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Glucocorticoid use and colorectal cancer: risk and postoperative outcomes

PhD dissertation

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Preface

This PhD dissertation is based on studies conducted during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark and at the Department Gastrointestinal Surgery, Aalborg University Hospital, Denmark. Study lll was conducted during my research stay at the Department of Medicine, the University of North Carolina at Chapel Hill, United States.

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I. Ostenfeld EB, Erichsen R, Thorlacius-Ussing O, Riis AH, Sørensen HT. Use of systemic glucocorticoids and the risk of colorectal cancer. *Aliment Pharmacol Ther. 2013;37:146-52.*

II. Ostenfeld EB, Erichsen R, Thorlacius-Ussing O, Riis AH, Sørensen HT, on behalf of the Danish Colorectal Cancer Group. Preadmission use of glucocorticoids 30-day mortality following colorectal cancer surgery: a Danish nationwide cohort study. *Aliment Pharmacol Ther. 2014;39:148-53.*

III. Ostenfeld EB, Erichsen R, Baron JA, Thorlacius-Ussing O, Iversen LH, Riis AH, Sørensen HT, on behalf of the Danish Colorectal Cancer Group. Preadmission use of glucocorticoids and risk of anastomotic leakage following colon and rectal cancer surgery: a Danish nationwide cohort study, *submitted*.

List of abbreviations

BCC: Basal cell carcinoma

CD: Crohn's disease

CI: Confidence interval

CRC: Colorectal cancer

CRS: Civil Registration System

DCCG: Danish Colorectal Cancer Group

DCDR: Danish Cause of Death Registry

DCR: Danish Cancer Registry

DNRP: Danish National Registry of Patients

FAP: Familial adenomatous polyposis

MM: Malignant melanoma

NHL: Non-Hodgkin's lymphoma

IBD: Inflammatory bowel disease

IPAA: Ileal pouch-anal anastomosis

IRA: Ileorectal anastomosis

MR: Mortality ratio

NSAID: Non-steroidal anti-inflammatory drug

OR: Odds ratio

SCC: Squamous cell carcinoma

UC: Ulcerous colitis

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1. Introduction

Worldwide, colorectal cancer (CRC) is the third most common malignancy and the fourth most common cause of cancer-related death and thus imposes a substantial burden.[1] In Denmark, 4400 new cases of CRC were diagnosed in 2012, with a median age at diagnosis of 72 years.[2] The age-standardized incidence of CRC has increased up to 14% during the past decade in Denmark,[2] in contrast with its concurrent decline in the United States.[3]

CRC incidence increases with age,[4] as do the prevalence of chronic diseases.[5] Consequently, a large proportion of CRC patients are burdened with coexisting diseases.[3,6,7] Therefore, polypharmacy, is a matter of concern in the management of CRC[8,9] and knowledge is urgently required regarding interactions between drug effects and CRC risk and prognosis.

Glucocorticoids are standard treatment for various chronic conditions that share an inflammatory or immunological basis.[10] In 2012, 8% of the Danish population aged 65 years or older redeemed prescriptions for systemic glucocorticoids;[11] this appears to be the highest prevalence of redemption according to recent international reports.[12-15] Glucocorticoids have potent immunologic and metabolic effects that may influence CRC development and prognosis. The aim of this thesis was to examine the association between glucocorticoid use and risk of CRC and postoperative outcomes.

Before going into detail about the studies, an introduction to CRC risk, treatment, and prognosis, as well as glucocorticoids and their use, is warranted.

1.1 Definition

When referring to CRC in this dissertation, we consider adenocarcinomas originating from the glandular epithelium of the colorectal mucosa, because this histological type includes more than 90% of all CRCs.[16]

1.2 Studying risk of colorectal cancer

In medicine, risk is the probability that an individual will develop a certain disease.[17] Factors that are associated with an increased risk of disease are referred to as risk factors.[17] Identifying risk factors for CRC is important for understanding and predicting the cancer, for reducing incidence by primary prevention and for improving early detection by recognizing individuals at increased risk. Some risk factors such as age, cannot be eliminated, however, evidence of associated cancer risk may help guide changes in the organization of health care, such as the decision to introduce CRC screening programs in Denmark from 2014.

1.2.1 Risk factors for colorectal cancer development

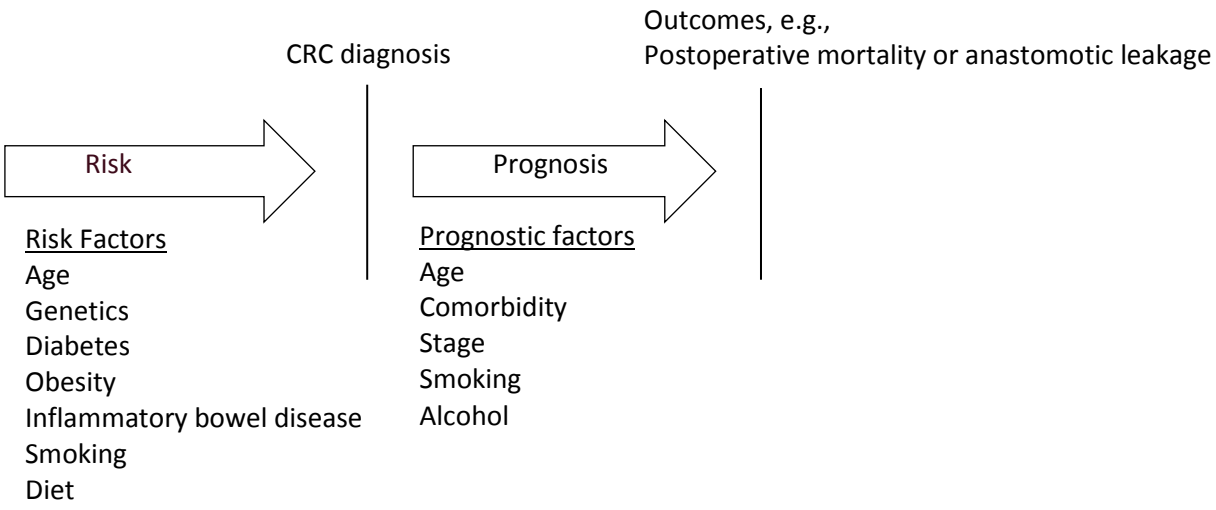
CRC develops slowly over a period of 10-15 years.[18] Age is a strong risk factor for CRC development, and more than 90% of cases occur in individuals 50 years of age or older.[19] Several other risk factors for CRC have been identified, including inflammatory bowel disease (IBD), diabetes, obesity, high-fat/low fiber diet, smoking, high alcohol consumption, and low levels of exercise (Figure 1.1).[20] In addition, hereditary syndromes (e.g., Lynch syndrome or familial adenomatous polyposis) and family history are strongly associated with CRC occurrence.[18] The vast majority of CRC cases arise sporadically (i.e., without genetic disposition to CRC), suggesting that environmental factors are essential in the etiology of the disease.[18] Interestingly, migration studies demonstrate that people moving from low-incidence areas to high-incidence areas adapt the high risk of CRC, indicating that the westernized lifestyle as a whole is related to colorectal carcinogenesis.[21]

Pharmacological treatments and CRC risk

Certain medications have been suggested as chemopreventive agents in CRC development, including aspirin, non-steroidal inflammatory drugs (NSAIDs), and postmenopausal hormone replacements, although their utility is limited by their side effect profile.[20] Studies also indicate

that calcium supplements reduce CRC risk.[20] Current evidence regarding the effects of immune modulators including glucocorticoids on CRC risk is sparse and conflicting, as will be discussed later (Study I).

Figure 1.1 Concept of colorectal cancer (CRC) risk and prognosis



1.3 Studying prognosis after colorectal cancer

Prognosis can be defined as a prediction of the outcome of a disease.[22] In this thesis, prognosis refers to the outcome after CRC surgery (Studies II, III). Factors that are associated with outcome are referred to as prognostic factors, and should not be confused with risk factors, although some, such as age, may affect both risk and prognosis[23] (Figure 1.1). Identifying prognostic factors for CRC outcomes has obvious implications because clinicians and patients may improve prognosis by eliminating or reducing their influence. Also, knowledge about such factors improves understanding of the postoperative course after CRC treatment and may clarify clinical requirements during the perioperative period.

1.3.1 Colorectal cancer surgery

The mainstay curative treatment for CRC is surgical resection of the tumor-involved bowel segment and its regional lymph nodes. For colon cancer, standard procedure involves segmental bowel resection with central ligation of supplying arteries, draining veins and lymph vessels, wide mesenteric resection, and creation of an anastomosis.[24] Occasionally, colon cancer manifests with acute obstruction, in which case treatment with self-expanding metal stents may be useful to

convert acute surgery associated with high morbidity and mortality to elective surgery after medical restitution of the patient.[25] Stents are also used in the palliative setting when surgery is not an option. Sited in the rectum, tumor resection includes a total or partial mesorectal extension and ligation of the inferior mesenteric artery.[24] Preoperative chemoradiation may be offered to selected rectal cancer patients.[24]

Whether the optimal surgical treatment (i.e., tumor resection) can be performed depends strongly on the extent of tumor spread.[24] In Denmark, CRC has been categorized into four Union for International Cancer Control (UICC) stages according to the Dukes system until the end of 2003 and the tumor, node, metastasis (TNM) stage classification hereafter[26,27] (Figure 1.2). Overall, surgical CRC treatment is performed with curative intent in most stage l-lll patients, as well as in certain stage lV patients with resectable metastases in the liver or lung.[24] Another important determinant of treatment choice is comorbidity. Thus, resection rates are 15-19% lower among Danish CRC patients with a Charlson Comorbidity Index (CCI) Score of 3+ at diagnosis (2004-2006) than among those with a score of 0.[28] CCI is described in detail in section 4.7.

