Increased risk of colon cancer after acute appendicitis: a nationwide, population-based study

Manon Viennet,[a] Solène Tapia,[b] Jonathan Cottenet,[b] Alain Bernard,[b] Pablo Ortega-Deballon,[a,c,d,*] and Catherine Quantin[b,c]

[a]Department of Digestive Surgical Oncology, Dijon University Hospital, Dijon, France
[b]Department Medical Information, Dijon University Hospital, Dijon, France
[c]Inserm CIC 1432 Clinical Investigation Unit, Dijon University Hospital, Dijon, France
[d]Inserm Unit 1231, Locoregional Therapy in Surgical Oncology, Dijon, France

eClinicalMedicine 2023;63: 102196
Published Online 30 August 2023
https://doi.org/10.1016/j.eclinm.2023.102196

Summary

Background Acute appendicitis is the most common digestive disease requiring emergency surgery. Colorectal cancer is the third most common cancer in France. An increased risk of colorectal cancer after acute appendicitis has been suggested. We aimed to assess the frequency of hospitalization for colon cancer after appendicitis in a nationwide analysis.

Methods Using the French Hospital Discharge Database (PMSI), we included all patients aged 18–59 years presenting with acute appendicitis between 2010 and 2015. Univariate and multivariate analyses were performed to compare colon cancer occurrence in these patients vs a control-matched population with a hospital stay for trauma in the same period. Patients presenting strong risk factors for colorectal cancer were excluded.

Findings A total of 230,349 patients with acute appendicitis (exposed group) were included. We used a propensity score to match each exposed patient with two unexposed patients (controls) to ensure the comparability of the groups, resulting in a control group of 460,698 patients. Univariate analysis found significantly more colon cancer in the appendicitis group, especially during the first year after appendicitis (5 per 10,000 vs 1 per 10,000, $p < 0.000$, this corresponds to 111 patients in the appendicitis group), namely within the first 6 months. Survival analysis confirmed patients treated for appendicitis present a 4 times higher risk of being diagnosed with colon cancer than control patients during the first year of follow-up (sHR = 4.67 (95% CI: 3.51–6.21), and 8 times higher during the first 6 months (sHR = 8.39; 95% CI: 5.41–12.99). The association was even more marked for right-sided colon cancer (sHR = 8.25; 95% CI: 5.03–13.54 during the 1st year). While the risk of diagnosis of colon cancer was also significant for patients over 40 years, it was even greater in patients under 40 years, who had between a 6-fold and 12-fold increase in risk.

Interpretation In this population-based study, we found that acute appendicitis seems to be a warning sign for colon cancer (reverse causality) in both middle-aged and younger adults. The risk of presenting with cancer colon was higher during the first six months after acute appendicitis. This raises the issue of routine diagnostic work-up in adults presenting with acute appendicitis.

Funding Regional Council of Burgundy.

Keywords: Acute appendicitis; Colon cancer; Colon cancer screening

Introduction

Appendicitis is the most common digestive surgical emergency in the world. In France, almost 130,000 patients underwent an appendectomy for acute appendicitis in 2012. Appendicitis can appear at any age, but men between 10 and 30 years old have the highest risk.[1] Its incidence worldwide grew by 63.5% between 1990 and 2019.[2]

Colon cancer is the third most common cancer among men in France and the second among women with 44,000 new cases per year.[3] Approximately 150,000 new cases are diagnosed in the USA each year and

*Corresponding author. Service de Chirurgie Générale, Digestive, Cancérologique et Urgences, CHU de Dijon, 14, Rue Paul Gaffarel, Dijon Cedex 21079, France.
E-mail address: pablo.ortega-deballon@chu-dijon.fr (P. Ortega-Deballon).

Research in context

Evidence before this study

It has been suggested that there is an increased risk of colorectal cancer after acute appendicitis, in particular in patients older than 40 years in Norway and the United Kingdom. In a meta-analysis, acute appendicitis was also associated with a 10-fold increase in the risk of colorectal cancer as compared to the general population. If a relationship is confirmed between acute appendicitis and the risk of colon cancer, the question of the mechanism arises. Does acute appendicitis induce the onset of colon cancer? Is appendicitis a symptom of pre-existing cancer? Do they perhaps have a common cause (microbiota disorder or any inflammatory condition)?

Added value of this study

Using a national database of hospitalized patients, we included more than 200,000 patients in the appendicitis group and more than 400,000 matched controls without appendicitis. Our results show that within the first year after acute appendicitis, the risk of colon cancer was higher than in the population without acute appendicitis (subdistribution hazard ratio = 4.67; 95% CI: 3.51–6.21). The association was even more marked for right-sided colon cancer, since we also found an even higher risk within the first year for patients with appendicitis (sHR = 8.25; 95% CI: 5.03–13.54) compared to control patients.

