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Meta-Analysis and Systematic Review of the Role of Appendectomy in the Pathogenesis of Colorectal Cancer

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Aim. Given the potential for physiological alterations in the gastrointestinal tract following appendix removal, which may influence carcinogenesis, we embarked on a systematic review and meta-analysis to explore the possible association between appendectomy and the subsequent risk of colorectal cancer (CRC).
Methods. Our systematic investigation utilized sources including the Cochrane Library, Embase, PubMed, ClinicalTrials.gov, and Web of Science, covering research up to February 1, 2023. We assessed the impact of appendectomy on colorectal cancer, employing a random effects model to calculate the pooled hazard ratio (HR) for developing CRC post-appendectomy and its 95 % confidence interval (CI).
Results. This review and meta-analysis incorporated a total of 10 studies, comprising 1,001,693 cases of appendectomy and 39,463 instances of CRC. The meta-analysis revealed a pooled HR of 1.04 (95 % CI: 1.0–1.08) for developing CRC following appendectomy. Notably, the HR for CRC development increased to 1.20 (95 % CI: 0.69–1.69) when considering only cases with more than 10 years of follow-up.
Conclusion. The findings indicate a marginally increased risk of colorectal cancer in cases without a specified follow-up period. However, this elevated risk did not persist over the long term (exceeding 10 years). The heterogeneity of the included studies appears to have influenced our results. Nevertheless, it is advisable for physicians to weigh the potential benefits of alternative therapies and consider the future complications that may arise from an unnecessary appendectomy.
Keywords: colorectal cancer, appendectomy, colon cancer
Conflict of interest: the authors declare no conflict of interest.

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Метаанализ и систематический обзор роли аппендэктомии в патогенезе колоректального рака

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Цель. Учитывая возможность физиологических изменений в желудочно-кишечном тракте после удаления аппендикса, которые могут влиять на канцерогенез, мы выполнили систематический обзор и метаанализ с целью изучения возможной связи между аппендэктомией и последующим риском колоректального рака (КРР).
Методы. В систематическом исследовании использовались такие источники, как Кокрейновская библиотека, Embase, PubMed, ClinicalTrials.gov и Web of Science, охватывающие исследования до 1 февраля 2023 г. Проведена оценка влияния аппендэктомии на колоректальный рак, при этом была использована модель случайных эффектов для расчета объединенного отношения рисков (ОР) развития колоректального рака после аппендэктомии и его 95%-ный доверительный интервал (95% ДИ).
Результаты. В данный обзор вошли 10 исследований, включающих 1 001 693 случая аппендэктомии и 39 463 случая КРР. Метаанализ выявил совокупный ОР, равный 1,04 (95% ДИ: 1,0–1,08) для развития колоректального рака после аппендэктомии. Примечательно, что ОР развития КРР увеличился до 1,20 (95% ДИ: 0,69–1,69) при рассмотрении только случаев с периодом наблюдения более 10 лет.
Заключение. Результаты указывают на незначительно повышенный риск колоректального рака в случаях без определенного периода наблюдения. Однако этот повышенный риск не сохранялся в долгосрочной перспективе (более 10 лет). Гетерогенность включенных исследований, по-видимому, повлияла на наши результаты. Тем не менее врачам рекомендуется взвесить потенциальную пользу альтернативных методов лечения и принять во внимание будущие осложнения, которые могут возникнуть в результате ненужной аппендэктомии.
Ключевые слова: колоректальный рак, аппендэктомия, рак толстой кишки
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Surgical appendectomy, the standard treatment for appendicitis, is the most common cause of abdominal surgery worldwide. This procedure is predominantly performed in cases of concern for acute appendicitis (AA) [1]. While appendectomy remains the preferred method, there is growing evidence that alternatives, like antibiotics, may effectively treat uncomplicated AA [2]. Furthermore, incidental appendectomy is frequently performed in women, often during procedures such as salpingectomy or hysterectomy [3].

