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ANTIBIOTICS USE IN RELATION TO COLORECTAL CANCER RISK, SURVIVAL AND POSTOPERATIVE COMPLICATIONS

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Akademisk avhandling

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Antiobiotics use in relation to colorectal cancer risk, survival and postoperative complications

Background: Growing evidence suggests that antibiotic-induced dysbiosis of gut microbiota potentially contributes to colorectal cancer development and oncological outcomes. However, the role of antibiotics in colorectal cancer incidence, survival and postoperative outcomes at a population level remains incompletely understood.

Aims: The overall aim of the thesis is to investigate prescription antibiotics use in relation to colorectal cancer risk, survival and postoperative complications, particularly surgical site infections including anastomotic leakage.

Methods: The thesis work includes matched case-control and cohort studies, leveraging complete population-based data from Swedish national registers. Paper I is a matched case-control study that consists of 40 545 colorectal cancer cases and 202 720 matched controls, aiming to investigate antibiotics use and risk of incident colorectal cancer. Multivariable conditional logistic regression was used. Paper II is a cohort study, including 47 303 colorectal cancer cases, investigating antibiotics use in relation to cancer-specific survival. Stratified Cox proportional-hazards regression was used. Paper III includes 38 839 colorectal cancer cases who had undergone abdominal tumour-resection surgery and assesses antibiotics use in relation to surgical site infections, including anastomotic leakage, within 30 days after surgery. Logistic regression with multi-level mixed-effects models was used.

Results: In paper I, a dose-response association between antibiotics use and a higher risk of proximal colon cancer was found, whereas a slight inverse association with rectal cancer was observed, mainly in women. A null association was found between methenamine hippurate, assessed as a negative control due to no known effect on gut microbiome, and the risk of colorectal cancer. In paper II, the findings did not support any substantial negative effect of antibiotics on cancer-specific survival, except for very high cumulative exposure (>180 days) in stage I-III diseases. In stage IV colorectal cancer, modest inverse relationships between antibiotics use and survival were noted. In paper III, prescription antibiotics use up to 4.5 years before surgery was associated with a higher risk of surgical site infections, including anastomotic leakage, after colon cancer surgery but not rectal cancer surgery. A null association was observed between methanamine hippurate and the risk of surgical site infections. For cardiovascular and/or neurological complications, also considered as a negative control due to expected negligible or null effects of gut microbiome on these outcomes after surgery, associations were null in both colon and rectal cancer.

Conclusion: These studies provided further support for antibiotics use as a modifiable risk factor for proximal colon cancer and identified antibiotics taken long before surgery as a novel risk factor for surgical site infections, including anastomotic leakage, after colon cancer surgery. In contrast, we did not find any substantial negative impact of antibiotics on cancer-specific survival. Taken together, the findings described in this thesis provide etiological insights and may contribute to strategies to prevent colon cancer and improve postoperative outcomes through prudent use of antibiotics, thereby aiding in the reduction of colorectal cancer incidence and mortality.

Keywords
Colorectal cancer, antibiotics, gut microbiome, dysbiosis, cancer-specific survival, surgical site infections, anastomotic leakage, register-based epidemiology

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