Implications of all the available evidence

These results could improve national screening of colon cancer in patients treated for acute appendicitis. It appears that acute appendicitis may be a warning sign of colon cancer (reverse causality) in younger and middle-aged adults. Ultimately, routine screening for colon cancer may be needed in all adult patients with acute appendicitis.

50,000 people die because of the disease. Colon cancer is the leading cause of cancer death in men 20–50 years old.[4]

An increased risk of colorectal cancer after acute appendicitis has been suggested, particularly in patients older than 40 years.[5–10] This age group could present a 10-fold increase in the risk of colorectal cancer as compared to the general population.[5] However, the current evidence is based on several monocentric series and not on population-based studies. On the contrary, other studies have found a decreased risk of cancer after appendectomy.[11]

Some authors have argued that routine colonoscopy is warranted in all patients presenting with appendicitis after the age of 40.[7,8] However, this recommendation would need to be supported by stronger evidence due to the high incidence of acute appendicitis and the risks of colonoscopy. This would be very significant at the time of increase in the nonoperative treatment of uncomplicated appendicitis.[12,13]

Moreover, if a relationship is confirmed between acute appendicitis and the risk of colon cancer, the question of the mechanism arises. Does acute appendicitis trigger the onset of colon cancer? Is it a symptom of an existing neoplasm? Or are both the consequence of a common cause? The aim of this study was to assess the frequency of hospitalization for colon cancer after appendicitis in a nationwide database and to analyze the timing of the two events in order to explore their relationship.

Methods

Data sources

This population-based nationwide study was conducted using the French Hospital Discharge Database (PMSI). It includes discharge summaries for all inpatients admitted to public and private hospitals in France. These records are anonymous and cover both medical and administrative data. The use of this database for the allocation of hospital budgets encourages high levels of data quality in terms of coherence, accuracy and exhaustiveness. Quality improvements are obtained through internal and external validation. Therefore, these hospital data have been used in medical research for many years.[14,15] Diagnoses identified during the hospital stay are coded according to the 10th edition of the International Classification of Diseases (ICD-10). Surgical procedures performed during hospital stays are coded according to the French Common Classification of Medical Procedures (CCAM).

Study design and eligibility criteria

All patients between 18 and 59 years old who received a diagnosis of acute appendicitis and an associated appendectomy procedure between January 2010 and December 2015 were included. National guidelines published by the French High Authority for Health (HAS) in 2012 stipulate that a diagnosis of appendicitis leads to appendectomy; medical treatment is not offered. Patients undergoing appendectomy for a reason other than appendicitis were excluded (e.g., appendicular tumors, incidental appendectomy at the time of surgery for abdominal malignancies or other abdominal diseases). Patients with a previous personal history of colon polyps or colorectal cancer, as well as those with genetic (any diagnosis of hereditary digestive cancer) or personal (chronic inflammatory bowel disease) risk factors for colon cancer were also excluded. Finally, patients who received a diagnosis of colon cancer (including appendix cancer) within thirty days of appendectomy were excluded since we considered that the

diagnosis was made at the time of appendectomy thanks to clinical, imaging or pathology findings suggesting cancer. Patients meeting the inclusion criteria constituted the exposed group, referred to as the "appendicitis group". All codes used for inclusion and exclusion are shown in Supplementary File S1.

An unexposed group, referred to as the "control group" and including patients 18–59 years old hospitalized during the same period for any kind of trauma, was constituted. Patients with a previous history of appendicitis and those presenting appendicitis during the follow-up period were excluded from the control group. We also excluded patients presenting with any of the criteria previously described in the appendicitis group (previous history of colorectal cancer, polyps or chronic inflammatory bowel disease, family history of hereditary digestive cancer, or colon cancer diagnosis within 30 days of inclusion).

Outcomes

Our primary outcome was the occurrence of colon cancer. Secondary outcomes were the occurrence of right-sided colon cancer and left-sided colon cancer. Patient characteristics such as sex and age (four age groups were defined: <30, 30–39, 40–49, 50–59) were retrieved at baseline, as was the Charlson Comorbidity Index (CCI), which was used as a marker of comorbidity. We also looked for obesity, defined as a body mass index (BMI) of 30 kg/m^2 or greater, and for dyslipidemia in the previous 3 years.

Statistics

To ensure the comparability of the "appendicitis" and "control" groups, we performed propensity-score matching (calculated from age, gender, dyslipidemia, obesity and Charlson Comorbidity Index) with two controls for each exposed patient.