The primary indications for this frequent surgery are threefold: 1) The appendix, especially the vermiform appendix, is historically regarded as a vestigial organ. 2) The long-term effects of losing the appendix are thought to be negligible. 3) AA is a potentially fatal disease; though the findings are mixed, some studies have indicated an increased risk of cancer, particularly in individuals with a history of appendectomy [4].

Considering the appendix's role in immune functions, it is essential to evaluate whether its presence or absence is linked to the development of other diseases, including colorectal cancer, inflammatory diseases, and infections [5]. The outcomes of previous studies in this area have been inconsistent [6–11]. Consequently, a comprehensive review study is needed to amalgamate these findings. Given that appendectomy is often undertaken for elective indications, the objective of our study is to determine whether the surgeries in question might increase the risk of developing CRCs.

Material and methods

Search strategy and selection criteria

To identify relevant studies, we conducted searches on Web of Science, Cochrane Library, PubMed, Embase, and ClinicalTrials.gov, up to February 2023, without restrictions on publication date, language, or article type. Our search strategy employed both free text terms and Medical Subject Headings (MeSH) with the keywords "appendectomy", "colon cancer", "rectal cancer", and "colorectal cancer". This study adhered to the MOOSE guidelines and the Cochrane Handbook. Additionally, we manually searched the references of included studies to ensure comprehensive coverage.

Data extraction and outcome measures

Data were independently extracted by two authors (MA and NP) using a standardized template. The Newcastle-Ottawa Quality Assessment Scale was utilized to evaluate the quality of the studies. Any disagreements were resolved through discussion, and a third researcher verified the quality assessment and accuracy of data extraction.

Statistical analysis

The primary outcome of interest was the odds ratio (OR) of post-appendectomy colorectal cancer (CRC). For our meta-analysis, we used hazard ratios (HR) to evaluate survival outcomes. In cases where studies did not present HRs or ORs, we calculated these ratios using the provided information (exposed, non-exposed, and incidence of CRC). Given the low incidence of CRC, standardized incidence ratios (SIR), HRs, and relative risks (RR) were treated as equivalent to ORs. Analytical tools included the Cochran Q test, I^2, tau test, and DerSimonian — Laird random-effects models.

Statistical significance was set at a p-value < 0.05. Heterogeneity among studies was assessed using the I^2 statistic, with I^2 values of 76–100 %, 61–75 %, 31–60 %, and 0–30 % indicating considerable, substantial, moderate, and low heterogeneity, respectively.

To evaluate publication bias, we employed Egger's funnel plot (trim-and-fill method). Meta-regression was conducted to identify sources of heterogeneity. Sensitivity analyses were performed to assess the impact of individual studies on the overall results or heterogeneity. All analyses were conducted using Stata v. 14.1 (StataCorp, College Station, USA), with a p-value of 0.05 determining statistical significance.

Results

Study selection

During the initial screening, we identified 526 non-duplicated articles through database searching. Two reviewers selected potentially relevant studies published between 2013 and 2023, eventually including 10 studies in the review. The study selection process is detailed in the PRISMA flow chart shown in Figure 1.

A total of 10 studies encompassing 16,659,230 subjects were included, all of which were retrospective in nature. Among these, three studies originated from Korea, three from China, two from the USA, one from Hungary, and one from Sweden. The overall mean follow-up duration was 12 years (Table 1).

The Association between appendectomy and developing CRC

The current analysis included 1,001,693 cases of appendectomy, of which 39,463 resulted in CRC. Out of the 10 studies, three found no significant association between appendectomy and CRC risk, one indicated a reduced risk of CRC

