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REVIEW ARTICLE

Association of appendectomy with colorectal cancer: a systematic review and meta-analysis

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ABSTRACT

Background: Appendectomy is a common surgical procedure done worldwide. The appendix is known as a sanctuary for commensal organisms in the gut, and an inflamed appendix may alter the gut microbiome, leading to inflammation and oncogenesis. An association between appendectomy and subsequent colorectal cancer development has been postulated; however, previous studies have differed in study design and results.
Method: We performed a systematic review and meta-analysis of studies evaluating the association between appendectomy and colorectal cancer in adults. A literature search of MEDLINE and EMBASE was conducted through September 2022. Search terms included "appendectomy" and "colon cancer" or "rectal cancer" or "colorectal cancer." Odds ratios and sensitivity analyses were calculated.
Result: Of the 541 studies identified in our search, 10 studies met our inclusion criteria. The eight papers that studied the association between appendectomy and colorectal cancer reported no association with the odds ratio (OR) of 1.30 (0.92, 1.83). However, studies on the association of appendectomy and proximal versus distal colon cancer reported a statistically significant increase in proximal colon cancer compared to distal colon cancer OR of 1.48 (1.29, 1.69).
Conclusion: Our study demonstrates that appendectomy is associated with the development of proximal colon cancer but not distal colon cancer.
Relevance for patients: Patients who have had an appendectomy should be aware of the potentially increased risk for colon cancer. Consequently, they should provide this information during routine clinic visits, especially if they are having gastrointestinal symptoms.

1. Introduction

According to the World Health Organization, colorectal cancer was the third most common cancer worldwide with approximately 1.93 million cases reported in 2020. Despite increasing screening measures, colorectal cancer remained the second most common cause of cancer death (916,000 deaths in 2020) [1]. Identifying possible risks for colorectal cancer is important because colorectal cancer screening can result in early detection. Common risk factors include age over 50 years, a family history of colorectal cancer, certain predisposing genes, and long-standing inflammatory bowel disease. Potentially modifiable factors include obesity, smoking, and heavy alcohol consumption [2]. Surprisingly, several studies have suggested that an appendectomy is a risk factor for developing colorectal cancer; however, this association has not been established [3-5].

Appendectomy is a common surgical procedure done worldwide. The previous studies have shown appendectomy can alter the gut microbiome, depriving the colon of a backup reserve of diverse commensal bacteria in case of diseases, such as diarrhea [6]. It may also

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alter the balance that controls immune tolerance from gut antigens and gut inflammation, a process considered to be a mechanism for the development of colorectal cancer [7]. Appendectomy may be a potential risk factor in developing colorectal cancer; however, differences in study design, such as the definition of the interval between appendectomy and the initial diagnosis of colorectal cancer, follow-up period, and location of colorectal cancer, need consideration. Therefore, we performed a systematic review and meta-analysis to evaluate the association between appendectomy and the development of colorectal cancer.

2. Methods

We conducted this meta-analysis according to Cochrane's manual of diagnostic test accuracy, and the manuscript was prepared according to the preferred reporting items for systematic reviews and meta-analysis of diagnostic test accuracy (PRISMA-DTA) guidelines [8,9].

A literature search of MEDLINE and EMBASE databases was conducted from their inception through September 2022. Search terms included (a) appendectomy, (b) colorectal cancer, colon cancer, and rectal cancer. Only studies evaluating adult population were included in the study. Case series, case reports, and non-English publications, and studies with appendiceal carcinoma and mucinous appendiceal neoplasm were excluded from the study. The titles and abstracts were reviewed by two independent authors (B.S. and N.T.). Discrepancies were resolved through discussion between the two independent authors and the senior author (K.N). Two independent authors compiled data from each study, including study characteristics, study population characteristics, and study results (B.S. and N.T.). Study characteristics included author, year of publication, start and end dates for data collection, country, and type of study design. Study population characteristics included number of patients, age, gender, number of patients who underwent appendectomy, number of control patients (those without appendectomy), number of colorectal cancers, location of colon cancers (classified as proximal colon which includes cecum, ascending colon, hepatic flexure, and transverse colon and distal colon which includes splenic flexure, descending colon, and sigmoid colon) and rectal cancer if data were available), and number of patients without colorectal cancers. The quality of each study was independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale [10]. Any discrepancies were resolved through discussion between the two independent authors with the senior author (K.N.).