We were interested in the time-to-onset of our outcomes (colon cancer, right-sided and left-sided colon cancers). All patients were followed-up until December 2020, thus ensuring 5 years of follow-up for all patients. For both our "appendicitis" and "control" group, we start the follow-up from hospital admission: admission for appendicitis for exposed patients and admission for trauma for matched unexposed patients.

In the main analysis, we performed a Fine & Gray model to study the effect of appendicitis on each outcome. With this model, in-hospital mortality was considered as a competitive event, meaning we followed individuals until either the first hospitalization for the outcome, or in-hospital mortality for any cause, or the end of the follow-up period. We checked the proportional hazard assumption. For this aim, we introduced an interaction of the effect with time in the model,[16,17] which allowed us to estimate the effect of the exposure variable at different times (3 months, 6 months and 1 year). We also performed a stratification on obesity to estimate the risk of colon cancer separately in obese and non-obese patients. Then, we performed a stratification by age to study a possible differential effect on the risk of colon cancer.

Patients diagnosed with colon cancer within 30 days of appendectomy were excluded from the main analysis, as the diagnosis was considered to have been made at the time of appendectomy. However this may result in underestimation of the risk of colon cancer in patients with acute appendicitis. We therefore performed a sensitivity analysis without excluding these patients.

Qualitative variables are provided as frequencies (percentages) and were compared between the two groups using the Chi-2 test or the Fisher's exact test. Statistical significance was set at a p value of 0.05. To interpret out results we used subdistribution hazard ratio (sHR) and 95% confidence interval (CI) given by Fine & Gray models. We used SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) for all analyses.

Ethics

PMSI data are available for researchers who meet the criteria for access to these French confidential data. Access is submitted to the approval of the National Committee for data protection (CNIL) and from the national agency for the management of hospitalization (ATIH–Agence Technique de l'Information sur l'Hospitalisation). According to the French law, no individual informed consent was required for this study. All data used in this analysis were anonymous and no personal medical records were consulted.

Role of the funding source

The Regional Council of Burgundy had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We included 2,326,773 patients from January 2010 to December 2015: 230,719 patients who presented with acute appendicitis and 2,096,054 patients hospitalized for trauma. After excluding patients diagnosed with colon cancer within 30 days, each exposed patient was matched to two controls according to their propensity score (calculated from age, sex, dyslipidemia, obesity and CCI), leading to an "appendicitis" group of 230,349 patients and a "control" group of 460,698 patients (Fig. 1). Characteristics of both groups are presented in Table 1. After propensity-score matching, we did not find any statistically or clinically significant differences between the two groups.

Primary outcome: colon cancer

Table 2 shows the occurrence of colon cancer within 5 years after appendectomy for patients with acute appendicitis and for controls. During the first year of follow-up, we observed significantly more colon cancer

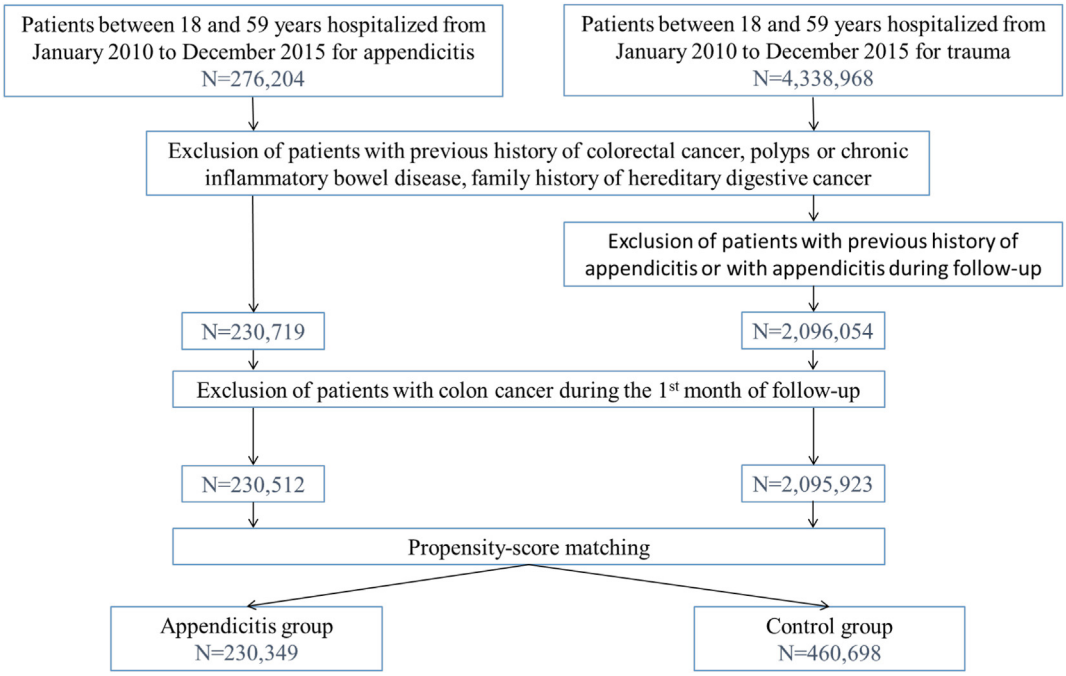

Fig. 1: Flow chart of the population.

