



Increased incidence of bowel cancer after non-surgical treatment of appendicitis

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Abstract

Background: There is an ongoing debate on the use of antibiotics instead of appendectomy for treating appendicitis but diagnostic difficulties and longstanding inflammation might lead to increased incidence of bowel cancer in these patients. The aim of this population-based study was to investigate the incidence of bowel cancer after non-surgical treatment of appendicitis.

Patients and methods: Patients diagnosed with appendicitis but lacking the surgical procedure code for appendix removal were retrieved from the Swedish National Inpatient Register 1987–2013. The cohort was matched with the Swedish Cancer Registry and the standardised incidence ratios (SIR) with 95% confidence interval (95% CI) for appendiceal, colorectal and small bowel cancers were calculated.

Results: Of 13 595 patients with non-surgical treatment of appendicitis, 352 (2.6%) were diagnosed with appendiceal, colorectal or small bowel cancer (SIR 4.1, 95% CI 3.7–4.6). The largest incidence increase was found for appendiceal (SIR 35, 95% CI 26–46) and right-sided colon cancer (SIR 7.5, 95% CI 6.6–8.6). SIR was still elevated when excluding patients with less than 12 months since appendicitis and the incidence of right-sided colon cancer was elevated five years after appendicitis (SIR 3.5, 95% CI 2.1–5.4). An increased incidence of bowel cancer was found after appendicitis with abscess (SIR 4.6, 95% CI 4.0–5.2), and without abscess (SIR 3.5, 95% CI 2.9–4.1).

Conclusion: Patients with non-surgical treatment of appendicitis have an increased short and long-term incidence of bowel cancer. This should be considered in the discussion about optimal management of patients with appendicitis.

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Keywords: Appendicitis; Non-surgical treatment; Appendiceal cancer; Colorectal cancer

Introduction

Appendectomy is still standard treatment for acute appendicitis, but non-surgical treatment is emerging [1]. The association between longstanding inflammation and cancer is well known, for instance in inflammatory bowel disease (IBD) [2] and hepatitis [3]. Treating appendicitis with antibiotics theoretically puts the patient at risk by creating a contained inflammation. Randomised trials [4,5] and meta-analyses [6,7] have focused on the risk of complications compared to standard surgical management, but one meta-analysis reported that 1.2% of 2771 patients

with non-surgical treatment of appendiceal abscess or phlegmon were later diagnosed with a malignancy [8]. However, there are no studies on the risk of bowel cancer in larger population-based materials.

The aetiology of appendiceal neoplasms is likely to be related to that of colon cancer, but the organ's unique anatomy might lead to distinct pathways of neoplastic transformation and spread. An association between appendectomy and later onset of colorectal cancer and other forms of cancer has been reported [9–11] and the appendix has been suggested to play a protective role in the defence against cancer. On the other hand, others report no association between appendectomy and later diagnosis of cancer [12–14].

The incidence of appendiceal, colorectal and small bowel cancer after non-surgical treatment of appendicitis

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is unknown and has to be further investigated before appendectomy is replaced by antibiotics as standard treatment of appendicitis. The aim of this population-based study was therefore to investigate the incidence of bowel cancer after non-surgical treatment of appendicitis.

Patients and methods

Study design

This is a population-based cohort study comparing the incidence of bowel cancer in patients with non-surgical treatment of appendicitis with the incidence of cancer in the total population of Sweden, using standardised incidence ratios (SIR).

Participants

Patients diagnosed with appendicitis in Sweden between 1987 and 2013 were identified from the Swedish National Inpatient Register (IPR) using the Swedish version of the International Classification of Disease (ICD) codes, ninth (ICD-9) [15] and tenth version (ICD-10) [16] (Supplementary Table 1). All Swedish residents have a unique personal 10-digit identification number [17], making it possible to identify patients in the registers. The IPR is held by the Swedish National Board of Health and Welfare (NBHW) and provides data for research and evaluation of health care. It has a complete national coverage of hospitalisations since 1987 [18]. Patients who underwent surgical removal of the appendix at the time of appendicitis were identified from the IPR using surgical procedure codes [19,20]. Patients were excluded if a surgical code implying appendectomy, i.e. code for appendectomy, ileocecal resection, right hemicolectomy, or colectomy (Supplementary Table 2) was registered at the time of appendicitis. Patients with appendicitis and a surgical procedure code for appendectomy prior to a hospitalisation period with a diagnosis of appendiceal abscess without surgery were also excluded. In addition, patients with surgical procedure codes for “other operations on appendix” or “inversion of appendix” were excluded. Finally, patients not automatically excluded before data extraction due to wrong coding of appendectomy in the IPR were excluded. After exclusions, patients with non-surgical treatment of appendicitis remained for analysis.

Outcome and follow-up

The cohort was linked with the Swedish Cancer Registry (held by NBHW) to which health care providers are required to report all recently diagnosed malignancies. Approximately 99% of the cases are morphologically verified [21]. The register was complete for 2013 at the time of data extraction in 2015. Patients with bowel cancer, defined as malignant tumours of the small bowel, appendix, colon and rectum, were identified with ICD codes

(Supplementary Table 3) [15,22,23]. Histopathological characteristics are described by Systematised nomenclature of medicine (SNOMED) codes in the registry. Information on the subsequent surgical removal of the appendix, colon, and rectum was retrieved for the cohort from the IPR. To receive information on vital status and emigration, the cohort was linked to the Cause of Death Register (held by NBHW) and the Register of Total Population (held by Statistics Sweden) for the same time period. The study was approved by the Regional Ethics Committee of Uppsala County, Sweden (reference number 2014/421).

Statistical analysis

The incidence of cancer in the cohort was compared with the incidence of cancer in the total population of Sweden using SIR. The year of diagnosis, age, sex, and site-specific incidence rates were extracted from the Swedish Cancer Registry [21] and multiplied by the numbers of accumulated person-years at risk in each stratum. Patients were considered at risk until the date of cancer diagnosis, surgical removal of the organ, death, emigration, or end of study period (31 December 2013). The ratio of observed to expected number of cases was expressed as SIR with 95% confidence interval (95% CI). CIs were calculated by assuming that the observed number of cases followed a Poisson distribution, and by using Byar's normal approximation [24]. For site-specific SIR analysis (small bowel, appendix, right-sided colon, left-sided colon, and rectal cancer), a previous cancer at the same site resulted in exclusion. For non-site-specific SIR analysis (colon, colorectal, and bowel cancer), the first cancer was analysed and a cancer prior to appendicitis did not result in exclusion since the risk of cancer remained. For all SIR analyses, a cancer diagnosed at time of appendicitis (same hospitalisation period) resulted in exclusion. SIR was calculated for all remaining cases of cancer and stratified for cancer diagnosed within six months versus after six months from non-surgical treatment of appendicitis. The latter was repeated excluding patients with removal of appendix within six months. SIR analysis was also repeated using a 12-month limit. In addition, SIR analysis of bowel cancer was analysed separately for appendicitis without abscess and appendicitis with abscess (ICD-9 540B, ICD-10 K351) and SIR analysis of appendix and right colon were stratified by attained age.

Numbers needed to treat with appendectomy to avoid one appendiceal cancer were estimated using the probability of appendiceal cancer between six months and 25 years after non-surgical treatment of appendicitis (excluding patients who underwent appendectomy within six months). This was compared with the probability of appendiceal cancer among patients who underwent appendectomy (probability = zero) and numbers needed to treat were calculated as the inverse of the absolute risk reduction. Statistical analysis was performed with R version 3.1.2 (R foundation for Statistical Computing, Vienna, Austria).

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