2.1. Statistical analysis

A DerSimonian-Liard random-effects meta-analysis was performed using the "meta" package (version 5.0-1) in R statistical software (version 4.2.2) to examine the pooled odds ratio representing the associations between colorectal cancer and the history of appendectomy. Additional random-effects meta-analyses were performed to pool the odds ratios of studies examining the associations between appendectomy based on the anatomical site of colorectal cancer (i.e., proximal vs. distal colon cancer vs. rectal cancer). The proximal colon consists of cecum, ascending colon, hepatic flexure, and transverse colon whereas the distal colon consists of splenic flexure, descending colon, and sigmoid colon.

The consistency of the findings of all meta-analyses was further examined using leave-one-out sensitivity analyses. The likelihood of publication bias was explored using funnel plots, and the effect sizes of missing (i.e., unpublished/unreported) studies were imputed through the trim-and-fill method [11,12]. Funnel plot asymmetry was confirmed using Egger's tests [13]. Heterogeneity of effect sizes was quantified by calculating the Higgins' I^2 statistic [14,15]. Meta-regression analyses were not attempted due to the small number of studies included in each meta-analysis [15,16].

3. Results

Figure 1 provides a graphical representation of the study screening and selection process. A total of 919 articles were found using the above search criteria. After removal of duplicates, 541 articles were evaluated. Of these, 23 articles were potentially relevant to the study goals. Thirteen studies were removed because the study was a non-English publication (n = 3), used the same study cohort (n = 1), was a review article (n = 1) or a letter to the editor (n = 1), or had missing data (n = 7). Therefore, 10 studies were included in this meta-analysis [4,5,17-24]. Table 1 reports the characteristics of each study. Of these studies, one was abstract, and nine were full articles. A total of 39,711 colorectal cancers and a total of appendectomies 384,278 were analyzed. Two studies did not classify patients based on the specific location but reported results just as colorectal cancer [5,22]; eight studies classified patients based on a specific location of colorectal cancer [4,17-21,23,24]. Table S1 demonstrates an association

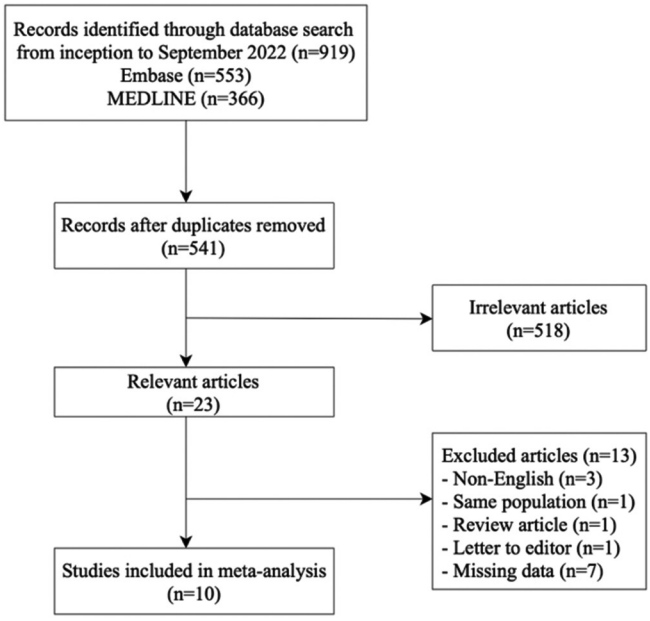

Figure 1. A visual representation of the search strategy.