Figure 1.2. Correlation between staging systems

Dukes	TNM	UICC
A	T1-2 N0 M0	L
B	T3-4 N0 M0	Ll
C	T_{any} N1-2 M0	Lll
D	T_{any} N_{any} M1	lV

1.3.2 Outcomes after colorectal cancer surgery

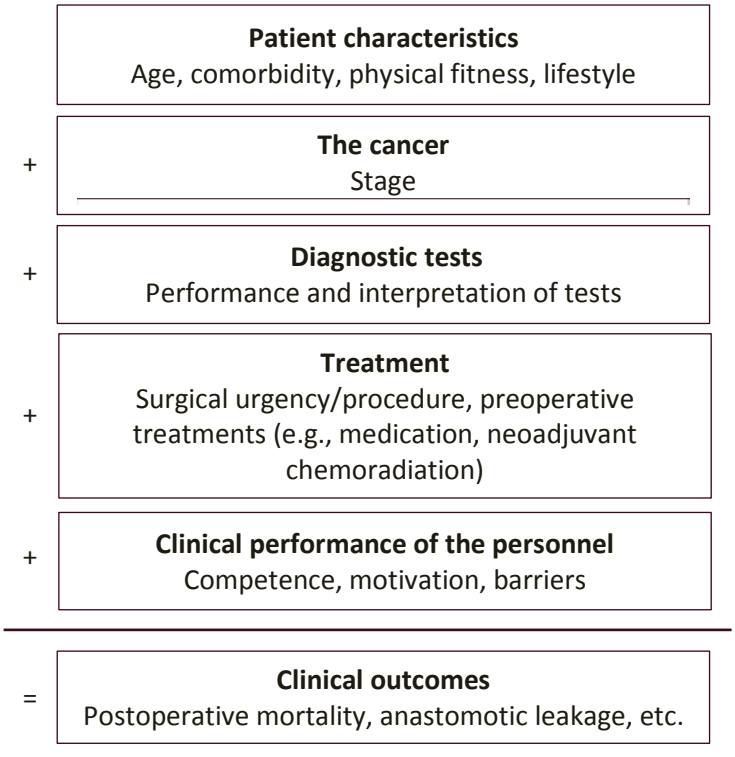
Although surgical techniques and perioperative care have improved, surgery inevitably carries a risk. In 2012, 25% of Danish CRC patients experienced postoperative surgical complications,[29] and 5% of patients died within 30 days after surgery.[30] Postoperative mortality has decreased in Denmark during the last decade, but ranks highest in Nordic comparisons for unknown reasons.[31,32] This inferior short-term outcome may also contribute to the inferiority of 5-year survival in Denmak,[33,34] which remains below 50%.[6] Compared with our neighbouring countries, a more adverse stage distribution at CRC diagnosis has been observed in Denmark,[35,36] which may account for some of the discrepancy in outcomes.[30] Accordingly, dissimilarities in patients' general health

(including comorbidity and polypharmacy), as well in surgical treatment or perioperative care, may play a role.

1.3.3 Prognostic factors for postoperative outcomes of colorectal cancer

The outcome after CRC depends on several factors (Figure 1.3). Patients' characteristics, particularly age and comorbidity, have a substantial adverse effect on postoperative outcomes.[37-39] Accordingly, postoperative mortality among CRC patients increases dramatically with increasing American Society of Anesthesiologists Physical Status Classification (ASA) score.[4] The ASA score measures the preoperative physical fitness of the patient and can be considered a surrogate of the severity of comorbidity. Categories of ASA scores range from ASA I (characterizing a healthy individual) to ASA V (characterizing a moribund patient that is not expected to survive without the operation). Other important determinants of postoperative outcomes are CRC stage[38] and urgency of the surgery. Based on Danish data, overall 30-day mortality was 3% after elective CRC surgery, while mortality reached 17% after acute resections.[29] Preoperative medical treatments (e.g., glucocorticoids) may likewise influence postoperative outcomes, and a description of this influence constitutes the aims of Studies II and III in this thesis.

Figure 1.3. Determinants of the outcomes after CRC surgery, modified from *Sackett*[40]



1.4 Glucocorticoids: physiologic functions and pharmacologic effects

Glucocorticoids are a class of steroid hormones. Cortisol, the natural occurring glucocorticoid, is synthesized in the adrenal cortex after the activation of the hypothalamic-pituitary-adrenal (HPA) axis and acts to maintain homeostasis.[41] Synthetic glucocorticoids were introduced into clinical practice in 1948 for the treatment of rheumatoid arthritis.[10] Today, glucocorticoids are standard therapy for reducing immune activation in various acute and chronic inflammatory diseases, as well as in haematological malignancies and after organ transplantations. Most of glucocorticoids' effects are mediated through the intracellular glucocorticoid receptor, which is situated in almost all tissues.[41] Resultant pleiotropic effects include the tight regulation of physiological and cellular processes, such as metabolism, immune function, cell growth, proliferation, and apoptosis.[41]

However, at supraphysiologic doses, the pleiotropic actions of glucocorticoids have diverse and serious side effects. Among others, these side effects can involve (1) carbohydrate metabolism, by increasing gluconeogenesis and insulin resistance, thereby leading to prolonged hyperglycaemia and risk of overt diabetes; (2) lipid metabolism, resulting in an increase in circulating free fatty acids; (3) immune function, as a result of fewer lymphocytes and inhibition of their production of several factors that are critical to generate an inflammatory response (leading to, for example, increased susceptibility to infections and impaired wound healing); and (4) the cardiovascular system, by inducing hypertension and dyslipidaemia and reducing fibrinolysis, thereby predisposing to atherosclerosis and coronary heart disease.[10,41] Furthermore, continued glucocorticoid therapy causes adrenal suppression through negative feedback at several levels of the HPA axis, which may be life-threatening under stressful circumstances, such as surgery or by abrupt cessation.[10,42] Thus, glucocorticoid therapy is associated with widespread side effects, some of which may affect CRC risk and prognosis, as discussed in Section 2.

1.5 Causal versus prediction studies on risk or prognosis of colorectal cancer

When reviewing the literature regarding the effects of glucocorticoids on risk of and outcomes after CRC, it is important to distinguish between causality and prediction. The aim of causal studies is to assess whether an outcome might be attributable to a particular risk factor. In causal studies, the association may be affected by other variables (i.e., confounding factors). Confounders are

unique to the particular hypothesis and should be selected a priori based on evidence of their association with both the specific outcome and the particular exposure. Also, confounders must not be a step on the causal pathway.[43] All three studies in this thesis were designed as causal studies, each based on well-defined hypotheses about potential causal relations between glucocorticoids and CRC risk, postoperative mortality, or leakage.[22]

Contrary to causal studies, the aim of a prediction study is to predict an outcome for future patients given a number of factors that do not necessarily influence the outcome.[22,44] Candidate factors are usually examined in multivariate models but only if they have sufficient statistical impact on the outcome. Although this approach may lead to statistically strong associations between covariates and the outcome, it provides no information about causal relationships. Because prediction studies have no underlying hypothesis, it is not relevant to discuss confounding in the context of prediction studies. Results from a prediction study can help define high-risk groups, but should not address questions of causality. Ideally, the statistical model is developed in one cohort and validated in another to ensure its quality at predicting the outcome.[22,45] Many studies use methods that can be characterized as a mix of prediction and etiological studies[22] and the interpretation of the results should reflect the methods used.[46]

2. Background and existing literature

2.1 Glucocorticoids and colorectal cancer risk (Study I)

It has been recognized that developing tumors are exposed to and commonly eliminated by an intact immune system.[47] Both the innate and adaptive immune systems guard the host against cancer development through complex mechanisms of immunosurveillance.[48,49] As potent immunosuppressants, glucocorticoids may facilitate CRC development. Also, glucocorticoids may increase risk through diabetogenic effects and dyslipidemia.[50,51] In contrast, anti-proliferative and pro-apoptotic effects of glucocorticoids[41] might also protect against cancer development. Furthermore, glucocorticoids belong to the same steroid superfamily as estrogen and progesterone, which appear to be inversely associated with risk of colorectal cancer.[52] Thus, glucocorticoids may influence CRC risk through several mechanisms.

2.1.1 Existing literature on glucocorticoids and colorectal cancer risk

We searched Medline for English-language literature using the following query:

("Colorectal Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Risk Factors"[Mesh]

This search revealed 6 hits, none of which were relevant. However, reviewing abstracts of articles that were related to them by citing the same references, we found one relevant recent review associating IBD medications including glucocorticoids with CRC risk (Table 2.1a).[53] We then broadened the search to include neoplasms in general, using the following query:

("Carcinogenesis"[Mesh] OR "Neoplasms"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Risk Factors"[Mesh]

This query yielded 85 hits, including five studies that associated glucocorticoid therapy with the risk of specific cancers other than those of the colon and rectum.[54-58] By reviewing their reference lists and articles that were related to them by citing the same references, we found four additional studies of interest.[59-62] Finally, we were aware of a relevant study that was not identified through our literature search.[63] (Tables 2.1b)

A recent review included nine relevant studies, all but one[64] of which demonstrated inverse associations between glucocorticoids and CRC risk.[64-72] In contrast, in a US-based case-control study that included 18 440 CRC cases and 368 800 age-, sex-, and calendar year-matched population controls, a univariate analysis of glucocorticoid users (defined as using glucocorticoids during the year before the CRC diagnosis) revealed that glucocorticoid use was a predictor of CRC (odds ratios (OR) = 1.25, 95% CI: 1.19-1.32).[64]

Studies that associated glucocorticoids with cancer risk in general revealed no clear tendencies. Five population-based studies with sample sizes ranging from 1405 to 59 043 individuals reported that glucocorticoids increased the risk of non-Hodgkin lymphomas and non-melanoma skin cancers, as well as cancers of the bladder and the prostate.[55,57,59,60,62] However, no association was observed between glucocorticoid therapy and risk of non-Hodgkin lymphomas in a meta-analysis of 8 population-based case-control studies completed between 1992 and 2006[61] or between glucocorticoid therapy and risk of breast cancer in two Danish population-based studies.[54,56] In a US cohort study of 10 474 patients with chronic obstructive pulmonary disease, an inverse association was reported between use of inhaled corticosteroids (≥1200 µg/day) and lung cancer when compared with non-use (OR=0.39, 95% CI: 0.16-0.96).[63] Finally, in an Italian single-centre case-control study, glucocorticoid therapy appeared to be protective against melanoma; compared with never-use, OR was 0.39 (95% CI: 0.25-0.74) for any use during the past 5 years and 0.26 (95% CI: 0.05-1.32) for duration of use exceeding 6 months.[58]

2.1.1.2 Limitations of the existing literature

There is little published data on glucocorticoids and CRC development, and only one study examined risk in a general population.[64] However, because the primary exposure of interest was 5-aminosalicylic acid, glucocorticoid use was examined only as a covariate and additional adjusted or stratified analyses were not provided. Furthermore, the definition of glucocorticoid exposure as glucocorticoid use during the year before the CRC diagnosis seemed clinical inappropriate given a time interval from development of adenoma to CRC of approximately 10 years.[73] The remaining studies were restricted to IBD patients, who *a priori* had an increased risk of cancer.[65-72] Again, glucocorticoids were not the main exposure of interest in any study, and thus have been investigated only to a very limited extent.

Studies associating glucocorticoid use and risk of cancers other than those of the colon and rectum also had limitations. A Danish cohort study on glucocorticoids and risk of non-Hodgkin lymphoma and skin cancers did not include data on comorbidity or sun exposure, which in stratified analyses might have revealed important differences in risk between subgroups of patients.[57] Two case-control studies from the United States[60,62] and one from Italy[58] were based on self-reported glucocorticoid use and thus may suffer from information bias.[60,62] In addition, results from the Italian single-centre study were based on only a few exposed cases. Overall, evidence regarding associations between glucocorticoids and risk of CRC is limited. We therefore conducted a population-based case-control study to address this gap in the literature.