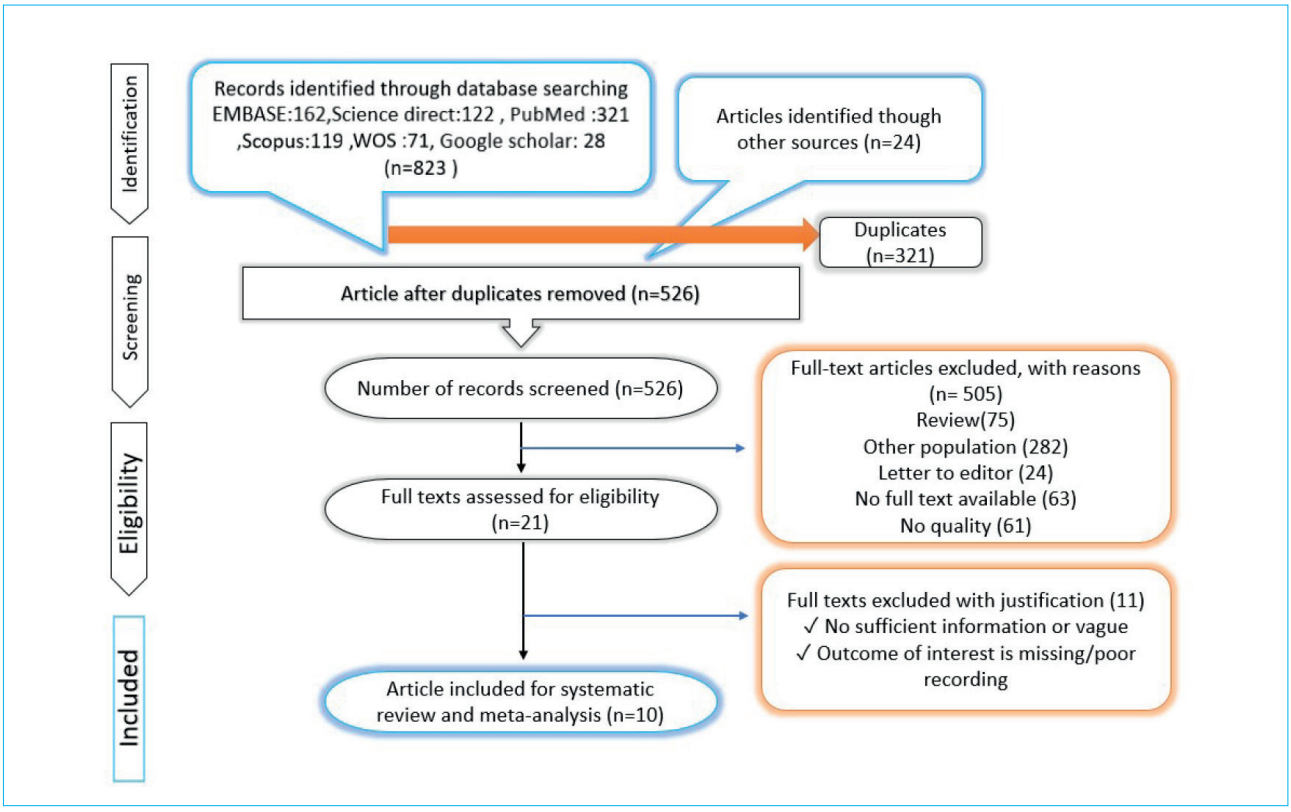

Figure 1. PRISMA flow diagram for the inclusion of the studies

Table 1. General characteristics of the included studies

First author	Publication year	Country	Design	Sample size	Age	Follow up	Gender (%)	
							Female	Male
van den Boom [36]	2022	Netherlands	Retrospective	7136	>55 (69.8 ± 9.3)	13.3	60.3	39.7
Shi [37]	2021	China	Retrospective	135.468	>18	N/A	N/A	N/A
Mándi [38]	2021	Hungary	Retrospective	860	38.5	15	N/A	N/A
Lee [39]	2021	Korea	Retrospective	486.844	N/A	12.31	47.7	52.3
Dahabra [40]	2021	USA	Retrospective	13.689.430	>30	5.0	N/A	N/A
Park [41]	2020	Korea	Retrospective	632.404	44.06 ± 14.09	5.6	57.02	42.98
Lee [9]	2018	Korea	Retrospective	707.663	41.70 ± 14.7	13.66	49.09	50.91
Song [8]	2016	Sweden	Retrospective	480.382	32.5 ± 19.6	18.6 ± 10.9	45.30	54.70
Wu [10]	2015	China	Retrospective	379.619	31.8 ± 18.38	12.31	51.71	48.29
Ugai [42]	2022	USA	Retrospective	139.424	N/A	N/A	N/A	N/A

