterations, indicating that the findings were not significantly altered by any single study (Fig. 5).

Discussion

In the present study, 12 eligible observational studies involving 415,313 patients were identified for analysis. After pooling the data, no association between laxative use and the risk of CRC was found. Subgroup analyses of different laxative types revealed that the fiber laxative group had fewer patients with CRC than the non-fiber laxative group. Other types of laxatives, including anthranoid, phenolphthalein and magnesium laxatives, had no identified effect on the incidence of CRC.

To diagnose patients with CRC earlier, both CRC-related symptoms and strong risk factors for CRC should be considered. Staging at detection dramatically impacts survival outcomes, with 5-year survival rates of 91% for localized disease (Stage I) versus merely 14% for metastatic cases (Stage IV) (31). Then, late diagnosis increases surgical morbidity risks and permanent ostomy rates, severely compromising quality of life (32). In addition to commonly examined characteristics, including age, family history of cancer, history of smoking, diabetes and the frequency of food intake (8-10), drug use, including macrolide and lincosamide use, has also been reported to be a risk factor for CRC (33). Drugs might change the gut microbiota composition and destroy immune responses, which could lead to chronic inflammation and tumor progression (34-36). Additionally, quinolones (a type of antibiotic) can damage DNA, which increases the risk of cancer (37).

Laxatives are also widely used and might influence CRC. Certain studies have reported that non-fiber laxatives are associated with an increased risk of CRC (15,17,19). A previous study examining 41,670 cases demonstrated that laxative use increased the risk of colon cancer (16). Conversely, other studies revealed that the risk of CRC decreased with fiber laxative use (15,19), and Charlton *et al* (18) reported that macrogol reduces the risk of CRC. Additionally, other studies did not find an overall association between laxative use and CRC (20-26), and a previous systematic review and meta-analysis indicated that there was no association between anthraquinone laxative use and the development of CRC (38). Therefore, there is notable controversy regarding whether laxatives have harmful effects, protective effects or no effect on the incidence of CRC.

Long-term medication or drug abuse might damage the intestinal environment. Some biological evidence has shown that ecological imbalance, especially in some bacterial strains, might promote cancer by altering cell growth, differentiation and apoptosis (39,40). Some non-fiber laxatives including anthranoid laxatives and phenolphthalein were found to have mutagenic and genotoxic effects, which might be the mechanisms underlying the development of CRC risk (19,41,42). The potential mechanism underlying the protective effect of fiber laxatives might be that high dietary fiber intake could dilute carcinogens and bind carcinogenic bile acids. Additionally, fiber helps produce short-chain fatty acids, which can normalize cell proliferation and differentiation as well as promote anticarcinogenic action (43-45). However, the association between laxative use and CRC risk is complex, and the present study, as a synthesis of observational data, could not clarify the mechanisms underlying various laxative types.

To the best of our knowledge, the present study represented the largest and most comprehensive pooled analysis to date on the association between laxative use and CRC risk. The findings of the present study resolved existing controversies, that have notable implications for clinical practice and may pave the way for future investigations into the mechanisms underlying laxative effects on CRC risk. However, the present study has several limitations. First, the results might have a bias accounting for the frequency of laxative intake. However, there were not enough data for a dose-response meta-analysis. Second, 3 of the 12 included studies only analyzed colon cancer cases, although both colon cancer and rectal cancer originate from epithelial cells (46), which may have led to the high heterogeneity of the studies. Third, some of the included studies were old, which might limit the universality of the study findings. Fourth, while funnel plot asymmetry suggested potential publication bias, statistical confirmation was limited by the small number of included studies (n=7). This pattern may reflect the selective reporting of positive outcomes. Therefore, additional long-term randomized controlled trials that investigate the relationship between the dosage of laxatives administered and the incidence of CRC are needed to determine the potential mechanisms and effects of different types of laxatives.

In conclusion, the standardized use of laxatives for treatment is safe. Moreover, fiber laxatives may decrease the risk of CRC. However, more studies are needed to determine whether laxative abuse increases the risk of CRC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

LXR conceived the study. LXR and ZXM designed the search strategy, performed the literature search and data extraction and assessed the risk of bias. LXR and ZXM confirm the authenticity of all the raw data. ZXM performed the data analysis and wrote the first draft of the manuscript. LXR and ZXM revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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