Table 2.1a. Studies reporting effects of glucocorticoids on colorectal cancer risk[1]

Author, year	Design, country	Study population, period	Exposure of interest	Outcome of interest	Results on glucocorticoids, comments
Subramanian, 2011[53]	Review, England	Review of studies on IBD agents and CRC risk. Studies reporting effects of glucocorticoids included 48-1536 patients, 1997-2009.	Glucocorticoids	CRC or dysplasia	No summary estimate provided, each study is described below.
Tang, 2009[74]	Single-centre case control study, USA	Source population: IBD patients 18 CRC cases and 30 controls matched for IBD type, age at IBD diagnosis, sex, race, extent of disease, and duration of disease, 1970-2005	Several potential predictors for CRC Steroids y/n	CRC	Univariate analysis: p=1.00
Gupta, 2007[66]	Single-centre cohort study, USA	Study population: Patients with UC for ≥7 years that had a colonoscopy between 1996-1997, N=418	Histologic inflammation As covariate: Steroid use >4 months y/n	CRC or dysplasia	Univariate analysis: HR=0.6 (0.4–1.1)
Terdiman, 2007[64]	Multi-centre case control study, USA	Source population A: General population; 18 440 CRC cases and 368 800 controls, 2001-2003. B: Restriction to IBD patients: 364 CRC cases and 1172 controls	5-aminosalicylic acid As covariate: Glucocorticoids in the year before CRC diagnosis y/n	CRC	Univariate analysis: A: OR=1.25 (1.19-1.32) B: OR=1.43 (1.09-1.87)
Velayos, 2006[67]	Single-centre case control study, USA	Source population: UC patients; 188 CRC cases and 1528 controls, 1976-2002	Several potential predictors for CRC Prednisone >1 year y/n	CRC	Multivariate analysis: OR=0.4 (0.2-0.8)
Seigel, 2006[68]	Single-centre case control study, USA	Source population: Patients with Crohn's disease; 27 CRC cases and 27 controls, 1990-2004	Several potential predictors for CRC Regular/current use of oral steroids y/n	CRC	Univariate analysis: OR=0.56 (0.15-1.85)
Van Staa, 2005[69]	Multi-centre nested case control study, England/Wales	Source population: IBD patients; 100 CRC cases, 600 controls, 1987-2001	5-aminosalicylic acid As covariate: Oral glucocorticoids 6 months before CRC y/n	CRC	Univariate analysis: OR=0.85 (0.25-2.94)
Eaden, 2000[70]	Multi-centre case control study, England/Wales	Source population: UC patients; 102 CRC cases and 102 controls. Study period unknown	5-aminosalicylic acid As covariate: Systemic glucocorticoids 5-10 years before CRC y/n	CRC	Univariate analysis: OR=0.26 (0.01-0.70)
Shetty, 1999[71]	Single-centre matched cohort study, USA	UC patients with primary sclerosing cholangitis (PSC) N=132 compared with UC patients without PSC N=196, during 1976-1994	PSC As covariate: Prednisone ≥6 months	CRC or dysplasia	Multivariate analysis: HR=1.03 (1.00-1.06) Adjusted for age, calendar year, and extent of UC
Lashner, 1997[72]	Single-centre cohort study, USA	Patients with UC for >8 years during 1986-1992, N=98	Folic acid As covariate: Prednisone ≥6 months y/n	CRC or dysplasia	Multivariate analysis: HR=1.52 (0.55-4.16) Adjusted for age and calendar year

[1]Abbreviations: CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease

Table 2.1b. Studies examining an association between glucocorticoid use and cancer risk[1]

Author, year	Design, country	Study population, period	Exposure of interest	Outcome of interest	Results, comments
Sørensen, 2012[54]	Nationwide case control study, Denmark	9488 breast cancer cases diagnosed 1994-2008; 94 876 population controls	Glucocorticoids (systemic) Compared to use of ≤2 prescriptions	Breast cancer	Multivariate analysis: >2 prescriptions ever: OR=1.0 (0.96-1.1) Duration of use >5 years: OR=1.2 (0.96-1.6) Adjusted for postmenopausal hormone replacement therapy, immunosuppressants, comorbidity, obesity
Severi, 2010[59]	Multi-centre cohort study, Australia	16 934 men enrolled during 1990-1994, end of follow-up 2007.	A: Systemic glucocorticoids B: Inhaled glucocorticoid C: Topical glucocorticoids Compared to never-use	Prostate cancer	Multivariate analysis: A: HR=1.71 (1.08-2.69) B: HR=1.39 (1.03-1.88) C: HR=0.95 (0.49-1.83) Adjusted for country of birth *Note: glucocorticoid use noted at enrollment; 18% did not complete medication audit. Excluding these yielded almost similar results.*
Jensen, 2009[55]	Population-based case control study, Denmark	5422 BCC, 935 SCC, 983 MM, and 481 NHL cases during 1989-2003. Controls 4 per case, matched for age and sex	Glucocorticoids y/n	BCC, SCC, MM, NHL	Multivariate analysis: BCC: IRR=1.15 (1.07-1.25) SCC: IRR=1.14 (0.94-1.39) MM: IRR=1.15 (0.94-1.41) NHL: IRR=1.11 (0.85-1.46) Adjusted for comorbidity and immunosuppressants
Dietrich, 2009[60]	Population-based (New Hampshire State) case control study, USA	786 Bladder cancer cases during 1994-2001, 1083 controls	Self-reported glucocorticoid use Compared to never-use	Bladder cancer	Multivariate analysis: -Any oral use: OR=1.85 (1.24-2.76) -Duration of use >5 years: OR=3.39 (0.98-11.74) -Any oral use, by disease stage Non-invasive, low grade OR=1.66 (1.03-2.70) Non-invasive, high grade OR=2.03 (0.68-6.06) Invasive OR=2.12 (1.17-3.85) Carcinoma in situ OR=3.55 (0.98-12.85) Adjusted for age, gender, smoking status
Bernatsky, 2007[61]	Meta-analysis, Canada	8 population-based case-control studies completed during 1992-2006; 6897 NHL cases and 8881 controls	Glucocorticoids	NHL	Multivariate analysis: Adjusted OR=1.13 (0.99-1.29)
Parimon, 2006[63]	Multi-centre cohort study, USA	COPD patients enrolled during 1996-1999, N=10 474. End of follow-up 2001. Median follow-up time 3.8 years	Inhaled glucocorticoids >180 days before the index date Compared to never-use	Lung cancer	Multivariate analysis: <1,200 µg/day OR=1.13 (0.67-1.90) ≥1,200 µg/day OR=0.39 (0.16-0.96) Adjusted for age, smoking status and intensity, malignancies, comorbidity, bronchodilator use
Sørensen, 2005[56]	Population-based cohort study, Denmark	Comparison of observed and expected numbers of cases of cancer among 32 336 glucocorticoid users during 1989-1996. End of follow-up 1998.	Systemic glucocorticoids Compared to never-use	Breast cancer	All prescriptions: SIR=1.03 (0.93-1.14) ≥15 prescriptions: SIR=0.86 (0.47-1.44)

Sørensen, 2004[57]	Population-based cohort study, Denmark	Comparison of observed and expected numbers of cases of cancer among 59 043 glucocorticoid users during 1989-1996. End of follow-up 1998.	Systemic glucocorticoids Compared to never-use	BCC, SCC, MM, NHL	All prescriptions BCC: SIR=1.16 (1.06-1.26) SCC: SIR=1.32 (1.09-1.59) MM: SIR=1.17 (0.95-1.43) NHL: SIR=1.30 (1.06-1.58) ≥15 prescriptions BCC: SIR=1.52 (1.09-2.07) SCC: SIR=2.45 (1.37-4.04) MM: SIR=1.37 (0.44-3.19) NHL: SIR=1.62 (0.65-3.33) *Note: No data on comorbidity or sun exposure*.
Karagas, 2001[62]	Population-based (New Hampshire State) case control study, USA	592 BCC and 281 SCC cases during 1993-1995, 532 age- and sex-matched controls	Self-reported glucocorticoid use Compared to never-use	BCC, SCC	Multivariate analysis: Any oral use BCC: OR=1.49 (0.90-2.47) SCC: OR=2.31 (1.27-4.18) Duration of use >3 years BCC: OR=2.15 (0.74-6.25) SCC: OR=2.52 (0.73-8.69) Adjusted for age, gender (SCC also for skin reaction to sun exposure)
Landi, 2001[58]	Single-centre case control study, Italy	183 MM cases during 1994-1999, 179 controls	Self-reported glucocorticoid use Compared to never-use	MM	Multivariate analysis: Any use: OR=0.39 (0.25-0.74) Any use >6 months: OR=0.26 (0.05-1.32) Adjusted for age, gender, skin characteristics Routes of administration (oral vs. topical) and indication for treatment (dermatologic disease vs. other) did not change the association significantly.

[1] Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma; NHL, non-Hodgkin's lymphoma

2.2 Preadmission glucocorticoids and postoperative mortality after colorectal surgery (Study II)

Glucocorticoid use has several side effects that might affect postoperative mortality, including impaired immune function and wound healing, hyperglycemia, hypertension, atherosclerosis, arrhythmias, and thrombosis. Accordingly, preadmission glucocorticoids have been linked with severe postoperative complications, such as infections,[75-79] impaired wound healing,[80] and cardiac and renal events.[77] Proposed explanations for these associations include glucocorticoid-induced immunosuppression and atherosclerosis.[75-77] In addition, glucocorticoid therapy may blur symptoms of early postoperative complications (e.g., fever),[81] thereby delaying diagnosis and treatment, and subsequently leading to death. Finally, adrenal suppression caused by prolonged drug use may hinder the usual cortisol response to such stressors as surgery, and may eventually induce life-threatening secondary adrenal insufficiency.[42]

However, even acknowledging that glucocorticoid therapy per se may increase the risk of postoperative adverse outcomes, underlying comorbidities also influence risk.[28,38,82] Therefore, given their medical history, glucocorticoid users represent a population at particular risk. Increased susceptibility to postoperative mortality, whether based on glucocorticoid use, pre-existing comorbidities, or a combination of the two, might form the basis of a link between preadmission glucocorticoids and early mortality after CRC surgery.