Note: N/A — data not available.

post-appendectomy, five reported a significant increase in CRC risk following appendectomy, and one identified a significant association specifically among women and the elderly (Table 2).

Meta-analysis of the HR of developing CRC after appendectomy

Our meta-analysis revealed a pooled HR of 1.04 (95% CI: 1.0–1.08) for the risk of developing CRC post-appendectomy (Table 2, Fig. 2).

Analysis based on follow-up time yielded a pooled HR of 1.20 (95% CI: 0.69–1.69) for developing CRC after more than 10 years post-appendectomy (Table 2, Fig. 3).

Subgroup analysis was conducted according to the country of the included studies. The results showed the highest HR (1.14) in China, followed by Korea (1.12), the USA (1.07), Hungary (0.92), and Sweden (0.70) (Fig. 4).

Table 2. Systematic review of the studies regarding the association between appendectomy and risk of CRC development

Author	Appendectomy cases	Result	CRC cases	HR (95% CI)	≥ 60	Men to women HR
van den Boom	1373	Appendectomy cases have reduced risk of CRC	216	0.65 (0.43–0.95)	N/A	N/A
Ugai	N/A	No significant association was found between appendectomy and risk of CRC	2819	0.52 (0.33–0.84)	N/A	N/A
Mandi	185	No significant association was found between appendectomy and risk of CRC	6000	0.92	N/A	1.06
Wu	84,408	Appendectomy cases might have increased risk of CRC	10,637	1.14 (1.02–1.28)	12.8	1.15
Song	480,382	No significant association was found between appendectomy and risk of CRC	3733	0.7 %	N/A	N/A
Lee	243,422	Appendectomy cases had higher risk of developing CRC at the first post-operative year	4324	2.97 (2.72–3.24)	N/A	N/A
Park	158,101	Women and elderly patients are at higher risk of developing CRC after appendectomy	2699	1.034 (0.973–1.098)	N/A	0.695
Dahabra	N/A	Appendectomy cases have increased risk of CRC	0.08	1.52 (1.23–1.69)	N/A	1.84
Lee	N/A	Appendectomy cases might have increased risk of CRC	N/A	0.80 (0.57–1.13)	N/A	N/A
Shi	33,822	Appendectomy cases have increased risk of CRC	N/A	N/A	N/A	1.19

Note: N/A — data not available.