diagnoses in patients treated for appendicitis than in matched controls (0.05% vs 0.01%, $p < 0.0001$). For the "appendicitis" and "control" groups, the absolute numbers of colon cancer cases are presented by age group in Supplementary Table S2. Later on, after the first year of follow-up, the rates of colon cancer were similar between patients treated for appendicitis and controls ($p > 0.10$ for all comparisons up to 5 years). We therefore decided to focus subsequent analyses on the first year of follow-up.

The results of the survival analyses are presented in Table 3. The risk of developing colon cancer was more than 4 times higher in patients treated for appendicitis than in control patients during the first year of follow-up

	Appendicitis group N = 230,349	**Control group N = 460,698**	**Statistical difference**
	n (%)	n (%)	
Women	112,632 (48.90)	225,276 (48.90)	NS
Age			
Mean (SD)	32.38 (11.67)	32.38 (11.67)	NS
Median (Q1–Q3)	30 (22–41)	30 (22–41)	NS
<30	115,044 (49.94)	230,027 (49.93)	NS
30–39	52,376 (22.74)	104,776 (22.74)	
40–49	35,487 (15.41)	70,988 (15.41)	
50–59	27,442 (11.91)	54,907 (11.92)	
Dyslipidemia	2949 (1.28)	5903 (1.28)	NS
Obesity (BMI ≥ 30 kg/m^2)	8252 (3.58)	16,551 (3.59)	NS
Charlson Comorbidity Index			
0	222,687 (96.68)	445,426 (96.68)	NS
1	5862 (2.54)	11,694 (2.54)	
≥2	1803 (0.78)	3578 (0.78)	

NS: non-significant. [a]Calculated using age, gender, dyslipidemia, obesity and Charlson Comorbidity Index.

Table 1: **Characteristics of patients after matching on the propensity score[a]: two matched unexposed patients for one exposed patient.**

	Appendicitis group N = 230,349	Control group N = 460,698	p value
	n (%)	n (%)	
Colon cancer			
At 1 year	111 (0.05)	49 (0.01)	<.0001
Between 1 and 2 years	45 (0.02)	64 (0.01)	0.0782
Between 2 and 3 years	27 (0.01)	49 (0.01)	0.6851
Between 3 and 4 years	42 (0.02)	76 (0.02)	0.6025
Between 4 and 5 years	42 (0.02)	75 (0.02)	0.5563
Right-sided colon cancer			
At 1 year	65 (0.03)	18 (0.00)	<.0001
Between 1 and 2 years	23 (0.01)	13 (0.00)	0.0001
Between 2 and 3 years	12 (0.01)	18 (0.00)	0.4368
Between 3 and 4 years	16 (0.01)	22 (0.00)	0.2513
Between 4 and 5 years	18 (0.01)	21 (0.00)	0.0894
Left-sided colon cancer			
At 1 year	26 (0.01)	18 (0.00)	0.0003
Between 1 and 2 years	18 (0.01)	33 (0.01)	0.7664
Between 2 and 3 years	11 (0.00)	21 (0.00)	0.9005
Between 3 and 4 years	18 (0.01)	35 (0.01)	0.9226
Between 4 and 5 years	16 (0.01)	33 (0.01)	0.9195

[a]Calculated using age, gender, dyslipidemia, obesity and Charlson Comorbidity Index.

Table 2: **Year-by-year onset of colon cancer, right-sided and left-sided colon cancer on 2010–2015 matched propensity score[a] patients.**

(subdistribution hazard ratio (sHR) of 4.67; 95% CI: 3.51–6.21).

After stratification on obesity, we found that appendicitis was still associated with a higher risk of developing colon cancer within one year, both in obese patients (sHR = 3.08; 95% CI: 1.36–7.00) and in non-obese patients (sHR = 4.91; 95% CI: 3.66–6.65) (results not shown).