2.2.1 Existing literature regarding preadmission glucocorticoid use and postoperative mortality after colorectal surgery

We searched Medline English-language literature using the following query:

("Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh]) AND ("Colorectal Surgery"[Mesh] OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh] OR "Anastomosis, Surgical"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Mortality"[Mesh]

This search revealed 3 hits, none of which were relevant. We then widened the search by not restricting it to a population of CRC patients:

("Colorectal Surgery"[Mesh] OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh] OR "Anastomosis, Surgical"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Mortality"[Mesh]

This query resulted in 27 hits; however, no studies were relevant to our research question. Next, we widened the search to include free text:

("Colorectal Surgery"[Mesh] OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh] OR "Anastomosis, Surgical"[Mesh]) AND ("Glucocorticoids"[Mesh] OR corticosteroids OR steroids) AND ("Mortality"[Mesh]) OR mortality)

This query resulted in 185 hits, of which 5 studies were reviewed thoroughly after reviewing titles and abstracts.[78,83-86] Two studies, published in 1976[85] and 1967,[86] respectively, included patients from as far back as 1955; for this reason, we considered the studies outdated. One US-based single-centre cohort study of 150 patients that underwent elective colon surgery and 35 patients that underwent emergent colon surgery reported that glucocorticoid use was a predictor of death after emergent operations.[83] Proportions of postoperative deaths among glucocorticoid users and never-users were similar in a single-centre study from France (which included 606 patients that had an elective left-sided colorectal anastomosis[78]) and a single-centre study from Germany (which included 397 patients with Crohn's disease that had a primary gastrointestinal anastomosis) (Table 2.2).[84]

2.2.2 Limitations of the existing literature

Studies associating preadmission glucocorticoid use and postoperative mortality after colorectal surgery are sparse.[78,83,84] Unfortunately, available studies are limited by relatively small sample sizes (ranging from 35-606 patients) that may not necessarily represent the general population. These studies also lack a specific study aim[78,83,84] and a clear definition of glucocorticoid exposure.[83] The French study presented multiple descriptive tables of patient characteristics and postoperative outcomes that appeared difficult to understand and interpret in the absence of any proposed study aim.[78] The German study did not provide any estimates comparing proportions of deaths within exposure groups, although results were presented in a figure.[84] Finally, mortality was not a primary endpoint in any study, and the results lacked adjustment in multivariate models.[78,84] Therefore, in Study ll, we aimed to investigate associations between preadmission glucocorticoid use and postoperative mortality in a nationwide cohort of CRC patients, while adjusting for important potential confounders.

Table 2.2. Studies reporting effects of glucocorticoids on postoperative mortality after colorectal surgery

Author, year	Design, country	Study population, period	Exposure of interest	Outcome of interest	Results, comments
Tresallet, 2008[78]	Single-centre cohort, France A comparison between steroid users and non-users with regard to several outcomes	Patients that had a left-sided colorectal anastomosis from 1995-2005 (N=606). Exclusions: patients with inflammatory bowel disease, emergency surgery, mid/low rectal anastomoses	Steroids >1 month of use at the time of surgery y/n	Several including 60-day in-hospital mortality	Death occurred in: 1 steroid user (1.9%) vs. 10 non-users (1.8%) Univariate analysis: p=0.97 *Note: Unclear aim and methodology. Only 1 exposed case. No estimates. Only in-hospital mortality recorded and up to 60 days after surgery.*
Yoo, 2006[83]	Single-centre cohort, USA Multiple variables including steroid use were examined to determine potential predictors for several outcomes	Patients that underwent elective (N=150) or emergent (N=35) colon surgery (not defined) from 1997-2002.	Multiple Steroids y/n	Several including 30-day mortality	Death occurred after 6 emergent procedures (17.1%; p=0.007) and 5 elective procedures (3%; no p-value provided). Steroid use reported as a predictor of postoperative mortality in the emergent group: Multivariate analysis: p=0.01 *Note: Unclear aim and methodology, no detailed exposure definition, no estimates for the association, no numbers of exposed cases. 17% had ischemic bowel and 11% had traumatic perforation (i.e., they had an extremely poor prognosis a priori).*
Bruewer, 2003[84]	Single-centre cohort, Germany A comparison between steroid users and non-users with regard to several outcomes	Patients with Crohn's disease that had a resection with primary anastomosis from 1982-2000 (N=397).	Steroids ≥1 month of use at the time of surgery y/n. Use categorized: Low-dose ≤20 mg/day High-dose >20 mg/day	Several including postoperative mortality (not defined)	Proportion of death did not differ significantly for any steroid group vs. the non-steroid group. *Note: Postoperative mortality not defined. Results were presented using a figure, no numbers of deaths within exposure groups or estimates provided.*

2.3 Preadmission glucocorticoid use and anastomotic leakage (Study lll)

Anastomotic leakage is a severe complication after colon and rectal cancer surgery that sharply increases morbidity, mortality, and hospital resource utilization.[87,88] Apart from the immediate clinical consequences, which can include peritonitis, sepsis, and abscess and fistula formation, anastomotic leakage may also negatively affect the risk of local cancer recurrence and long-term survival.[89] Recognized patient-related risk factors for anastomotic leakage include age, male gender, poor physical fitness, metastatic cancer, smoking, alcohol abuse, and malnutrition.[39] In Denmark, anastomotic leakage accounts for almost 25% of postoperative surgical complications after CRC resections;[29] it has been reported to occur in 6% of colon cancer patients and 16% of rectal cancer patients.[29] Thus, postoperative leakage poses a major challenge to the surgical treatment of CRC.

It is well documented that glucocorticoids impair wound healing in skin.[10] Suggested mechanisms of action involve interference with key mediators of the inflammation, proliferation, and remodeling phases that occur after tissue injury.[10,90] However, evidence of an association between glucocorticoids and the healing of intestinal anastomoses is surrounded by controversy.[78,91-101] Some animal studies of intestinal anastomoses have shown that glucocorticoids impair healing and wound tensile strength,[91-93] while others have not.[94,95] Human data are also mixed. Several reports have indicated that glucocorticoid use might predict leakage,[96-99] although others have not.[78,100,101] Surgeons may therefore question the safety of primary anastomoses in patients that are taking glucocorticoids.

2.3.1 Existing literature on preadmission glucocorticoid use and anastomotic leakage

We searched Medline English-language literature using the following query:

("Colonic Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh]) AND ("Colorectal Surgery"[Mesh]) OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh] OR "Anastomosis, Surgical"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Anastomotic Leak"[Mesh]

The search yielded no hits. As for Study ll, we then widened the search by not restricting it to a population of CRC patients:

("Colorectal Surgery"[Mesh]) OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh] OR "Anastomosis, Surgical"[Mesh]) AND "Glucocorticoids"[Mesh] AND "Anastomotic Leak"[Mesh]

This search resulted in 2 hits, of which one was relevant.[46] We repeated the search including a broader MESH term for the outcome and free text:

("Colorectal Surgery"[Mesh] OR "Colectomy"[Mesh] OR "Proctocolectomy, Restorative"[Mesh]) OR "Anastomosis, Surgical"[Mesh]) AND ("Glucocorticoids"[Mesh] OR corticosteroids OR steroids) AND ("Anastomotic Leak"[Mesh] OR "Postoperative Complications"[Mesh] OR anastomotic leak)*

This search revealed 318 hits, of which 12 studies on humans were relevant regarding the outcome of anastomotic leakage after our review of titles and abstracts.[78,84,97,98,100,102-108] In addition, we were aware of a recent published review from Denmark.[109] Reviewing reference lists, we found seven additional relevant studies[96,99,101,110-113] (Table 2.3). The vast majority of studies examined potential predictors of anastomotic leakage.[46,96-104,106,107,110-113]

A recent Danish review evaluated current evidence regarding glucocorticoid use and the risk of anastomotic leakage after colorectal resection. Based on 12 studies published between 1996 and 2012, Eriksen et al. provided combined cumulative incidences for leakage: 6.8% (95% CI: 5.5-9.1%) in 1034 patients exposed to steroids preoperatively versus 3.3% (95% CI: 2.9-3.6%) in 8410 unexposed patients.[109] In addition, eight prediction studies (four of which were incorporated into the Danish review) including up to 5123 colorectal resected patients, demonstrated that glucocorticoid use predicted anastomotic leakage; ORs from multivariate analyses ranged from 1.81 (95% CI: 1.02-3.45) to 26.98 (95% CI: 2.89-251.10).[96-99,102-104,107] Four additional prediction studies that included up to 797 patients reported associations between glucocorticoids and leakage, although interpretations were based on ORs from univariate analyses or p-values.[106,110-112] One cohort study of 417 IBD patients indicated that glucocorticoids were protective against leakage; the multivariate analysis revealed an OR of 0.36 (95% CI: 0.17-0.76).[46] Seven studies were unable to demonstrate any statistical differences in the proportion of cases with leakage when glucocorticoid users were compared with non-users.[78,84,100,101,105,108,113] Overall, evidence is conflicting regarding glucocorticoid use and anastomotic leakage, although the majority of studies have reported an association between the two.

2.3.2 Limitations of the existing literature

During a thorough review of the literature, we discovered noteworthy limitations. The bulk of studies were performed at single institutions and comprised relatively small study populations that might not be representative for the general population.[78,84,98,100-108,111-113] Also, by design, these studies examined glucocorticoids among several potential predictors of anastomotic leakage; as a result, thorough investigations of glucocorticoid exposure were not performed, and the studies lacked data regarding formulas, dose, and duration of use. Three studies that reported an association between glucocorticoid use and leakage only provided results from univariate analyses[110-112] or only provided data regarding statistical significance (p-values), and did not discuss the strength of the association (relative estimates).[106] In addition, two studies that did not demonstrate statistically significant differences in the proportions of leakage among glucocorticoid users versus never-users failed to provide either p-values or relative estimates;[84,105] another study erroneously reported a p-value based on null exposed cases.[101] Finally, several studies considered colon and rectal surgery together, rather than separately.[78,96-98,105,106,110-112] It is important to distinguish between colon and rectal procedures because the anatomy and surgical techniques differ, and the leakage rate is more than twice as high after rectal resections as after colon resections.[114] Given these limitations, we conducted a nationwide population-based study to explore the possible causal relation between preadmission glucocorticoid use and risk of leakage in a nationwide cohort of resected colon and rectal cancer patients.

Table 2.3. Studies reporting effects of glucocorticoid use on anastomotic leakage after colon and rectal resection[1]

Author, year	Design, country	Study population, period	Exposure of interest	Outcome of interest	Results on glucocorticoid use, comments
Eriksen, 2013[109]	Review, Denmark	12 studies published between 1996 and 2012 including a total of 9444 patients: 1034 glucocorticoid users versus 8410 non-users	Glucocorticoids	AL/IASC	Combined leakage rates: 6.8% (95% CI: 5.5-9.1%) in glucocorticoid users versus 3.3% (95% CI: 2.9-3.6%) in non-users *Note: Studies on preoperative glucocorticoid administration were also included. Preadmission glucocorticoids were not the primary exposure of interest in any study.*
Slieker, 2012[97]	Multicentre cohort study, The Netherlands. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent left-sided colorectal resection for benign or malignant disease during 2007-2009, N=259	Several; Steroids y/n, use categorized: Long-term use (not defined) Preoperative use (5 days preoperatively)	Clinical AL	AL occurred in 19 (7.3%) patients: 3 (50.0%) long-term users and 4 (19.0%) perioperative users vs. 12 (5.2%) non-users Univariate analysis Long-term use: p=0.02; OR=4.29 (95% CI: 1.25-14.76) Preoperative use: p=0.001; OR=18.25 (95% CI: 3.32-100.15) Multivariate analysis Long-term use: OR=26.98 (95% CI: 2.89-251.10) Preoperative use: not reported *Note: Long-term use not defined, at maximum 4 exposed cases*
Ziegler, 2012[99]	Multicentre cohort study, USA. Potential predictors of AL were examined in univariate and multivariate analyses	Patients with and without diabetes that underwent colectomy (unknown indication) during 2008-2010, N=5123	Several; Steroids (oral/parental) >1 month of use preoperatively y/n	AL	AL occurred in 19 patients with diabetes: 3 (8.8%) steroid users vs. 16 (1.9%) non-users Univariate analysis: p=0.03 Multivariate analyses: OR=4.60 (95% CI: 1.25-16.9) AL occurred in 124 non-diabetic patients; no association was observed between steroids and AL *Note: Only 3 exposed outcomes, generalizability limited*
Gorissen, 2012[110]	Two-centre cohort study, The Netherlands. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent primary colorectal anastomosis from 2008-2010, N=795	NSAIDs In a secondary analysis several exposures Steroids y/n	Clinical AL	AL occurred in 79 (9.9%) patients Univariate analysis: p=0.20; OR=1.64 (95% CI: 0.76-3.47)
El-Hussuna, 2012[46]	Multicentre cohort study, Denmark. Potential predictors of AL were examined in univariate and multivariate analyses	Patients with CD that underwent resection and anastomosis during 2000-2007, N=417	Several biologic treatments or immunomodulators; Steroids >4 weeks, last use within 1 week preoperatively y/n. Use categorized: Low-dose ≤20 mg/day High-dose >20 mg/day	IASC	IASC occurred in 52 patients: 13 (19.7%) high-dose users vs. 39 (11.1%) non-users Univariate analysis: p=0.04 Multivariate analysis: OR=0.36 (95% CI: 0.17-0.76) *Note: Not clear whether the reference (non-users) also included low-dose users*

