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Research Article

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Appendicitis and Colon Cancer: Exploring the Connection through a Retrospective Cohort Analysis

Varun Rachakonda B.S.[1]*, Anuttham Kandhadai B.S.[2], Hassan Arif B.S.[1], Joshua Katz B.S.[1] and Aya Akhras M.D.[3]

[1]Kiran C. Patel College of Allopathic Medicine at Nova Southeastern University, Ft. Lauderdale, FL, USA

[2]University of Texas Medical Branch John Sealy School of Medicine, Galveston, TX, USA

[3]HCA Aventura Hospital Department of Internal Medicine, Aventura, FL, USA

***Corresponding Author**
Varun Rachakonda, Kiran C. Patel College of Allopathic Medicine at Nova Southeastern University, Ft. Lauderdale, FL, USA.

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Abstract

Purpose: *Appendicitis and colon cancer are medical conditions with unique clinical implications. While both conditions have been extensively studied individually, the potential relationship between appendicitis and subsequent development of colon cancer remains unclear. Understanding this association could impact preventive strategies. This study aimed to investigate whether a history of appendicitis is a risk factor for the development of colon cancer.*

Methods: *A retrospective cohort study was conducted using the TriNetX database. The study cohorts were defined based on the index event of a colonoscopy, with one group comprising patients with a history of appendicitis prior to colonoscopy and the other without. Individuals with a history of colonic polyps, neoplasms, or secondary malignancies of the colon prior to colonoscopy were excluded. Propensity-score matching was performed based on comorbidities. The primary outcomes of interest were the 5-year rates of mortality and malignant neoplasms of the colon.*

Results: *After matching, there were 16,651 patients in each cohort. The rate of colon cancer in patients with a history of appendicitis was 2.14%, compared to 1.50% in patients without a history of appendicitis (RR: 1.42, 95% CI: 1.21-1.67). Interestingly, mortality rates were lower in the group with a history of appendicitis, with a rate of 4.07% compared to 5.98% in the group without appendicitis (RR: 0.68, 95% CI: 0.62-0.75).*

Conclusion: *This study suggests that a history of appendicitis may be associated with an increased risk of developing colon cancer. Additionally, the findings reveal a lower mortality rate in patients with a history of appendicitis. Understanding the association between appendicitis and colon cancer can improve screening strategies and patient management in clinical practice. Further research is needed to elucidate the underlying mechanisms and explore potential preventive measures in individuals with a history of appendicitis.*

Keywords: Colonoscopy, Retrospective Study, Appendicitis, Colon Cancer, Mortality.

1. Introduction and Background

Appendicitis and colon cancer represent two gastrointestinal (GI) conditions that have been extensively studied independently. Colon cancer, a highly prevalent GI malignancy, is associated with established risk factors such as obesity, alcohol consumption, red meat intake, a low-fiber diet, and smoking [1]. Appendicitis, characterized by inflammation of the appendix, presents a substantial immediate challenge as a prevalent and emergent abdominal condition, however, its long-term consequences are poorly understood [2]. The goal of this paper is to understand the relationship, if any, that exists between acute appendicitis and chronic GI pathologies such as colon cancer, in particular.

Since 2010, there has been a 2-3% rise in the incidence of colon cancer among individuals under 65 years for regional distant disease [3]. Additionally, with an average lifetime risk of nearly 25%, appendicitis stands out as the most common emergency abdominal surgery. Given the escalating occurrence of colon cancer and appendicitis as a predominant surgical emergency, we found it crucial to investigate the potential correlation between these seemingly independent gastrointestinal conditions [4]. Understanding this relationship could enable healthcare professionals to devise preventive strategies, explore long-term health implications of apparently self-limited conditions like appendicitis, and bridge knowledge gaps for enhanced patient care.

We investigated the association between a history of acute appendicitis and the development of colon cancer through a retrospective cohort study using the TriNetX database, a

multinational electronic medical record (EMR) network that supplies anonymized patient data. We compared mortality as well as the incidence of colon cancer in patients with and without a history of acute appendicitis.