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Table 1. Characteristics of studies evaluating the association between appendectomy and colorectal cancer

Author	Year	Country	Publication type	Study type	Number of patients (n)	Start date	End date	Mean age (year)	Male (n)	Number of appendectomy (n)	Number of CRC (n)	Duration between appendectomy and time of diagnosis of CRC
Abraham	2020	Hungary	Full paper	Retrospective	604	2015	2017	66.5±11.5	350	100	604	NR
Ergul	2009	Turkey	Full paper	Retrospective	621	NR	NR	NR	410	205	455	3 years
Friedman	1990	USA	Full paper	Retrospective	7625	1964	1972	40.2	3256	1590	7625	9.8 years
Lee	2018	Korea	Full paper	Retrospective	707633	2002	2015	41.7±14.7	347411	16094	4324	No lag period
Lee	2021	Korea	Full paper	Retrospective	486844	Jan 2005	Dec 2013	32.4±17.0	284546	243422	2804	1 year
Mandi	2021	Hungary	Full paper	Retrospective	901	Jan 2018	Feb 2021	70.2	515	133	457	40.9 years
Qu	2021	China	Full paper	Retrospective	20739	Jan 2014	Dec 2018	61.5	12360	794	20739	NR
Shi (Cohort 1)	2021	Hongkong	Abstract	Retrospective	136953	Jan 2000	April 2020	NR	NR	44587	748	1 year
van den Boom	2021	Netherlands	Full paper	Prospective	7136	1989	1993	69.8±9.3	2836	1374	277	NR
Wu	2015	Taiwan	Full paper	Retrospective	379619	1997	1999	31.8	196317	75979	1678	30 months

CRC: Colorectal cancer; NR: Not reported

between appendectomy and colorectal cancer in each study group. These studies did not report the indication for appendectomy or the histology of the resected appendices.

3.1. Association between colorectal cancer and history of appendectomy

Eight studies reported a comparison of the history of appendectomy and development of colorectal cancer compared with control patients who underwent appendectomy but did not develop colorectal cancer. The number of patients with colorectal cancer was 11,897, and the number of control patients (i.e., those without colorectal cancer) was 1,873,936.

Our result demonstrated that the association between colorectal cancer and a history of appendectomy was not significant (OR = 1.30 [95% CI: 0.92, 1.83], $P = 0.132$; Figure 2). The observed result remained consistent in all leave-one-out sensitivity analyses except with the omission of Lee *et al.* (2018) which resulted in a significant association (OR = 1.42 [95% CI: 1.01, 1.99], $P = 0.041$). The funnel plot was asymmetric indicating possible publication bias (Figure S1). Three effect sizes were imputed using trim-and-fill method to restore funnel plot symmetry, and reanalysis of the data including these three effect sizes revealed a significant association between colorectal cancer and a history of appendectomy (OR = 1.79 [95% CI: 1.19, 2.71], $P = 0.005$). Between-study heterogeneity was high ($I^2 = 97.8\%$; $\tau^2 = 0.226$; $P < 0.001$). Meta-regression analyses were not attempted due to the small number of studies included in the study.

3.2. Association between proximal versus distal colon and rectal cancer and history of appendectomy

Four studies were analyzed to compare the history of appendectomy and the development of proximal colon cancer with the history of appendectomy and development of distal colon cancer and rectal cancer. In this subgroup analysis, the number of proximal colon cancers was 4,647, and the number of distal colon cancers and rectal cancers was 17,608. Our result demonstrated that the association between proximal or right-sided colon cancer and a history of appendectomy was significant (OR = 1.48 [95% CI: 1.29, 1.69], $P < 0.0001$; Figure 3). The funnel was symmetrical, indicating no publication bias (Figure S2), and study heterogeneity was low ($I^2 = 10.80\%$; $\tau^2 = 0$; $P < 0.0001$). Meta-regression analyses were not attempted due to the small number of studies included in the study.

3.3. Association between colon versus rectal cancer and history of appendectomy

Six studies were analyzed to compare a history of appendectomy and development of colon cancer with rectal cancer. The number of colon cancer was 4676; the number of rectal cancers was 3078. Our result demonstrated that the association between colon cancer and a history of appendectomy was not significant (OR = 0.96 [95% CI: 0.67, 1.37], p = 0.01; Figure 4). The funnel was symmetric indicating no publication bias (Figure S3) and heterogeneity was moderate ($I^2 = 64.70\%$; $\tau^2 = 0.13$; $P = 0.01$).