After stratification on age groups (Table 4), in patients younger than 39 years, the risk was between 6 and 12 times higher for patients treated for appendicitis compared to matched controls (for patients under 30 years: sHR = 6.00; 95% CI: 1.55–23.30, and for patients between 30 and 39 years: sHR = 11.74; 95% CI: 3.83–35.97). For patients over 40 years of age, the risk of colon cancer was between 3 and 6 times higher

	Appendicitis group N = 230,349	Control group N = 460,698	p value	sHR [95% CI] (Fine & Gray model)
	n (%)	n (%)		
Colon cancer				
30–180 daysμ[b]	81 (0.04)	20 (0.00)	<.0001	8.385 [5.414–12.986]
180–365 days	30 (0.01)	29 (0.01)	0.0043	2.070 [1.378–3.112]
1 year	111 (0.05)	49 (0.01)	<.0001	4.665 [3.507–6.206]
Right-sided colon cancer				
30–180 days	48 (0.02)	8 (0.00)	<.0001	13.447 [6.527–27.704]
180–365 days	17 (0.01)	10 (0.00)	0.0011	3.604 [1.863–6.971]
1 year	65 (0.03)	18 (0.00)	<.0001	8.250 [5.027–13.541]
Left-sided colon cancer				
30–180 daysμ[b]	16 (0.01)	6 (0.00)	<.0001	5.194 [2.370–11.379]
180–365 days	10 (0.00)	12 (0.00)	0.2278	1.667 [0.857–3.241]
At 1 year	26 (0.01)	18 (0.00)	0.0003	2.807 [1.739–4.530]

[a]Calculated using age, gender, dyslipidemia, obesity and Charlson Comorbidity Index. [b]Patients with a diagnosis of cancer within the 1st month after appendicitis were excluded.

Table 3: **Effects of appendicitis on the occurrence of colon cancer, right-sided colon cancer and left-sided colon cancer during the 1st year of follow-up, on 2010–2015 matched propensity score[a] patients.**

	sHR [95% CI] (Fine & Gray model)
Patients under 30 years	6.000 [1.545–23.301]
Patients aged 30–39 years	11.744 [3.834–35.971]
Patients aged 40–49 years	6.182 [3.468–11.020]
Patients aged 50–59 years	3.313 [2.306–4.760]

[a]Calculated using age, gender, dyslipidemia, obesity and Charlson Comorbidity Index.

Table 4: **Effects of appendicitis on colon cancer occurrence at 1 year by stratification in age groups on 2010–2015 matched propensity score[a] patients.**

according to the age group but higher for patients aged 40–49 (sHR = 6.18; 95% CI: 3.47–11.02) than for patients aged 50–59 (sHR = 3.31; 95% CI: 2.31–4.76).

After splitting the first year into two periods of time (Table 3), we found that the risk of colon cancer was highest during the first 6 months after appendicitis, with a 8-fold increased risk of developing colon cancer in patients treated for appendicitis compared to other patients (sHR = 8.39; 95% CI: 5.41–12.99). During the second half of the first year, the risk was multiplied by 2 for patients treated for appendicitis as compared to controls (sHR = 2.07; 95% CI: 1.38–3.11). After considering the interaction of appendicitis with time in the model, we also found that the effect of appendicitis was more pronounced at the beginning of follow-up and decreased over time (Supplementary Table S3).

The sensitivity analysis in which we included patients with colon cancer detected within the first month of follow-up yielded results that were similar results to the main analysis (Supplementary Table S4).

Right-sided colon cancer

The trends for right-sided colon cancer were similar to those observed for colon cancer both in the main analysis (Tables 2 and 3) and in the sensitivity analysis (Supplementary Table S4). There were significantly more right-sided colon cancer in patients treated for appendicitis than in controls during the first year (0.028% vs 0.004%, $p < 0.0001$, Table 2) and the second year (0.010% vs 0.003%, $p = 0.0001$, Table 2), but not in the following years ($p > 0.10$).

With the survival analysis (Table 3), we observed an 8-fold increase in the risk of right-sided colon cancer within one year for patients with appendicitis (sHR = 8.25; 95% CI: 5.03–13.54) compared to control patients. As observed for colon cancer as a whole, the highest risk was found during the first 6 months after inclusion (sHR = 13.45; 95% CI: 6.53–27.70). During the last 6 months of the first year, the risk was still more than 3 times higher for patients treated for appendicitis (sHR = 3.60; 95% CI: 1.86–6.97).

For the period running from the 1st year to the 2nd year we found an almost 4-fold increase in risk of right-sided colon cancer (sHR = 3.70; 95% CI: 2.10–6.52).

Left-sided colon cancer

The trends for left-sided colon cancer were similar to those observed for colon cancer in the main analysis (Tables 2 and 3) and in the sensitivity analysis (Supplementary Table S4). There was significantly more left-sided colon cancer in patients treated for appendicitis than in controls during the first year (0.011% vs 0.004%, $p < 0.0001$, Table 2) but not in the following years ($p > 0.10$).