2. Materials and Methods

The TriNetX database underwent querying on February 4, 2023. Mentioning the date of query is important as the database is constantly uploading new patient data, therefore values may change with time. Patient cohorts and outcomes were defined based on specific International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. The first group comprised patients with a positive history of appendicitis (App.) who underwent a colonoscopy, while the second group included patients who did not have a history of appendicitis (No App.) who also underwent a colonoscopy at some point in their life. Exclusions were made for patients with a previous history of colonic polyps, inflammatory bowel disease, primary and secondary malignant neoplasms. Patient cohorts were carefully matched for various factors, including age, sex, ethnicity, race, cerebrovascular disease, GI pathologies, BMI, diabetes, and tobacco use. In the context of this study, undergoing a colonoscopy served as the index event: the initial and significant event from which outcomes were measured. The primary outcomes of interest included the incidences of colon cancer and mortality within a 5-year timeframe post-colonoscopy.

After matching, there were a total of 16,651 patients in each group. There were no statistically significant differences in demographics between groups. The mean age at colonoscopy for each group was 48.7 ± 17.4 yrs ($p<0.05$), 44.5% of the patients were male, and 11.2% were Black. Categorical differences for incidence of colon cancer and 5-year mortality rates were compared for each cohort using risk ratio (RR) and 95% confidence interval. P-values were calculated for each respective cohort based on a Z- test.

2.1. About Tri Net X

Tri Net X is a global research network that includes patient data from more than 170 healthcare organizations (HCO) and over 400 million patients [5]. The available data includes demographics, diagnoses based on the International Classification of Diseases, medications, medical procedures, and other comorbidities for each patient. Multiple studies have used TriNetX to better understand the risk and trends among various diseases [6].

2.2. Ethical Statement

TriNetX is a federated network that is compliant with the Health Insurance Portability & Accountability Act as well as the General Data Protection regulation. The Western Institutional Review Board has approved TriNetX's request for a waiver of informed consent. This decision stems from the fact that the TriNetX platform exclusively compiles totals and statistical overviews derived from de-identified data. No protected health information is exchanged in retrospective analyses.

3. Results

After matching for each patient cohort group, there were no statistically significant differences in the demographics between both groups. There were a total of 16,651 patients in each group. Patients with a history of appendicitis were more likely to develop colon cancer (2.13 % vs. 1.44%, RR=1.48, 95%CI: 1.26-1.74, $p<0.01$). It was also found that patients who had no prior history of appendicitis had a higher 5-year mortality rate post-colonoscopy than patients who had a history of appendicitis (5.9% vs. 4.09%, RR= 0.75, 95%CI: 0.68-0.82, $p<0.01$). The data is displayed in table 1.

Outcome	Cohort	Incidences (%)	p	Hazard Ratio (95% Confidence Interval)
5- year Mortality	App.1	4.09	<0.01*	1.522 (1.291,1.794)
	No App.2	5.49		
Colon Cancer	App	2.13	<0.01*	0.534 (0.699,0.853)
	No App.	1.44		

Table: 1

Comparing and contrasting the differences in incidence of colon cancer and 5- year mortality after colonoscopy among patients with a history of appendicitis and patients without a history of appendicitis

[1]App., history of appendicitis

[2]No App., no history of appendicitis

4. Discussion

Colon cancer poses a significant concern within the healthcare industry, ranking as the second most deadly cancer in terms of mortality. Global incidences of colon cancer are expected to rise in the future [7]. What is particularly alarming is the escalating occurrence of colon cancer among the younger population. According to a study conducted by Sifaka-Pistolla et al., there was a 34.7% increase in colon cancer incidence among patients aged 20-34 from 2001 to 2011. In the 35-49 age group, there was a 37.2% increase during the same period, and projections suggest a 56% rise in incidence from 2022 to 2030 [8]. With such a rapid surge in the prevalence of the second deadliest cancer globally, it is crucial for clinicians to be aware of various factors that elevate a patient's risk of developing colon cancer. Additionally, we emphasize the necessity for further research into significant health comorbidities, such as appendicitis, that may be linked to the development of colon cancer.

With limited information on the correlation between appendicitis and colon cancer, we sought to explore a potential link between these two gastrointestinal (GI) pathologies. A comprehensive study spanning 204 countries and territories from 1990 to 2019 revealed an incidence of appendicitis at approximately 233 per

100,000 population, with an individual average incidence risk ranging from 6.7% to 8.6%. Given the prevalence of appendicitis in the general population, and the rising burden of colon cancer worldwide, we sought to investigate any correlation between these two GI pathologies. Our study unveiled a significant finding: individuals diagnosed with appendicitis were notably more likely to develop colon cancer in the future. While the precise reason for the correlation between these two GI pathologies remains unclear, there is a hypothesis suggesting that appendicitis might serve as an early warning sign for future colon cancer development, with the understanding that these pathologies are not directly linked [9].