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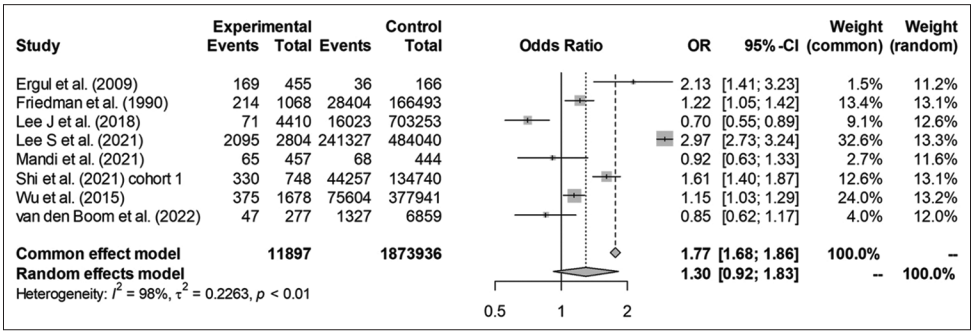

Figure 2. Forest plot of appendectomy in patients with colon cancer in comparison to control patients.

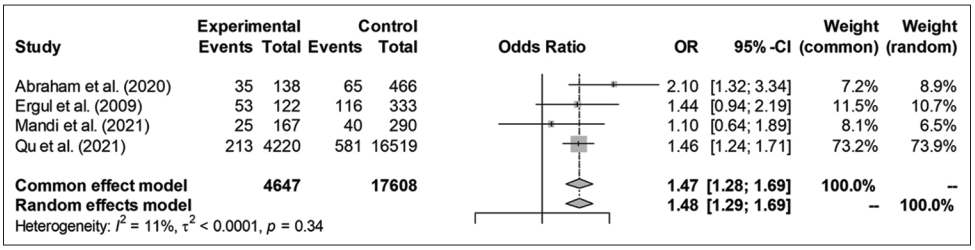

Figure 3. Forest plot of appendectomy in proximal colon cancer in comparison to distal colon cancer.

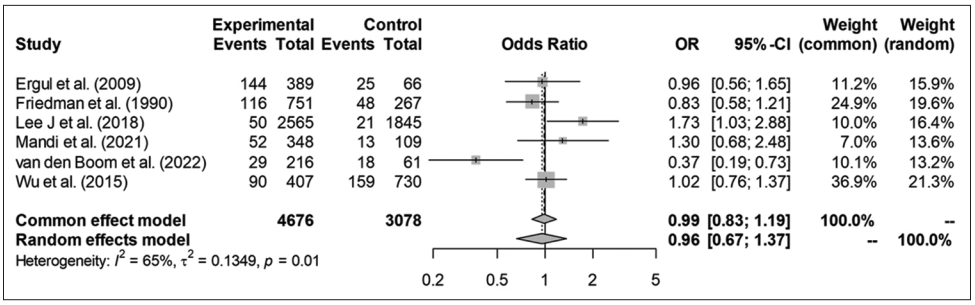

Figure 4. Forest plot of appendectomy in patients with colon cancer in comparison to patients with rectal cancer.

3.4. Quality assessment

During the article screening, there was good agreement between the two authors as demonstrated by a Newcastle-Ottawa score, shown in Tables S2 and S3. Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures.

4. Discussion

In this study, patients with distal colon and rectal cancer were compared to patients with proximal colon cancer because the cancers in these two locations have different clinical and genetic/molecular features. The prevalence of proximal colon cancer (40.4%) is higher than distal colon cancer (28.9%) and rectal cancer (30.7%) [25]. A study based on the SEER database reported that proximal colon has a worse prognosis compared than distal colon cancers, but the reason remains unclear [26]. Shi *et al.* reported a longitudinal study of 43,976 appendectomy cases and 85,179 age- and gender-matched non-appendectomy controls and the development of colon cancer [27]. During the 20-year follow-up period, the incidence of colorectal cancer was 73.1/100,000 person-years in the appendectomy group and 39.7/100,000 person-years in the control group. The overall risk of the development of colorectal cancer was increased by 73% in appendectomy cases, and these cases had significantly higher risk for the development of cancer in the proximal colon than in the distal colon and rectum.