The results of the survival analyses, presented in Table 3, showed an almost 3-fold increase in the risk of left-sided colon cancer within one year for patients with appendicitis (sHR = 2.81; 95% CI: 1.74–4.53) compared to control patients. Once again, the highest risk was found during the first 6 months after inclusion (sHR = 5.19; 95% CI: 2.37–11.38). During the last 6 months of the first year, the risk was almost 2 times higher for patients treated for appendicitis (sHR = 1.67; 95% CI: 0.86–3.24).

Discussion

Our results, obtained from a nationwide population-based study, confirm that adults presenting with acute appendicitis are at increased risk of colon cancer, particularly in the year following appendicitis. While the association was more marked for right-sided colon cancer, it was also observed with other types of colorectal cancer. Furthermore, this increased risk was present in adults younger than 40 years. These results suggest that there is a need to define appropriate methods to detect colon cancer in patients treated for acute appendicitis.

We found that patients had a higher risk of colon cancer within 1 year after acute appendicitis (sHR = 4.67; 95% CI: 3.51–6.21), but the risk was highest within the first 6 months, with a 6-fold increase in patients with appendicitis compared to controls (sHR = 8.39; 95% CI: 5.41–12.99). We excluded patients who were diagnosed with colon cancer in the first month after appendicitis in order to rule out cases diagnosed on initial admission imaging, during appendectomy, or on the appendectomy pathology report. Although these patients are interesting from an epidemiological point of view, the question of further routine diagnostic work-up is not a concern since the diagnoses for the two conditions were established simultaneously. Our aim was to focus on patients without any specific sign or condition suggesting an increased risk of colon cancer since they may benefit from a subsequent work-up. These results are consistent with those of a meta-analysis showing a standardized risk ratio of 10.65 (95% CI: 3.83–29.66, $p < 0.0001$) in patients with appendicitis.[5] An Asian population study from 2015 comparing patients with and without appendectomy also found that the incidence of colorectal cancer was higher in the appendectomy group, but most cancers

were diagnosed between 1.5 and 3.5 years after appendectomy (HR 2.13; 95% CI: 1.63–2.77).[10] These results are consistent with those from a recent Chinese study finding an increased risk of colorectal cancer diagnosis in the two years following appendectomy.[18] However, most studies on this subject are based on monocentric series and included only patients aged 40 years and over. Our study was population-based, used nationwide data, and included adult patients over and under 40 years. We were thus in a position to observe that acute appendicitis had an effect on the risk of colon cancer regardless of age group, and that the risk was even higher in patients younger than 40 years.[5,6,13]

Furthermore, although the risk is higher for right colon cancer (sHR = 8.250; 95% CI: 5.027–13.541 at 1 year), our results do not support that the focus should be narrowed to the ascending colon (sHR = 2.807; 95% CI: 1.739–4.530 for left-sided colon cancer at 1 year), as some authors have suggested.[7,8]

Regarding the underlying mechanisms of a relationship between acute appendicitis and colon cancer, several hypotheses have been raised in the literature. First, appendectomy could disturb the microbiota and lead to the development of colon cancerogenesis in the long term.[10,18] According to our results, most colon cancers after acute appendicitis are found within the first 6 months after the acute episode, even after removal of those detected at the time of the index hospitalization. Thus, the hypothesis of a common cause producing both diseases can be disregarded based on the duration of cancerogenesis.[19,20] The hypothesis of appendectomy disturbing the microbiota and leading to colon cancer in the long-term is also unsuitable due to the short delay between appendicitis and the diagnosis of colon cancer. But we cannot exclude a further increase in the risk of colon cancer after 10 years, although this is not supported by the current literature.[18] Furthermore, a recent prospective population-based cohort studying the incidence of cancer after appendectomy observed a decreased risk of developing colon cancer in the long term (HR 0.65; 95% CI: 0.43–0.97).[11]

Another hypothesis is that appendicitis could be an early manifestation of colon cancer.[6–8] The fact that most cases of colon cancer in our results were found within 6 months after acute appendicitis strongly supports this second hypothesis. This is also consistent with the results obtained by the two cited Asian studies.[10,17] This manifestation could be explained by an increase in the colon pressure patterns induced by the tumor, leading to acute appendicitis. The higher risk found for right-sided colon cancer (sHR = 8.25; 95% CI: 5.03–13.54) also supports this hypothesis and is consistent with data from other authors.[5–8,21]

The last hypothesis considers that appendicitis might be the consequence of lymphoid hyperplasia in response to colon cancer.[22] This hypothesis is also plausible considering that our results suggest that colon cancer may already be present at the time of appendicitis. Whatever the mechanism (manifestation or consequence), our results show that appendicitis acts as a warning sign for ongoing colon cancer rather than as a risk factor for its development. We could be in a situation of reverse causality, defined as a phenomenon in which the outcome precedes and causes the exposure,[23] because the cancer would precede and trigger appendicitis.