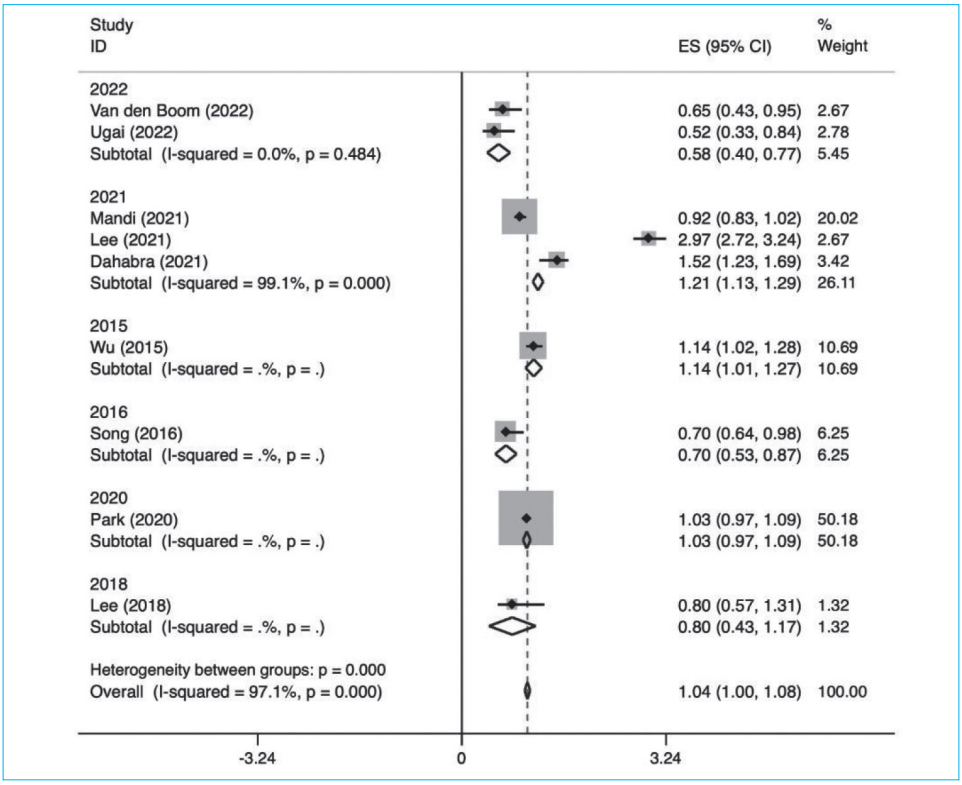

Figure 2. Meta-analysis of the HR of developing CRC after appendectomy

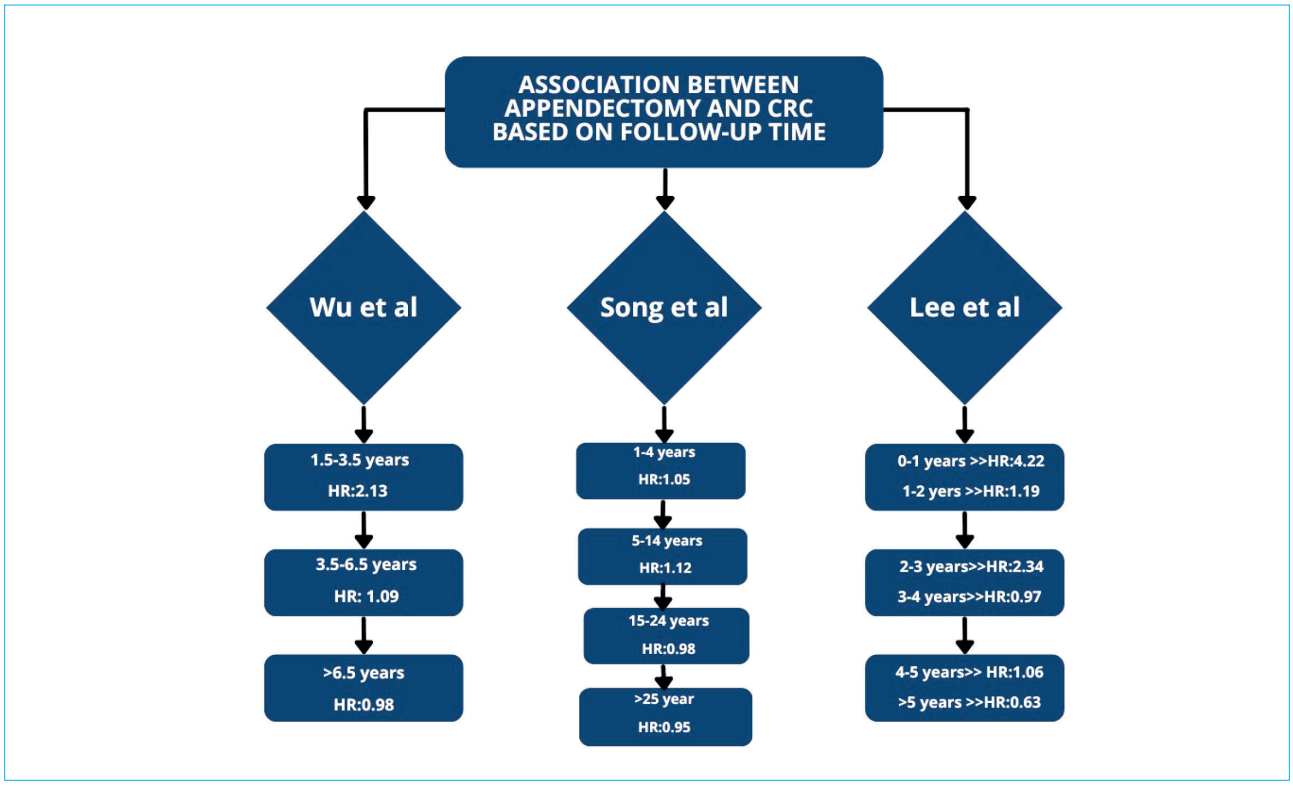

Figure 3. The association of the HR of developing CRC and appendectomy based on follow-up time in three included studies

