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# MODULATING THE INFLAMMATORY RESPONSE AFTER COLORECTAL CANCER SURGERY: FRIEND OR FOE?

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## Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Sal B, Byggnad 1D, Trapphus T, 9 trappor, Norrlands Universitetssjukhus, fredagen den 24:e maj, kl. 13:00.

Avhandlingen kommer att försvaras på engelska.

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Modulating the inflammatory response after colorectal cancer surgery: friend or foe?

**Abstract**
Anastomotic leakage is a feared complication after colorectal cancer surgery, affecting both morbidity and mortality. Whether or not non-steroidal anti-inflammatory drugs (NSAIDs), which act by inhibition of cyclooxygenase (COX) enzymes, alter the risk for anastomotic leakage remains uncertain. Activation of COX enzymes, and other proteins stimulated by leakage itself, may also enhance minimal residual disease and confer an increased risk of cancer recurrence.

Study I and II were retrospective cohort studies using the Swedish Colorectal Cancer Registry to identify patients and acquire data. Study I included 1,341 patients who had undergone anterior resection for rectal cancer at 15 different Swedish hospitals during 2007–2012. Exposure was defined as at least two days of NSAID exposure during the first postoperative week. No recurrence-free survival benefit could be discerned for the NSAID-exposed. Study II included 6,945 patients who were resected for colorectal cancer at 21 Swedish hospitals during 2007–2012, and the hospitals' perioperative analgesia protocols were the basis for exposure. Cancer recurrence and anastomotic leakage were decreased for the NSAID-exposed. Study III and IV comprised matched cohorts of colorectal cancer patients: cases suffered a postoperative peritoneal infection and controls had a complication-free postoperative stay. Serum samples were retrieved from the Uppsala-Umeå Cancer Consortium biobank. Study III included 32 cases and 32 controls and found 77 differentially expressed proteins for the cases at a median of 41 days after surgery, with many of the top hub proteins being known actors in colorectal cancer progression. Study IV included 47 cases and 47 controls and evaluated whether the COX-2 gene promotor -765G>C polymorphism was related to anastomotic leakage. 2.1% were homozygous for the minor allele, and 25.5% were heterozygous. The minor allele demonstrated a non-significant decreased odds ratio, thus suggesting no link to leakage.

**Keywords**
Colorectal cancer, outcomes, complications, anastomotic leakage, inflammation, cox-enzyme, NSAID, proteomics, biological pathways

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