This meta-analysis included 384,297 appendectomies and 39,711 colon cancer cases and demonstrated that appendectomy has a significant association with proximal colon cancer (OR = 1.48 [95% CI: 1.29, 1.69], P < 0.0001) with low heterogeneity between studies. In the analysis which compared the frequency of appendectomy in all patients with colon cancer with the frequency of appendectomy in healthy controls, the association was not significant but did become significant when the Lee J study was excluded [19]. This might be explained by the effect of a lag period from appendectomy to the diagnosis of colorectal cancer. Lee J reported a positive association with no lag period (HR = 1.44 [95% CI: 1.14, 1.83]) but no association with a 3-year lag period (HR = 0.75 [95% CI: 0.50, 1.13]). Lai

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et al. reported that 16 patients out of 1873 patients with acute appendicitis were found to have colon cancer [28]. The median time interval before diagnosis was 5.8 months. The odds ratios of having an increase in cancer incidence were 38.5-fold in patients older than 40 with acute appendicitis. Consequently, older patients with acute appendicitis should be evaluated for colon cancer.

Since the proximal colon and distal colon have different embryological origins, this could contribute to differences in the prevalence and prognosis in colon cancers in these two regions. Furthermore, there are differences in the carcinogenic pathway and gene expression in proximal and distal colon cancers; proximal tumors more often have a microsatellite instable pathway and hypermutated DNA, whereas distal colon tumors often have large chromosomal alterations [29,30]. Proximal colon tumors have low chromosomal instability, whereas distal colon tumors have high chromosomal instability. These proximal cancers are associated with older age, higher tumor grade, mucinous differentiation, and dense infiltration of lymphocytes [29]. The genes that are overexpressed in these tumors include genes associated with inflammatory reactions and drug metabolism. Genetic alterations include microsatellite instability, hypermethylation, mutations in key tumor genic pathways, and BRAF mutants. These pathways may be stimulated by bacterial toxins and mutagenic metabolites and lead to tumor development.

The association of appendectomy with the development of proximal colon cancer requires consideration of the function of the appendix and the potential changes in colonic health associated with appendectomy. The mucosa in the appendix contains plasma cells which secrete IgA and IgG; it is the primary site for IgA production. The submucosa contains aggregates of lymphocytes, and the morphology is similar to the concentrated lymphoid tissue in Peyer's patch in the ileum. The appendix is a repository for commensal gut bacteria, such as *Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria,* and *Actinobacteria* [31,32]. Its immune function probably depends in part on these commensal organisms [6]. The existence of biofilm in the appendix has beneficial effects on the entire digestive system [6] and is thought to act as a sanctuary for commensal bacteria and to facilitate their reinoculation of the gut after a gastrointestinal infections and possibly episodes of antibiotic treatment. The changes in commensal bacteria and the development of "abnormal" biofilms could lead to alterations in colonic health and function [33].

The development of colorectal cancer is explained in part by alterations in genetic factors. However, environmental factors, such as local inflammation and microbiota, may also have an important role [24]. A study of the appendiceal tissue revealed increased numbers of natural killer (NK) T cells that can produce cytokines following activation [6]. The evidence of immune cells in appendiceal tissue is also supported by another study by Yaun-Kun which demonstrated that patients with appendiceal inflammation have lower NK cells; patients with colorectal cancer and a normal appendix have low NK cells [34]. The cells have a suppressor function and could limit the development and proliferation of malignant cells.