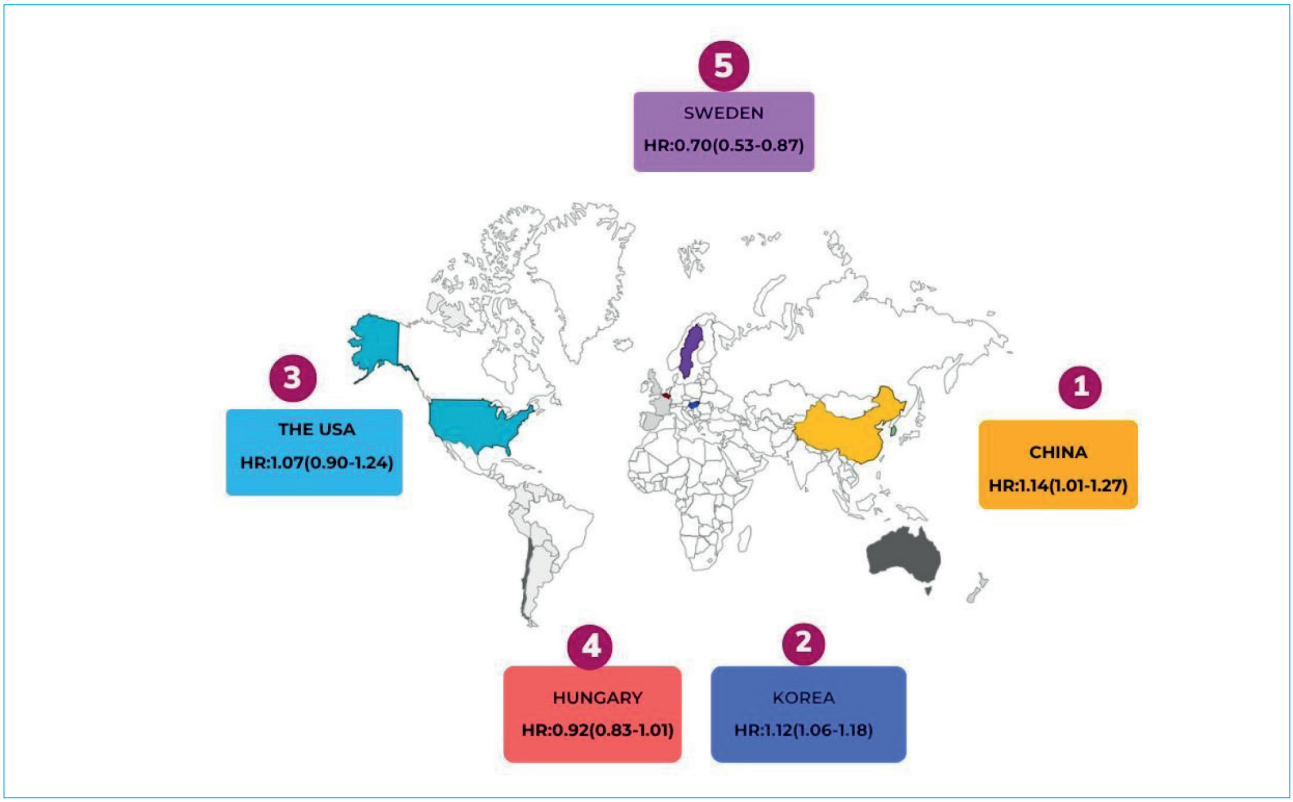

Figure 4. The association of the HR of developing CRC and appendectomy based on country of the included studies

Publication bias assessment

Figure 5 displays Egger's funnel plot for the studies included in our analysis, assessing the HR of developing CRC post-appendectomy. The plot suggests the possibility of publication bias (Fig. 5).

Discussion

The primary indication for an appendectomy is often acute appendicitis. However, there are instances where this surgery is considered in the absence of definitive imaging characteristics of appendicitis, primarily to address chronic abdominal pain [6]. Several research papers have evaluated the rate of colorectal cancer (CRC) in patients who previously underwent appendectomy [6, 7]. With advancements in medical imaging and CRC screening, leading to earlier diagnosis, our study aims to review more recent publications to ascertain the role of appendectomy in the pathogenesis of CRC in the general population.

Our study reported a pooled hazard ratio (HR) of 1.04 in patients who had undergone an appendectomy compared to those who had not. This finding is not entirely consistent with previous meta-analyses, which reported an HR of 1.31 for appendectomy patients [6]. Like our study, these analyses also noted high heterogeneity, possibly due to the lengthy follow-up periods and changing environmental factors over time [6]. Unfortunately, only three studies stratified HRs by follow-up time [8–10]. Each of these studies used different time frames for stratification, precluding a combined analysis. However, they all reported a higher risk of developing CRC in the years immediately following appendectomy [8–10], with this risk decreasing over longer follow-up periods.

The appendix, a domicile for diverse colonic microbiomes and part of the gut-associated lymphoid tissue, plays a role in immune function. Removal of the appendix might diminish host immune barrier functions and microbial diversity, leading to a higher susceptibility to dysbiosis. This dysbiosis can induce various diseases via the brain-gut axis, including celiac disease, inflammatory bowel disease, diabetes mellitus, rheumatoid arthritis, neurological disorders, and cardiovascular disease [11–17]. Cohort studies have observed significant correlations between these diseases and a history of appendectomy [18–24]. Dysbiosis is also linked to certain cancers, such as gastrointestinal and breast cancers [25–31]. The disruption of the microbial ecosystem in the gastrointestinal tract post-appendectomy is reported to critically affect the pathogenesis of malignancy [8, 10]. However, the high heterogeneity among the included studies precludes definitive conclusions.

Some studies, including one by J.A. Rothwell et al., reported an inverse association between appendectomy and CRC risk [32]. They suggested that the association found in some previous studies might be due to selection bias, as their study only included appendectomies unrelated to intestinal issues, revealing an inverse relationship between CRC and appendectomy history [32]. This raises the possibility that studies reporting high short-term CRC rates post-appendectomy could be biased [8–10]. However, excluding patients with appendectomies