Tzivanakis, 2012[102]	Single-centre cohort study, UK. Potential predictors of IASC were examined in univariate and bivariate analyses	Patients with CD that underwent ileocecal or ileocolic resection and had an primary anastomosis during 2000-2010, N=173	Several; Steroids ≥10 mg/day for more than 4 weeks before surgery *or* steroids stopped within 2 weeks before surgery y/n	IASC	IASC occurred in 19 patients Univariate analysis: p=0.05 Bivariate analysis: OR=2.67 (95% CI: 1.0-7.2)
Richards, 2011[101]	Single-centre cohort study, New Zealand. Potential predictors of AL were examined in univariate analyses	Patients that underwent low anterior resection for benign or malignant disease from 2000-2009, N=233	Several; Steroids y/n	AL	AL occurred in 33 patients: 0 (0%) steroid users vs. 33 (14%) non-users Univariate analysis: p=0.48 *Note: 0 exposed cases; may query the p-value.*
Luján, 2011[111]	Single-centre cohort study, USA. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent a gastrointestinal anastomosis during 2006-2008, N=797	Several; Steroids y/n	IASC	IASC occurred in 30 patients: 4 (9.8%) steroid users vs. 26 (3.4%) non-users Univariate analysis: p=0.05; OR=3.04 (95% CI: 1.01-9.15)
Tresallet, 2008[78]	Single-centre cohort study, France. A comparison between steroid users and non-users was made with regard to several outcomes using univariate and multivariate analysis	Patients that had a left-sided colorectal anastomosis during 1995-2005, N=606 Exclusions: IBD, emergency surgery, low anastomoses	Steroids >1 month of use y/n	Several; AL	Anastomotic leakage occurred in 1 (1.9%) steroid user vs. 11 (2.0%) non-users Univariate analysis: p=0.96 *Note: No specific aim, unclear methodology. Only 1 exposed case, exclusions limit external validity*
Suding, 2008[96]	Multi-centre cohort study, USA. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent elective open colorectal resection for benign or malignant disease during 2002-2005, N=672	Several; Steroids at the time of surgery: 0-40 mg/day y/n	Clinical AL	AL occurred in 24 (3.6%) patients: 4 (11.1%) steroid users vs. 20 (3.1%) non-users Univariate analysis: OR=3.85 (95% CI: 1.24-11.93) Multivariate analysis: OR=3.18 (95% CI: 0.97-10.43) *Note: only 4 exposed cases*
Alves, 2007[103]	Single-centre cohort study, France. Potential predictors of AL were examined in univariate and multivariate analyses	Patients with CD that had ileocecal resection without temporary stoma during 1984-2004, N=161	Several; Steroids >3 months preoperatively y/n	IASC	IASC occurred in 15 patients: 11 (18.6%) steroid users vs. 4 (3.9%) non-users Univariate analysis: p=0.02 Multivariate analysis: OR=5.95 (95% CI: 1.04-34.1)
Lim, 2007[104]	Single-centre cohort study, UK. Potential predictors of AL	Patients with UC that had a proctocolectomy and an IPAA during 1985-2005,	Several immune modulators; Steroids ≥5 mg/day for >30 days before surgery y/n	IASC	IASC occurred in 58 patients Univariate analysis: p=0.02; OR=1.82 (95% CI: 1.21-3.22) Multivariate analysis: OR=1.81 (95% CI: 1.02-3.45)

	were examined in univariate and multivariate analyses	N=445 (N=335 for the data analysis)			Dose-response relationship reported *Note: 110 patients excluded because of missing data on IASC/medication. No number of exposed cases.*
Konishi, 2006[98]	Single-centre cohort study, Japan. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent resection for CRC from 2000-2004, N=391	Several; Steroids, long-term use that required perioperative supplement y/n	Clinical AL	AL occurred in 11 (2.8%) patients: 2 (11.8%) steroid users vs. 9 (2.4%) non-users Univariate analyse: p=0.02 Multivariate analysis: OR=8.7 (95% CI: 1.2-45.1) *Note: only 2 exposed cases*
Lake, 2004[100]	Single-centre cohort study, USA. Potential predictors of AL were examined in univariate and multivariate analyses	Patients with IBD or FAP that had a proctocolectomy with IPAA during 1995-2001, N=100	Several; Steroids preoperatively y/n. Use categorized: Low-dose 1-20 mg/day High-dose >20 mg/day	AL	Anastomotic leakage occurred in 5 patients: 3 (5.6%) high-dose steroid users and 0 (0%) low-dose users vs. 2 (4.3%) non-users Univariate analysis: p=0.99 *Note: Only 3 exposed cases.*
Bruewer, 2003[84]	Single-centre cohort study, Germany. A comparison between steroid users and non-users with regard to several outcomes	Patients with CD that had an intestinal resection with primary anastomosis from 1982-2000, N=397	Steroid use >1 month preoperatively y/n. Use categorized: Low-dose ≤20 mg/day High-dose >20 mg/day	Several; AL	Proportions of leakage did not differ significantly for any steroid group vs. the non-steroid group. *Note: Results for anastomotic leakage were reported using a figure, no numbers of AL were provided overall or within exposure groups.*
Alves, 2002[112]	Single-centre cohort study, France. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that had a colorectal resection and a primary anastomosis for benign or malignant disease during 1990-1997, N=707	Several; Steroids (Recent use) y/n	IASC	IASC occurred in 43 of 707 patients. In a subgroup of IBD patients (N=171): IASC occurred in 7 (77.8%) steroid users vs. 2 (1.2%) non-users Univariate analysis: p=0.01 *Note: Unclear methodology, steroids not defined. Multivariate analysis not reported.*
Yamamoto, 2000[106]	Single-centre cohort study, Japan. Potential predictors of AL were examined in univariate and multivariate analyses	Patients with CD that underwent intestinal anastomosis during 1980-1997, N=343	Several; Steroids ≥1 month of use before surgery y/n	IASC	Preoperative steroid use was associated with anastomotic leakage. Univariate analysis: p=0.02 Multivariate analysis: p=0.03 *Note: This study has serious limitations. Data analyses are based on the number of operations (N=566), not the number of individuals. The number of IASC is unclear, and the tables reveal missing data that are not reported.*
Sugerman, 2000[105]	Single-centre cohort study, USA. An evaluation of one-stage stapled ileoanal pouch procedure without temporary	Patients that had a proctocolectomy and an IPAA from 1989-1999, N=201	Several; Steroids y/n	Several; AL	AL occurred in 19 patients. No differences observed in the proportion of leaks among steroid users vs. non-users. No dose-response relation. *Note: Unclear methodology; no specific aim; unclear whether data were analyzed for all patients included (N=201) or for a subgroup of*

	ileostomy diversion				*UC patients (N=178). Results, as presented, are difficult to interpret.*
Vignali, 1997[113]	Single-centre cohort study, USA. Potential predictors of AL were examined in univariate and multivariate analyses	Patients that underwent rectal/anal anastomosis for benign or malignant disease during 1989-1995, N=1014	Several; Steroids y/n	IASC	IASC occurred in 29 patients: 1/89 (1.1%) steroid users vs. 28/985 (3.0%) non-users Univariate analysis: p=0.30 *Note: Only 1 exposed case.*
Golub, 1997[107]	Single-centre cohort study, USA. Potential predictors of AL were examined in univariate analyses	Patients that had an anastomosis in the small or large intestine from 1988-1995, N=764	Several; Steroids y/n		Univariate analysis: Steroids were associated with AL in a predictive model. Multivariate analysis: OR=6.46 (95% CI: 1.87-22.28)
Ziv, 1996[108]	Single-centre cohort study, USA.	Patients with UC that had a proctocolectomy and an IPAA during 1983-1992, N=671	Steroid use >1 month preoperatively y/n. Use categorized: Low-dose ≤20 mg/day High-dose >20 mg/day	IASC	IASC occurred in 44 patients: 14 (8.3%) low-dose users and 12 (6.3%) high-dose users vs. 18 (5.8%) non-users Univariate analysis: p=0.57

[1]Abbreviations: AL, anastomotic leakage; IASC, intra-abdominal septic complication; CD, Crohn's disease; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; FAP, familial adenomatous polyposis

3. Aims of the thesis

The literature review revealed that although a number of studies have explored associations between glucocorticoid therapy and risk of developing CRC, their evidence is conflicting. No detailed investigations of glucocorticoid use and CRC risk have been conducted in a general population. Studies associating preadmission glucocorticoid use and mortality after surgical CRC treatment are few, and synthesizing current evidence is hampered by flaws in study design and methodology. Finally, although the bulk of studies that evaluate preadmission glucocorticoid use concluded that it was a potential predictor of colorectal anastomotic leakage, others observed no association. No studies have addressed the question of causality in a population-based setting while providing detailed information on exposure and adjusting for potential confounding factors.

To address these gaps in the existing evidence, we conducted three studies with the following aims:

Study l: To examine (1) the impact of glucocorticoid therapy on the risk of CRC development comparing CRC cases with an age-, sex-, and calendar year-matched sample of the general population; and (2) to explore whether glucocorticoid use affects the risk of more advanced disease (stage) at the time of CRC diagnosis.

Study ll: To evaluate whether preadmission use of glucocorticoids impacts 30-day mortality after CRC surgery and to explore interactions between comorbidity and postoperative mortality in a nationwide population-based setting.

Study lll: To investigate associations between preadmission glucocorticoid use and anastomotic leakage after CRC resection in a nationwide cohort of all Danish CRC patients.

4. Methods

4.1 Setting

We conducted Study I in Northern Denmark (former counties of Aarhus and North Jutland), which is a mixed rural and urban area with approximately 1.15 million inhabitants. Studies II and III were conducted using data from the entire Danish population of approximately 5.5 million people.[115] The Danish national health care provides free access to tax-supported health services for all residents of the country. Essentially all CRC patients are diagnosed and treated by public hospitals and their outpatient clinics.