With the novel concept of gut biofilm and dysbiosis in association with both benign and colorectal cancer due to ongoing colonic inflammation, alteration of intestinal biofilms after appendectomy has been proposed as a possible pathophysiology underlying colorectal cancer [33]. Dejea identified polymicrobial bacterial biofilms in 89% of proximal tumors but in only 12% of the distal tumors [35]. Bacterial biofilms were associated with increased epithelial permeability and activation of IL-6 and Stat3 [35]. In the normal colon mucosa, biofilms were associated with increased crypt epithelial cell proliferation and possibly initiate pro-carcinogenic tissue inflammation. In addition, IL-6 and Stat3 have been associated with increased epithelial proliferation, apoptosis, and/or angiogenesis. These authors suggest that the presence and organization of biofilm are important factors in the pathogenesis of colorectal cancer pathogenesis and this process may not depend on the types of bacteria in biofilm. Dejea reported that biofilms found in colorectal cancer patients had bacterial invasion into the tumor mass and this possibly changes tissue biology by enhancing cellular proliferation and oncogenic transformation. This feature was not detected in biofilm-negative tumors [35]. Shi and coinvestigators also analyzed the gut microbiome in 157 appendectomy cases and 157 normal controls using metagenomic sequencing [27]. The patients with appendectomy had a significant increase in the *Fusobacterium* phylum. Patients with appendectomy had lower microbiota diversity, and these changes persisted over a 2-year follow-up period. These changes were more pronounced in older patients (>50 years). Patients with appendectomy had an enrichment of colorectal cancer-associated species in the gut. There were 11 enriched species, and seven of them have been associated with colorectal cancer. Five possibly protective bacteria were depleted in these samples. Microbial genes were analyzed to determine the metabolic pathways in these microbiomes. In appendectomy cases, the pathways for the biosynthesis of deoxyribonucleotides, peptidoglycan, L-glutamine, L glutamate, and pyrimidine deoxyribonucleotides were increased; these pathways have been reported as cancer promoting. The biosynthesis L-proline was decreased, and this compound is thought to be protective. Overall, this study demonstrates that appendectomy causes microbial dysbiosis with increases in colorectal cancer-promoting bacteria and depletion of possibly beneficial microbes [27].

In summary, the association between appendectomy and the proximal colon cancer has several possible explanations. First, the proximal colon has higher levels of microbial biofilms (89%) than the distal colon (18%). The appendix is located on the cecum and the appendectomy can alter the microbiome and result in dysbiosis and bacterial invasion which stimulates tumor formation. Second, the loss of immune function after appendectomy leads to changes in the interaction between microbiota and colonic mucosa. Clinical investigations need to determine if there is a consistent alteration in colonic flora associated with pathogenic biofilms. This might lead to prospective studies on the development of colon cancer in patients with these changes in flora and eventually to determine whether or not strategies to replace pathogenic flora with normal flora have potential benefit [36].

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This meta-analysis has several limitations. First, the total number of studies in this meta-analysis is relatively small. Second, there are differences in the time interval between appendectomy and the diagnosis of colorectal cancer, and there are differences in study design. The lag time might have a role in tumor development [17]. Third, the age of patients when they were diagnosed with colorectal cancer was not available; therefore, it is unclear if patients who undergo appendectomy should have colorectal cancer screening earlier than general populations. There were no studies on the association of mucinous neoplasm of appendix and colon cancer or on the type of appendicitis, that is, acute on chronic appendicitis, and colon cancer.

5. Conclusions

This meta-analysis demonstrates an association of appendectomy the development of proximal colon cancer but not distal colon cancer. This study suggests that clinicians should consider the possibility of colorectal cancer in patients with prior appendectomy who develop new and persistent constitutional or gastrointestinal symptoms regardless of age.

Acknowledgments

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None.

Conflicts of Interest

The authors declare they have no competing interests.