An intriguing theory we propose is that it might not be the occurrence of appendicitis itself that increases the risk of colon cancer, but rather the act of undergoing an appendectomy following appendicitis that is directly associated with the development of colon cancer. A study conducted by Yuan-Kun et al. revealed that a reduction in the number of natural killer (NK) cells in appendix tissue correlates with a significant increase in the future development of right colon cancer [10]. Considering the appendix as a mucosal organ housing immune cells like NK cells, B cells, and T cells, the removal of this organ, and subsequently the reduction in immune cell production, could contribute to decreased host defenses within the colon and the observed increase in colon cancer development in our study [11].

One interesting finding from our study is that the 5-year mortality rate post-colonoscopy is higher for patients with no prior history of appendicitis compared to those with a previous history of appendicitis. Although existing literature does not offer an explanation for this phenomenon, we posit that patients with a history of appendicitis may be more inclined to undergo colorectal cancer screenings. A study conducted by Xuan et al. identified the top three factors influencing a patient's adherence to colorectal cancer screening: screening method, cost, and perceived importance [12]. In our context, the latter factor is particularly relevant. We propose that individuals with a history of appendicitis may be more predisposed to receiving colorectal screenings, and potentially broader health-maintenance screenings, compared to those without such a history. Consequently, it is plausible that these patients experience earlier detection of colon cancers and other health issues, leading to improved outcomes.

As the incidence of colon cancer continues to rise, it becomes imperative for healthcare providers to educate patients on proper screening measures. While numerous well-known risk factors for colon cancer exist, lesser-known factors such as appendicitis deserve special attention. Our study underscores the importance of healthcare providers emphasizing and educating patients with a history of appendicitis about the need to follow screening protocols for colon cancer. Furthermore, it would be prudent for healthcare professionals to collaborate and develop a screening protocol specifically tailored for patients with a history of gastrointestinal (GI) disease. This targeted approach aims to better address the needs of this specific population, contributing to the overall goal of diagnosing colon cancer in its earlier stages. Such tailored protocols have the potential to enhance the precision of cancer detection, leading to improved outcomes and increased chances of survival for patients.

While our study is able to shed light on potential associations between appendicitis and the development of colon cancer, it is important to acknowledge limitations and confounding variables that may impact the interpretation of findings. Firstly, our study relies on retrospective data found in the TriNetX database, which inherently carries the risk of selection bias and raises concerns about the representativeness of our study population. Patients with certain traits–such as comorbidities, past medical histories, and healthcare-utilization practices– may be more likely to undergo colonoscopies than other groups. Furthermore, despite matching on several demographic and clinical characteristics, unmeasured confounders may still exist within the study. These include genetic predispositions, dietary habits, and the socioeconomic status of each individual within cohorts–all of which can potentially influence both appendicitis and colon cancer risk–that are unable to be captured and accurately represented by the study. This can potentially impact the observed association between appendicitis and the subsequent development of colon cancer. In addition, the non-randomized nature of retrospective studies makes it difficult to establish a cause-and-effect relationship between two factors. The study does not provide insight into specific mechanisms or pathways that underlie our observed association, therefore, one should be cautious about generalizing findings to a broader population. While our data suggests a correlation may exist between a history of appendicitis and the development of colon cancer, it is imperative that future research controls for a more comprehensive set of confounding variables and explores causative pathways to enhance our understanding of the relationship between these two pathologies.

5. Conclusion

As the incidence of colon cancer continues to rise, it becomes crucial to explore additional factors that may potentially contribute to an increased risk of developing this disease. Involving over 30,000 patients, our study suggests that patients with a history of appendicitis experience a higher incidence of colon cancer. However, patients without a history of appendicitis experienced a significantly higher 5-year mortality rate following their first colonoscopy.

While this study provides valuable insights into the correlations between these common medical diagnoses, further research is warranted. Delving into potential causal links between appendicitis and the development of colon cancer can pave the way for enhanced treatment and management strategies. Moreover, additional exploration into the relationships between different gastrointestinal pathologies and colon cancer holds great importance and promises further advancements in our understanding of these conditions.

Statements and Declarations

No funding was received for this study.

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All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Varun Rachakonda and Anuttham Kandhadai. The first draft of the manuscript was written by Varun Rachakonda, Anuttham Kandhadai and Hassan Arif. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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