In any case, it appears that a number of patients already had colon cancer when they were treated for acute appendicitis, but it was neither diagnosed with radiological findings nor detected during surgery. This raises the question of whether a routine post-operative workup in patients admitted for appendicitis would be suitable. According to our results, this assessment should be performed within the year following appendicitis. A routine colonoscopy may not be warranted since the risk of cancer is probably lower than the iatrogenic risks of this type of invasive technique. In addition, there is a cost-effectiveness factor, and the workload of endoscopists should also be considered. Alternatives for colon cancer screening, such as CT-colonography and fecal immunohistochemistry testing, could be warranted after appendicitis, but further studies are needed to evaluate their use in this setting.

Our study has several limits, most of them inherent to nationwide analyses. We did not estimate the incidence but only the frequency of new cases in our population. As our study was based on hospital data, we could only estimate the frequency of new cases in the hospitalized population. We chose not to use the term "incidence" in this article because our analyses were not based on the general population. We could, of course, have estimated a hospital incidence rate, but considering that this disease is not frequent, we supposed that it would be very close to the frequency of new colon cancer cases calculated in the hospitalized population. It is therefore not easy to compare our figures with the incidence obtained in the general population from the French Network of Cancer Registries and a previous paper.[24] However, we found that the frequency calculated here in the hospitalized population of the "control" group is very close to the figures obtained in this national report: *Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018–Volume 1: Tumeurs solides: Étude à partir des registres des cancers du réseau Francim.*

Individual medical records were not available at the time of analysis, so we have no information regarding the reasons that lead to the discovery of colon cancer after appendicitis, nor do we have the results of tumor staging. Moreover, there is no specific code in France that can be used to accurately identify complicated appendicitis, so we could not analyze the specific effect of complicated appendicitis on colon cancer occurrence although some studies found an increased risk of cancer

after complicated appendicitis.[25,26] We could not gather any information regarding patient lifestyle, even though the influence of personal habits on the onset of colon cancer is well-known.[3,27] Clinical symptoms and some specific patient characteristics were not available in the PMSI database, which limits the scope of the analyses and the interpretation of results. For example, we could not consider risk factors such as smoking or alcohol consumption. Finally, we included mortality during the initial stay as a competing event. For deaths occurring after hospital discharge, we were able to include in-hospital mortality during subsequent stays. It would have been useful to include all-cause mortality, but unfortunately we do not have access to this information. We believe that the potential bias associated with not taking into account these out-of-hospital deaths is less substantial in people aged under 40, who are more likely to be hospitalized for severe conditions. This bias therefore would have a marginal impact on the major findings of this study, which are the results for the under 40 age group.

This is the first population-based nationwide study to be conducted in a Western country, including all adults presenting with acute appendicitis between 2010 and 2015 after exclusion of those with a relevant personal or family history. This study reveals a 4-fold increase in the risk of colon cancer (8-fold for right-sided colon cancer and almost 3-fold for left-sided colon cancer) during the first year after acute appendicitis, with a higher risk during the first six months. The risk of colon cancer was also increased for those younger than 40 years. Like patients older than 40 years, patients under 40 years presenting with acute appendicitis should be considered as carrying a higher risk of colon cancer, and particularly from the age of 30.[28] Specific screening for colon cancer may be warranted. Therefore, further studies are needed to define the best policy for colon cancer screening after acute appendicitis.

Contributors

Manon Viennet performed bibliographic search prior to the study design, participated to the interpretation of the results and wrote the manuscript.

Solène Tapia accessed the PMSI database, extracted data and performed statistical analysis, wrote parts of the manuscripts.

Jonathan Cottenet provided support for PMSI access and statistical analysis.

Alain Bernard contributed to the study design and to the interpretation of the findings.

Pablo Ortega-Deballon conceived the project at the beginning and provided clinical interpretation of the results, as well as support to the writing of the manuscript.

Catherine Quantin designed the methods, participated to data analysis and discussion of the results.

All authors verified the underlying data, read the successive versions of the manuscript and approved the final one.

Data sharing statement

The data that support the findings of this study are available from the authors upon reasonable request.

Declaration of interests

The authors have no conflict of interest to disclose.

Acknowledgements

The authors thank Ms. Gwenaelle Periard for her administrative support, and Pr Patrick Rat, Pr Nicolas Cheynel, Pr Olivier Facy and Dr Jean-Baptiste Lequeu for their thoughtful and critical review of the preliminary version of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102196.