4.2 Data sources

4.2.1 The Civil Registration System (Studies I-III)

The Civil Registration System (CRS) assigns a unique 10-digit identifier (CPR number) to each Danish citizen at birth and to residents upon immigration. This identifier facilitates unambiguous individual-level linkage of nationwide registries.[116] The CRS has recorded information on vital status (dead or alive), date of death, and residence since 1968 and is updated daily.[117]

4.2.2 The Danish Cancer Registry (Study I)

Based on notifications from hospital departments, specialists, and autopsy reports, the Danish Cancer Registry (DCR) has recorded cases of incident cancer since 1943.[118,119] Logged data include CPR number, date of cancer diagnosis, cancer type/site, and cancer stage at time of diagnosis. In 2004, several administrative changes occurred: (i) reporting to the DCR became electronic, and via the Danish National Registry of Patients; (ii) the date of diagnosis was defined as the date of the first cancer-related admission instead of the first month of hospitalization; and (iii) the classification system changed from the 7th revision of the International Classification of Diseases (ICD-7) to the 10th revision (ICD-10).[120] In addition, the recording of cancer stage was changed from the Dukes system to the Tumor Node Metastasis (TNM) system.[27]

4.2.3 The Danish Colorectal Cancer Group Database (Studies II, III)

Beginning in 2001, the Danish Colorectal Cancer Group (DCCG) has registered all patients with an incident colorectal adenocarcinoma diagnosed or treated in any surgical department in Denmark.

Data on tumor, patient, and treatment characteristics, as well as 30-day postoperative outcomes, are collected by the DCCG using standardized forms that are completed by physicians. Completeness of patient registration is validated monthly by linkage to the Danish National Registry of Patients, and ranged from 98% to 100% during 2001-2010.[4]

4.2.4 The Danish National Registry of Patients (Studies I-III)

The Danish National Registry of Patients (DNRP) has tracked all non-psychiatric hospitalizations since 1977 and outpatient visits since 1995.[121] The DNRP records CPR number, dates of admission and discharge, surgical and diagnostic procedures, and up to 20 discharge diagnoses (coded by physicians according to the 8th revision of the ICD until the end of 1993, and according to the ICD-10 thereafter). Since 1996, procedure codes have been recorded in accordance with the Nordic Medico Statistical Committee (Nomesco) Classification of Surgical Procedures.[122]

4.2.5 The Aarhus University Prescription Database (Study I)

Prescription data on reimbursable medicines have been electronically transferred from pharmacies in Northern Denmark to a research database at Aarhus University since 1989, with complete coverage from 1998 on.[123] Recordings to the research database include CPR number, information about the dispensed drug [name, package size, formulation, and quantity in accordance with the Anatomical Therapeutic Chemical (ATC) classification system], and the prescription redemption date. Over-the-counter medications, such as NSAIDs or paracetamol, are generally not registered in the database unless the patient receives individual reimbursements (e.g., because of chronic illness). Also, the indication for treatment and prescribed daily dose are not registered.

4.2.6 The National Registry of Medicinal Products (Studies II, III)

The National Registry of Medicinal Products (NRMP) records prescriptions dispensed at all Danish pharmacies, with complete coverage from 1995 on.[124] Main variables in the NRMP are similar to those mentioned in the Aarhus University Prescription Database.

4.2.6 The Danish Cause of Death Registry (Study II)

The Danish Cause of Death Registry (DCDR) has tracked all deaths in Denmark since 1970.[125] Recorded information includes the underlying cause of death and a chain of one to four contributing conditions that led to death, coded using the ICD-10. Data from the DCDR are not

regularly validated, and the reproducibility of diagnoses that appeared on death certificates during the study period is unclear.[125]

4.3 Study design

Study I was designed as a case-control study in Northern Denmark. Studies II and III were designed as nationwide population-based cohort studies.

4.4 Study population

Study I included all incident CRC patients recorded in the DCR between 1 January 1991 and 31 December 2010. For each CRC case, we used the CRS to randomly select 10 population controls matched for age and gender. Risk set sampling was applied (i.e., controls had to be alive and at risk of CRC at the date that the corresponding case was diagnosed [index date]).

Study II included all incident CRC cases recorded in the DCCG database that underwent surgical treatment between 1 May 2001 and 31 December 2011.

In Study III, we restricted the study population from Study II to patients that had a resection with a primary anastomosis. In the interest of exploring colon and rectal cancer patients separately, we excluded patients with incompatible or missing data regarding surgical approach, procedures, or anastomotic leakage (n=905).

4.5 Exposure

In all three studies, the exposure was glucocorticoid use; however, our definitions of exposure differed according to the outcome of interest. In Study I, we aimed to explore effects of prolonged exposure, because CRC development occurs over several years. In contrast, in Studies II and III, the timing of exposure was pivotal, particularly a time window just before the surgery. Below is a detailed description of the exposure definitions for each study.

Based on their potent systemic effects, the exposure of interest in Study I was systemic-acting glucocorticoids rather than inhaled or intestinal-acting glucocorticoids (we referred to the latter two as locally acting glucocorticoids). Because a number of patients were expected to use both systemic glucocorticoids and locally acting glucocorticoids, we categorized exposure based on (1) never/rare use of systemic glucocorticoids (defined as two or fewer prescriptions filled prior to the

index date); (2) frequent use of systemic glucocorticoids (more than two prescriptions); and (3) mixed use (i.e., treatment with systemic and locally acting glucocorticoids in combination, or locally acting glucocorticoids alone). Regarding frequent systemic glucocorticoid use, we further defined subgroups based on timing of use, duration, and dose. Time of treatment was categorized as recent use (most recent prescription filled ≤3 years prior to the index date) or former use (most recent prescription filled ≥4 years prior to the index date). Duration and dose were combined to identify the intensity of frequent systemic glucocorticoid use. The duration of use was grouped into short-term use (<5 years elapsing between the first and the most recent prescription) or long-term use (≥5 years between the first and the most recent prescription). Within duration groups, we defined three categories according to cumulative prednisolone-equivalent doses[41] used by cases and controls: low-dose (lowest quartile), medium-dose (middle quartiles), and high-dose (highest quartile). To minimize the risk of detection bias associated with glucocorticoid use owing to regular medical follow-up, we disregarded glucocorticoid prescriptions filled within 1 year before the index date. The definitions of glucocorticoid use are summarized in Table 4.1.

Table 4.1. Glucocorticoid exposure definitions in Study I

Never or rare users	Patients with 0-2 redemptions of prescribed systemic glucocorticoids
Frequent users	Patients that filled >2 prescriptions of systemic glucocorticoids
Recent users	Patients that filled the most recent prescription ≤3 years before the index date
Former users	Patients that filled the most recent prescription ≥4 years before the index date
Short-term users	Patients that had <5 years elapsing between the first and the most recent prescription filled
Low-dose	Patients that used a dose within the lowest quartile of cumulative prednisolone-equivalent dose used by cases and controls
Medium-dose	Patients that used a dose within the middle quartiles (25-75%) of cumulative prednisolone-equivalent dose used by cases and controls
High-dose	Patients that used a dose within the highest quartile of cumulative prednisolone-equivalent dose used by cases and controls
Long-term users	Patients that had ≥5 years elapsing between the first and the most recent prescription filled
Low-dose	Patients that used a dose within the lowest quartile of cumulative prednisolone-equivalent dose used by cases and controls
Medium-dose	Patients that used a dose within the middle quartiles (25-75%) of cumulative-prednisolone equivalent dose used by cases and controls
High-dose	Patients that used a dose within the highest quartile of cumulative prednisolone-equivalent dose used by cases and controls
Mixed users	Patients that filled prescriptions for both systemic and locally acting glucocorticoids, or for locally acting glucocorticoids alone, before the index date

In Studies II and III, we examined patients that underwent surgical treatment for cancer in the colon or rectum. In addition to detailed information about the timing of glucocorticoid use, we also considered the effects of locally acting glucocorticoids parallel to the effects of systemically acting glucocorticoids. We categorized exposure into five main groups: 1) non-use; 2) oral

glucocorticoid use; 3) inhaled glucocorticoid use; 4) intestinal-acting glucocorticoid use; and 5) mixed use (i.e., treatment with glucocorticoids from at least two of the previous three groups in this list). We further categorized oral and inhaled glucocorticoid use as current use (most recent prescription filled ≤90 days prior to the surgery date), recent use (most recent prescription filled within 91-365 days prior to the surgery date), or former use (most recent prescription filled >365 days prior to the surgery date). If the association were confounded by underlying comorbidity or lifestyle factors present during these periods, then we would expect an association in current, recent, and former users compared with never-users. In Study ll, current use was disaggregated into new use (first-ever prescription filled ≤90 days before the surgery date) and continuing use (first-ever prescription filled >90 days before the surgery date and most recent prescription filled ≤90 days before the surgery date). Intestinal-acting glucocorticoid use was not divided into subcategories because of the paucity of exposed subjects. The definitions of glucocorticoid use are summarized in Table 4.2.

Table 4.2. Glucocorticoid exposure definitions

Non-users	Patients with no redemptions of any prescribed glucocorticoids (oral, inhaled, or intestinal-acting) before the surgery date
Users of oral or inhaled glucocorticoids[a]	Patients that filled ≥1 prescription for a particular glucocorticoid type, but no prescriptions for the other two types of glucocorticoids, before the surgery date
Current users	Patients that filled their most recent prescription within 90 days before the surgery date
New users[b]	First-ever prescription filled within 90 days before the surgery date
Continuing users[b]	First prescription filled >90 days before the index date, but most recent prescription within 90 days before the surgery date
Recent users	Patients that filled their most recent prescription 91-365 days before the surgery date
Former users	Patients that filled their most recent prescription >365 days before the surgery date
Users of intestinal-acting glucocorticoids	Patients that filled ≥1 prescription for intestinal-acting glucocorticoids before the surgery date
Users of mixed glucocorticoids	Patients that filled prescriptions for >1 type of glucocorticoid before the surgery date

[a]Categories of glucocorticoid exposure were defined for both oral and inhaled glucocorticoids.
[b]Categories of new and continuing use were not applied in Study lll owing to a paucity of outcomes.

4.6 Study outcomes

4.6.1 Colorectal cancer risk (Study l)

In Study l, the primary outcome was a diagnosis of CRC during the 1991-2010 period. A secondary outcome was CRC stage. Approximately one-third of CRC patients logged in the DCR have missing

data on TNM classification.[126] Complete information on T, N, and M is necessary to derive a definite TNM stage and to further categorize colon or rectal cancers into localized or non-localized stages. To increase the proportion of staged cases we used a clinically based stage algorithm, allowing certain missing stage components, under the assumption that the remaining information was sufficient to provide a meaningful categorization.[126] Definitions of CRC stage are provided in Table 4.3. Both outcomes were ascertained in the DCR.