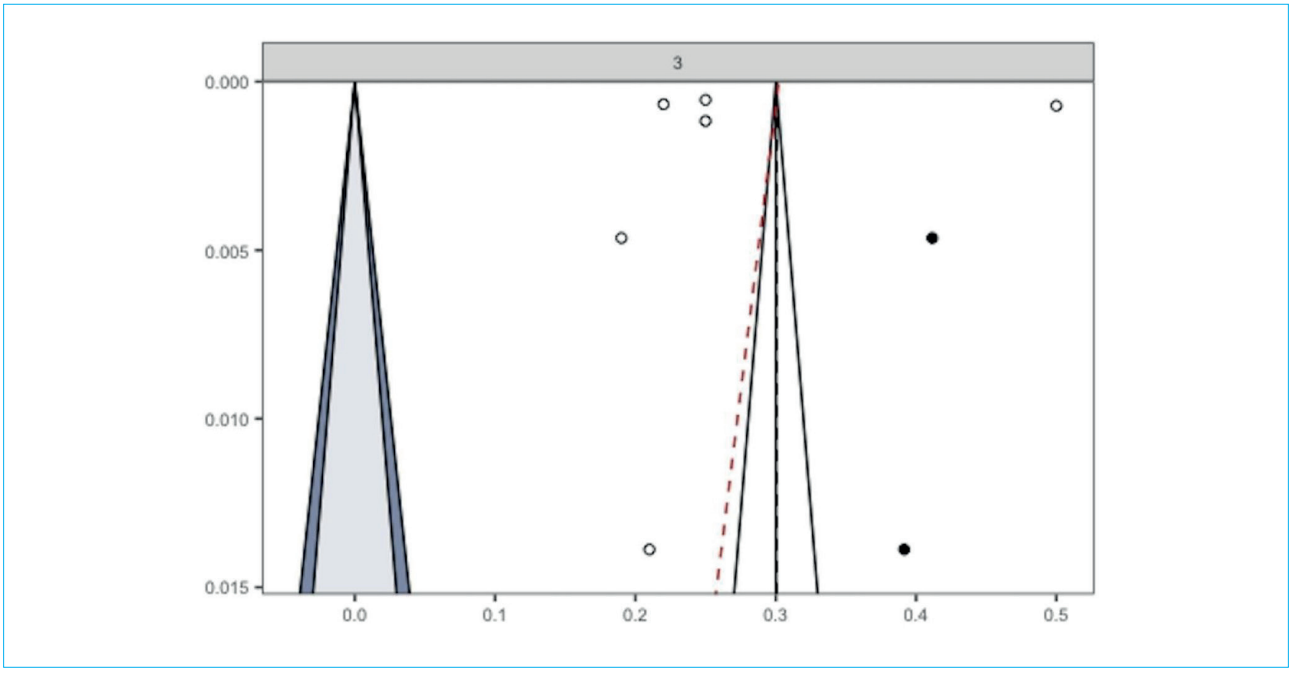

Figure 5. Egger's funnel plot for publication bias

due to intestinal problems could also introduce bias, possibly explaining the inverse association found by J.A. Rothwell et al. [32]. The appendix's role in lymphoid tissue development in the gut could imply that its absence limits inflammation and auto-reactive damage in the colorectal region [33, 34].

Given the varying follow-up periods in our included studies, we performed a subgroup analysis for HR after 10 years post-appendectomy, resulting in an HR of 1.20, aligning more closely with previous meta-analyses [6]. Due to the high heterogeneity in published papers, further prospective cohort studies are needed, taking into account factors such as the cause of appendectomy and follow-up duration.

The increased CRC risk should not influence physicians' decisions in acute complicated appendicitis cases. However, in uncomplicated cases, several studies suggest that antibiotic therapy is effective in treating 73 % of patients [35]. Considering the prevalence of incidental appendectomy, it is advisable for physicians to weigh the benefits and risks of appendectomy in non-emergent cases.

Limitations

Our study has limitations, including the inability to examine the impact of the appendectomy's cause on our findings due to insufficient data. Another limitation is the inclusion of L. Dahabra et al.'s abstract, as it is not a full-text paper. However, its inclusion was necessary due to its significant findings on the appendectomy-CRC link, despite the limitations typical of abstracts.

Conclusion

In conclusion, the risk of colorectal cancer was slightly increased with no specified follow-up period. However, this risk was not observed in the long term (more than 10 years). Our results appear to be influenced by the heterogeneity of the included studies. Nonetheless, it is recommended for physicians to consider alternative therapies and be mindful of potential complications associated with unnecessary appendectomies.

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