References

1 Mege D, Borie F. Appendicite aiguë. *EMC Gastroentérol*. 2020;38:1–12 [Article 9-066-A-10].
2 Yang Y, Guo C, Gu Z, et al. The global burden of appendicitis in 204 countries and territories from 1990 to 2019. *Clin Epidemiol*. 2022;14:1487–1499.
3 Manfredi S, Benhamiche-Bouvier AM. Cancer du côlon: épidémiologie. *EMC Gastroentérol*. 2022;39:1–6.
4 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73:17–48.
5 Hajibandeh S, Hajibandeh S, Morgan R, et al. The incidence of right-sided colon cancer in patients aged over 40 years with acute appendicitis: a systematic review and meta-analysis. *Int J Surg*. 2020;79:1–5.
6 Khan SA, Khokhar HA, Nasr ARH, et al. Incidence of right-sided colonic tumors (non-appendiceal) in patient's ≥40 years of age presenting with features of acute appendicitis. *Int J Surg*. 2013;11:301–304.
7 Sylthe Pedersen E, Stornes T, Rekstad LC, et al. Is there a role for routine colonoscopy in the follow-up after acute appendicitis? *Scand J Gastroenterol*. 2018;53:1008–1012.
8 Mohamed I, Chan S, Bhangu A, et al. Appendicitis as a manifestation of colon cancer: should we image the colon after appendicectomy in patients over the age of 40 years? *Int J Colorectal Dis*. 2019;34:527–531.
9 Liu Z, Ma X, Zhu C, et al. Risk of colorectal cancer after appendectomy: a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2023;38:350–358.
10 Wu S-C, Chen WT-L, Muo C-H, et al. Association between appendectomy and subsequent colorectal cancer development: an Asian population study. *PLoS One*. 2015;10:e0118411.
11 Van den Boom AL, Lavrijssen BDA, Fest J, et al. Appendectomy and the subsequent risk of cancer: a prospective population-based cohort study with long follow-up. *Cancer Epidemiol*. 2022;77:102120.
12 Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *Br J Surg*. 2016;103:656–667.
13 De Almeida Leite RM, Seo DJ, Gomez-Eslava B, et al. Nonoperative vs operative management of uncomplicated acute appendicitis: a systematic review and meta-analysis. *JAMA Surg*. 2022;157:828–834.
14 Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med*. 2021;9(3):251–259.
15 Magnin J, Bernard A, Cottenet J, et al. Impact of hospital volume in liver surgery on postoperative mortality and morbidity: nationwide study. *Br J Surg*. 2023;110(4):441–448.
16 Quantin C, Moreau T, Asselain B, Maccario J, Lellouch J. A regression survival model for testing the proportional hazards hypothesis. *Biometrics*. 1996;52(3):874–885.
17 Cox DR. Regression models and life tables (with discussion). *J R Stat Soc Ser B Methodol*. 1972;34:187–200.
18 Shi F, Liu G, Lin Y, et al. Altered gut microbiome composition by appendectomy contributes to colorectal cancer. *Oncogene*. 2023;42:530–540.
19 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759–767.
20 Hossain MS, Karuniawati H, Jairoun AA, et al. Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges,

risk factors, preventive and treatment strategies. *Cancers*. 2022;14:1732.
21 Lai H-W, Loong C-C, Tai L-C, et al. Incidence and odds ratio of appendicitis as first manifestation of colon cancer: a retrospective analysis of 1873 patients. *J Gastroenterol Hepatol*. 2006;21:1693–1696.
22 Girard-Madoux MJH, Gomez de Agüero M, Ganal-Vonarburg SC, et al. The immunological functions of the appendix: an example of redundancy? *Semin Immunol*. 2018;36:31–44.
23 Banack HR, Bea JW, Kaufman JS, et al. The effects of reverse causality and selective attrition on the relationship between body mass index and mortality in postmenopausal women. *Am J Epidemiol*. 2019;188(10):1838–1848.
24 Defossez G, Uhry Z, Delafosse P, et al. Cancer incidence and mortality trends in France over 1990-2018 for solid tumors: the sex gap is narrowing. *BMC Cancer*. 2021;21(1):726.
25 Keckler SJ, Tsao K, Sharp SW, et al. Resource utilization and outcomes from percutaneous drainage and interval appendectomy for perforated appendicitis with abscess. *J Pediatr Surg*. 2008;43:977–980.
26 Lietzén E, Grönroos JM, Mecklin J-P, et al. Appendiceal neoplasm risk associated with complicated acute appendicitis—a population based study. *Int J Colorectal Dis*. 2019;34:39–46.
27 Cappell MS. Pathophysiology, clinical presentation, and management of colon cancer. *Gastroenterol Clin North Am*. 2008;37:1–24.
28 Ladabaum U, Dominitz JA, Kahi C, et al. Strategies for colorectal cancer screening. *Gastroenterology*. 2020;158:418–432.