Table 4.3. CRC stage categories

CRC stage	Dukes	c-udbred <2004	TNM ≥2004
Localized	A,B	0,1,2,5	T1-4,x N0 M0 T1-2 N0 Mx T1 Nx M0,x
Non-localized	C,D	3,6,4,7	T1-4,x N1-3 M0-1,x T1-4,x N0 M1 T1-4,x Nx M1
Unknown	A, B, 9		T2-4,x Nx M0,x T3-4,x N0 Mx T0,a,is No-3,x M0-1,x

4.6.2 Postoperative mortality (Study ll)

The outcome in Study ll was all-cause death; for regression analysis, we considered from 30 days after CRC surgery until death. The date of death was identified in the CRS. In Study ll, we also included a secondary outcome of causes of death recorded in the DCDR. We defined the cause of death as the first recorded contributing condition (i.e., the immediate event that led to death). We collapsed categories of causes of death from the "14-grupperingen" in the DCDR[127] and defined the following groups of causes: cancer; infections; and cardiological, respiratory, gastrointestinal, and urogenital diseases.

4.6.3 Postoperative anastomotic leakage (Study lll)

The outcome of Study lll was anastomotic leakage. We identified patients with anastomotic leakage in the DCCG database or in the DNRP (using the ICD-10 diagnosis or reoperation codes for anastomotic leakage: DT81.3A and KJWF00, respectively). For analyses, we defined a cutoff point at 30 days after CRC surgery, although recording of postoperative outcomes in the DCCG database is arbitrarily defined as those occurring within this time window.

4.7 Confounders

As potential confounders, we considered factors that were associated with the exposure and the outcomes; however, we did not consider factors that were on the causal pathway between the exposure and the outcomes.[128] The index date was the date of CRC diagnosis (Study I) or the date of CRC surgery (Studies II, III). Comorbidities and associated treatments referred to diseases diagnosed before the index date. In Studies II and III, conditions occurring after the index date (e.g., postoperative complications) could be intermediate steps in the causal pathway between glucocorticoids and mortality or anastomotic leakage, and therefore were not considered as confounders. Data regarding potential confounding factors were obtained from several registries, including the CRS (age and sex) and the DNRP (comorbidity). In Studies II and III, we used the CCI to measure comorbidity.[129] This index assigns between one and six points to a range of diseases; these subscores are summed to create an aggregate score. We grouped patients according to their aggregate CCI score: 0 (low comorbidity), 1–2 (moderate comorbidity), and 3+ (severe comorbidity). The index has been adapted to administrative databases[130] and has been tested against other comorbidity indices in a CRC population.[131,132] To capture comorbidity that was not recorded in the DNRP and to identify potentially confounding medication, we searched the prescription databases for use of, for example, anti-diabetic medications, NSAIDs, and immunosuppressants. Finally, from the DCCG database, we obtained information about alcohol use, smoking, and the ASA score.

4.8 Statistical analysis

Statistical analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute INC., Cary, NC, USA). The Danish Data Protection Agency (record number 2011-41-6151) and the National Board of Health approved the studies (Studies II, III). Relevant codes used in each study are provided in the Appendix (Papers I, II) or in the Supplemental Digital Content (Paper III).

4.8.1 Characteristics

In Study I, we calculated the frequencies of colorectal cancer cases and population controls within categories of systemic glucocorticoid use, demographic variables, and potential confounders.

Accordingly, in Studies ll and lll, we tabulated frequencies of glucocorticoid use within characteristics of the patient, the tumour, and the surgery.

4.8.2 Logistic regression analysis (Studies l, lll)

In Study l (a case-control study), patients free of CRC were matched to CRC patients in strata of age, gender, and calendar time. Matching the controls to cases may introduce selection bias if the matched factors are associated with the exposure. Therefore, we used conditional logistic regression on the matched factors to estimate ORs and 95% confidence intervals (CIs) associating glucocorticoids and CRC risk. Given the risk set sampling of controls, these ORs represented unbiased estimates of the corresponding incidence rate ratios. Examining CRC risk by stage, cases were sub-classified according to the spread of the disease at the time of the diagnosis, (i.e., localized and non-localized cancer). Because our outcome was classified beyond a simple binary case/control, we estimated ORs using an extended logistic model (i.e., a polytomous logistic regression model).[133,134] CRC patients with missing stage data were excluded from this analysis. We adjusted for the following potential confounding factors: diagnoses of diabetes/use of anti-diabetic drugs, alcoholism/use of disulfiram, pulmonary diseases/use of beta-agonists, IBD, and rheumatoid arthritis; as well as use of non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin (75 or 150 mg tablets), high-dose aspirin (500 mg tablets), and immunosuppressants. We dissolved the matching when examining the secondary outcome (cancer by stage); therefore, we also adjusted for age and gender.

In study lll, we computed ORs and 95% CIs for anastomotic leakage after CRC resection adjusting for the following potential confounders: sex, age, CCI score, ASA score, IBD, autoimmune disorders/use of immunosuppressants, alcoholism/use of disulfiram, smoking status and/or COPD medications as its proxy, and NSAID prescriptions filled within 90 days before the date of surgery.

4.8.3 Cumulative incidence proportions (absolute risks) (Studies ll, lll)

In Study ll, we used the Kaplan-Meier method to estimate 30-day cumulative mortality according to our predefined glucocorticoid exposure. In Study lll, we used Jeffreys' method to calculate the 30-day cumulative incidence proportion and 95% CI.[135]

4.8.4 Cox proportional hazard regression analysis (Study II)

In the study of postoperative mortality, we followed patients from the date of CRC surgery recorded in the DCCG database until death, emigration, or end of follow-up (30 days), whichever came first. We estimated mortality rate ratios (MRRs) using crude and adjusted Cox proportional hazard regression models to compute the hazard ratios for death and 95% CIs. In the final model, we included the following potential confounding factors: sex, age, year of surgery, cancer site, stage, CCI score, ASA score, IBD, autoimmune disease or use of immunosuppressive drugs, obesity, alcoholism or use of disulfiram, and use of tobacco, cardiovascular drugs, NSAIDs, high-dose aspirin, COPD agents, or anti-diabetics. We did not include urgency of CRC surgery in the model, because this factor most likely is unrelated to glucocorticoid use. However, if related, then it would be a part on the causal pathway and should not be adjusted for. The assumption of proportional hazards (i.e., that the hazard ratio remains constant over time) was assessed graphically using log-log plots and deemed appropriate.

4.8.5 Stratified analyses (Studies I-III)

All three studies included analyses stratified by certain covariates that represented subgroups of CRC patients. We performed these analyses because the effect of the exposure might differ between these subgroups of CRC patients (i.e., there might be an *effect measure modification*).

Study I included stratified analyses by subgroups of CRC patients according to comorbidity and drug use. We also stratified by time period in order to provide at least 5 years of prescription history for patients diagnosed towards the end of study period. For cases and controls in this period, left truncation of prescription data would therefore be less likely to influence the results.

Study 2 included stratified analyses by sex, age group, year of surgery, cancer site, cancer stage, CCI score, and ASA score, as well as surgical urgency, approach, and procedure.

Study 3 included stratified analyses by sex, age, year of surgery, cancer site, cancer stage, CCI score, and ASA score, as well as surgical urgency, approach, procedure, and blood transfusion.

4.8.6 Sensitivity analyses

To explore the robustness of our findings further, we performed a number of sensitivity analyses by systematically repeating the statistical analysis using different assumptions.[136] In Study I, our

sensitivity analyses primarily focused on the exposure definitions, changing the cutoff point for the number of (i) prescriptions in the reference category; (ii) years to define duration of use; and (iii) years to define recent and former use. In Study II, we restricted to patients that had a CRC resection. In addition, we examined colon and rectal cancer patients separately. In Studies II and III, we changed the cutoff point for filled glucocorticoid prescriptions to 60 and 120 days before the surgery date. In Study III, we restricted anastomotic leakage to patients being re-operated to heighten the validity of our outcome.

In Studies II and III, we used multiple imputations to handle missing data,[137,138] generating twenty imputed datasets. ORs were calculated as the average ORs of the twenty datasets, corrected for between- and within-imputation variation.[139-141] The imputation model included surgical procedures or outcomes (Study III) and all covariates (Studies II, III).

5. Results

5.1 Study I: Colorectal cancer risk

5.1.1 Characteristics of cases and controls

We identified 14 158 CRC cases and 141 580 population controls during the study period, of which 782 (5.5%) and 8434 (6.0%), respectively, were frequent users of systemic glucocorticoids (Table 5.1). More men (52.5%) than women (47.5%) had CRC, and most patients were diagnosed between the ages of 70 and 79 years (32.6%). The distribution of potential confounders was nearly the same for cases and controls.

Table 5.1. Characteristics of colorectal cancer cases and matched population controls, Northern Denmark, 1991-2010

Characteristics	Cases N (%)	Controls N (%)
Glucocorticoid use		
Never/rare systemic use	12 122 (85.6)	121 271 (85.7)
Frequent systemic use	782 (5.5)	8434 (6.0)
Combined use	1254 (8.9)	11 875 (8.4)
Sex		
Female	6727 (47.5)	67 270 (47.5)
Male	7431 (52.5)	74 310 (52.5)
Age at diagnosis, years		
<50	749 (5.3)	7505 (5.3)
50-59	1910 (13.5)	19 260 (13.6)
60-69	3668 (25.9)	36 404 (25.7)
70-79	4596 (32.5)	46 206 (32.6)
80+	3235 (22.9)	32 205 (22.8)
Diagnoses or related medication before index date		
Diabetes	1203 (8.5)	10 176 (7.2)
Obesity	352 (2.5)	3040 (2.2)
Alcoholism	366 (2.6)	3398 (2.4)
Pulmonary diseases	2191 (15.5)	20 868 (14.7)
Inflammatory bowel diseases	107 (0.8)	1036 (0.7)
Rheumatoid arthritis	154 (1.1)	1593 (1.1)
Medication before index date		
NSAIDs	8230 (58.1)	83 257 (58.9)
Low-dose aspirin (75/100/150 mg)	4038 (28.5)	40 180 (28.4)
High-dose aspirin (≥500 mg)	68 (0.5)	942 (0.7)
Immunosuppressants	176 (1.2)	1727 (1.2)

Among frequent users of systemic glucocorticoids, each individual filled a mean of 11 prescriptions (range, 3 to 311) during a mean period of 4.4 years. The mean cumulative prednisolone-equivalent dose prescribed was 4295 mg (range, 75 to 87 550 mg). Grouped according to quartiles, low, medium and high doses were 75-350 mg, 350-5500 mg, and >5500 mg, respectively.