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Supplementary File

Table S1. Association between appendectomy and colorectal cancer

Association between appendectomy compared with CRC	Number of studies included	Odds ratio (95% CI)
Appendectomy versus CRC and non-CRC	8	1.30 (0.92, 1.83)
Appendectomy versus proximal and distal colon cancer	4	1.48 (1.29, 1.69)
Appendectomy versus colon and rectal cancer	6	0.96 (0.67, 1.37)

CRC: Colorectal cancer

Table S2. The Newcastle-Ottawa quality assessment scale of the included cohort studies

Author (year)	Selection				Comparability	Outcome			Total score
	Representativeness	Selection of the non-exposed cohort	Ascertainment	Endpoint not presented at start	Comparability (confounding)	Assessment of outcome	Follow-up duration	Adequacy of follow-up	
Abraham (2020)	★	★	★	★	0	★		★	7
Friedman (1990)	★	★	★	★	★	★		★	8
Lee (2018)	★	★	★	★	★	★		★	8
Lee (2021)	★	★	★	★	★	★	0	★	7
Mandi (2021)	★	★	★	0	★	★	★	★	7
Shi (2021)	★	★	★	★	★	0	★	★	7
van den Boom (2021)	★	★	★	★	★	★	★	★	8
Wu (2015)	★	0	★	★	★	★	★	★	7

Table S3. The Newcastle-Ottawa quality assessment scale of the included case–control studies

Author (year)	Selection				Comparability	Outcome			Total score
	Representativeness	Adequate definition	Selection of controls	Definition of controls	Comparability	Assessment of exposure	Method of assessment	Non-response rate	
Ergul (2009)	★	★	★	★	0	★	★	★	6

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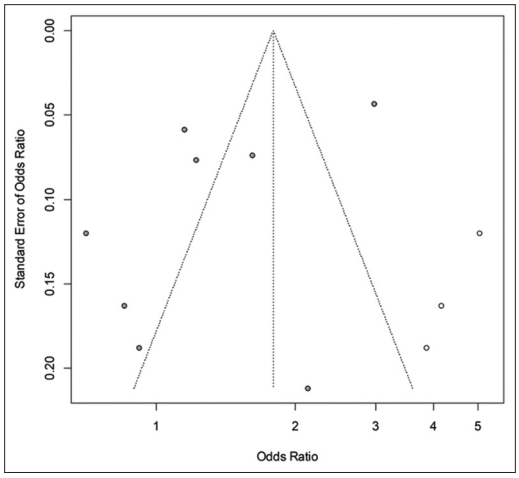

Figure S1. Funnel plot of the association between appendectomy and colorectal cancer versus non-colorectal cancer group.

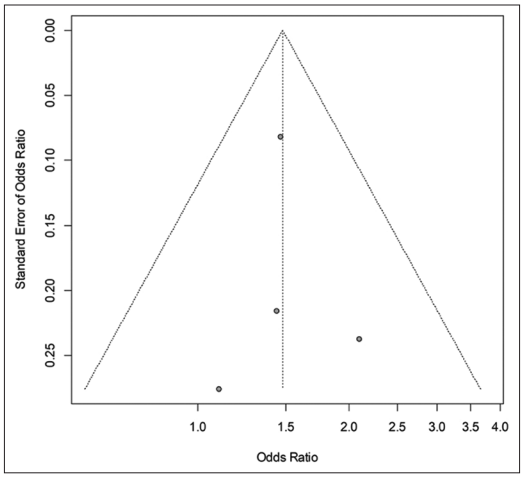

Figure S2. Funnel plot of the association between appendectomy and proximal colon cancer versus distal colon cancer.

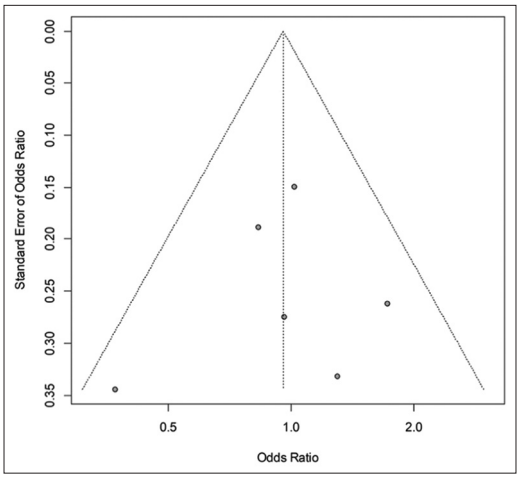

Figure S3. Funnel plot of the association between appendectomy and colon cancer versus rectal cancer.

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