5.1.2 Colorectal cancer risk

We observed no association between ever use of systemic glucocorticoids and risk of CRC; adjusted OR=0.93 (95% CI: 0.85-1.00). Recent versus former use did not affect risk (data not shown). Table 5.2 outlines the relative risk of CRC according to duration of glucocorticoid use and dose. Risk estimates virtually equalized the overall OR; however, short-term, high-dose systemic glucocorticoid use was associated with a slightly lower OR of 0.74 (95% CI: 0.59-0.94). In the analysis by CRC stage, associations between long-term use of medium-dose (OR=1.16, 95% CI: 0.89-1.53) or high-dose (OR=1.12, 95% CI: 0.81-1.55) systemic glucocorticoids and localized cancer were near the null (Table 3). Corresponding associations for metastatic cancer were also almost null (OR=0.79, 95% CI: 0.59-1.05; and OR=0.82, 95% CI: 0.59-1.14).

Table 5.2. Associations between systemic glucocorticoid use and risk of colorectal cancer

Systemic glucocorticoids	Cases n (%)	Controls n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Never/rare use	12 122 (85.6)	121 271 (85.7)	1.0 (referent)	1.0 (referent)
Short-term use				
Low-dose	142 (1.0)	1553 (1.1)	0.91 (0.77-1.09)	0.92 (0.78-1.10)
Medium-dose	276 (2.0)	2835 (2.0)	0.97 (0.86-1.10)	0.97 (0.85-1.10)
High-dose	79 (0.6)	1044 (0.7)	0.76 (0.60-0.95)	0.74 (0.59-0.94)
Long-term use				
Low-dose	54 (0.4)	666 (0.5)	0.81 (0.61-1.07)	0.81 (0.62-1.08)
Medium-dose	133 (0.9)	1318 (0.9)	1.01 (0.84-1.21)	1.01 (0.84-1.21)
High-dose	98 (0.7)	1018 (0.7)	0.96 (0.78-1.19)	0.95 (0.76-1.17)
Mixed use	1254 (8.9)	11 875 (8.4)	1.06 (0.99-1.12)	1.02 (0.95-1.10)

5.1.3 Stratified analyses

Sub-analyses across strata of comorbidities and drug use did not change the null association between ever use of systemic glucocorticoids and overall CRC risk, except for the use of NSAIDs (OR=0.89, 95% CI: 0.81-0.97). The sensitivity analysis stratified by time period (1991-2002 and 2003-2010) also yielded results near the null (data not shown).

5.1.4 Sensitivity analyses

Changing the cutoff point for exposure definitions with respect to the reference category, duration of use, and timing of use did not change the associations between glucocorticoids and risk of CRC.

5.2 Study ll: Postoperative mortality

5.2.1 Characteristics of the study cohort

We identified 34 641 patients that underwent CRC surgery between 2001 and 2011, of whom 3966 (11.5%) had filled at least one prescription for oral, inhaled, or intestinal-acting glucocorticoids within 1 year before their surgery date. Glucocorticoid users were more likely than non-users to be women, to be elderly, to have comorbid conditions, and to present with a high ASA score (Table 5.3). Accordingly, compared with non-users, a larger proportion of glucocorticoid users had prescriptions for cardiovascular drugs, NSAIDs, and COPD agents.

5.2.2 Thirty-day mortality after colorectal cancer surgery

Thirty-day mortality among current users and sub-cohorts of new and continuing users of oral glucocorticoids was 15.0%, 17.8%, and 14.2%, respectively (Table 5.4). Death occurred in 7.3% of non-users, a rate close to that for recent and former oral glucocorticoid users. Additionally, subgroups of patients that had been prescribed inhaled glucocorticoids exhibited mortality rates similar to non-users. Only 2.7% of users of intestinal-acting glucocorticoids died within 30 days postoperatively, compared with 12.1% of users of mixed glucocorticoids.

Compared with non-users, current users of oral glucocorticoids had increased 30-day mortality after CRC surgery (MRR=1.28, 95% CI: 1.03-1.58). Among new users, the MRR was 1.92 (95% CI: 1.30-2.83); among continuing users, the MRR was 1.13 (95% CI: 0.88-1.44). No increased risk was observed among recent or former glucocorticoid users (Table 5.4). Risk estimates for users of inhaled, intestinal-acting, or mixed glucocorticoids were all close to the null.

Table 5.3. Characteristics of patients undergoing surgery for colorectal cancer, categorized by use and non-use of any glucocorticoids, Denmark, 2001-2011

Characteristics	No glucocorticoid use N=27 011, n (%)	Any glucocorticoid use N=7630, n (%)
Sex		
Female	12 447 (46.1)	4016 (52.6)
Male	14 564 (53.9)	3614 (47.4)
Age, years		
<50	1284 (4.8)	269 (3.5)
50-59	3722 (13.8)	766 (10.0)
60-69	7665 (28.4)	1837 (24.1)
70-79	8587 (31.8)	2821 (37.0)
80+	5753 (21.3)	1937 (25.4)
Year of surgery		
2001-2004	9369 (34.7)	2,047 (26.8)
2005-2008	10 195 (37.7)	3028 (39.7)
2009-2011	7447 (27.6)	2555 (33.5)
Cancer site		
Colon	17,950 (66.5)	5336 (69.9)
Rectum	9061 (33.5)	2294 (30.1)
Stage		
Localized	12 599 (46.6)	3702 (48.5)
Non-localized	11 252 (41.7)	2929 (38.4)
Unknown	3160 (11.7)	999 (13.1)
Charlson Comorbidity Index score		
0	16 713 (61.9)	2764 (36.2)
1-2	7542 (27.9)	3213 (42.1)
3+	2756 (10.2)	1653 (21.7)
ASA score		
≤2	20 130 (74.5)	4629 (60.7)
>2	5693 (21.1)	2700 (35.4)
Unknown	1188 (4.4)	301 (3.9)
Inflammatory bowel disease	186 (0.7)	224 (2.9)
Autoimmune disorder or immunosuppressive drug use	724 (2.7)	740 (9.7)
Obesity	686 (2.5)	351 (4.6)
Alcohol (drinks per week)		
0	3931 (14.6)	1357 (17.8)
1-14	10 258 (38.0)	2745 (36.0)
>15	3188 (11.8)	782 (10.3)
Unknown	9634 (35.7)	2746 (36.0)
Tobacco use		
Current	4280 (15.9)	1095 (14.4)
Former	7733 (28.6)	2497 (32.7)
Never	6486 (24.0)	1575 (20.6)
Unknown	8512 (31.5)	2463 (32.3)
Cardiovascular drugs	16 694 (61.8)	5759 (75.5)
NSAIDs	17 888 (66.2)	6015 (78.8)
High-dose aspirin	414 (1.5)	203 (2.6)
COPD agents	2827 (10.4)	4382 (57.4)
Anti-diabetic drugs	2334 (8.6)	760 (10.0)
Surgical urgency		
Elective	23 117 (85.6)	6555 (85.9)
Acute	3885 (14.4)	1075 (14.11)
Unknown	9 (0.0)	0 (0.0)
Surgical approach		
Laparoscopy	5564 (20.6)	1737 (22.8)
Laparotomy	20 184 (74.7)	5437 (71.3)
Endoscopy	1262 (4.7)	456 (6.0)
Unknown	1 (0.0)	0 (0.0)
Surgical procedure		
Resection	24 031 (89.0)	6678 (87.5)
Other	2727 (10.1)	894 (11.7)
Missing	253 (0.9)	58 (0.8)

Table 5.4. Cumulative mortality rates and mortality rate ratios (MRRs) associating use of glucocorticoids and 30-day mortality after colorectal cancer surgery, Denmark, 2001-2011

Glucocorticoid use	N=34 641 n (%)	30-day mortality n (%)	Absolute risk % (95% CI)	Unadjusted MRR (95% CI)	Adjusted MRR (95% CI)
No use	27 011 (78.0)	1968 (72.4)	7.3 (7.0, 7.5)	Referent	Referent
Any glucocorticoid use	7630 (22.0)	751 (27.6)	9.8 (9.2, 10.5)	1.37 (1.26, 1.49)	1.06 (0.96, 1.17)
Oral use					
Current use	619 (1.8)	93 (3.4)	15.0 (12.4, 18.1)	2.14 (1.74, 2.64)	1.28 (1.03, 1.58)
New use	146 (0.4)	26 (1.0)	17.8 (12.5, 25.0)	2.57 (1.75, 3.79)	1.92 (1.30, 2.83)
Continuing use	473 (1.4)	67 (2.5)	14.2 (11.3, 17.6)	2.01 (1.58, 2.57)	1.13 (0.88, 1.44)
Recent use	377 (1.1)	34 (1.3)	9.0 (6.5, 12.4)	1.25 (0.89, 1.75)	0.92 (0.65, 1.29)
Former use	1809 (5.2)	165 (6.1)	9.1 (7.9, 10.5)	1.26 (1.08, 1.48)	1.03 (0.88, 1.22)
Inhaled use					
Current use	784 (2.3)	69 (2.5)	8.8 (7.0, 11.0)	1.21 (0.95, 1.54)	1.04 (0.81, 1.35)
New use	67 (0.2)	6 (0.2)	9.0 (4.1, 18.9)	1.22 (0.55, 2.73)	0.98 (0.44, 2.19)
Continuing use	717 (2.1)	63 (2.3)	8.8 (6.9, 11.1)	1.21 (0.94, 1.56)	1.05 (0.81, 1.37)
Recent use	416 (1.2)	33 (1.2)	7.9 (5.7, 11.0)	1.09 (0.77, 1.54)	0.88 (0.62, 1.25)
Former use	1334 (3.9)	90 (3.3)	6.8 (5.5, 8.2)	0.92 (0.75, 1.14)	0.97 (0.78, 1.20)
Intestinal-acting use	112 (0.3)	3 (0.1)	2.7 (0.9, 8.1)	0.36 (0.12, 1.11)	0.56 (0.18, 1.76)
Mixed use	2179 (6.3)	264 (9.7)	12.1 (10.8, 13.6)	1.71 (1.50, 1.94)	1.11 (0.95, 1.31)

5.2.3 Stratified analysis

The subgroup analysis revealed no major changes of the relative association between current use of oral glucocorticoids and 30-day mortality (Appendix, Figure 1). However, it was noted that risk estimates tended to be higher among patients with a CCI score of 0 (MRR=2.06, 95% CI: 1.35-3.15) and an ASA score of I-II (MRR=1.57, 95% CI: 1.06-2.32).

5.2.4 Causes of death

Cancer, infections, and diseases of the heart and respiratory system were the most frequent causes of death among subgroups of both glucocorticoids users and non-users; gastrointestinal causes of death were less frequent (Table 5.5). Although some results were statistically imprecise, respiratory, gastrointestinal, and urogenital diseases were more often reported as causes of death among users of glucocorticoids than among non-users.

5.2.5 Sensitivity analysis

Results from the sensitivity analysis of patients that had a colorectal resection were virtually identical to those from the main analysis (data not shown), as were results for colon and rectal cancer patients, respectively (data not shown). Likewise, changing the cutoff point for filled glucocorticoid prescriptions to 60 and 120 days before the surgery date did not affect the associations between glucocorticoids and mortality (data not shown). Finally, our findings across subgroups of glucocorticoid users were unchanged after imputation of missing values of potential confounders (data not shown).

Table 5.5. Immediate cause of death within 30 days after colorectal cancer surgery by use and non-use of glucocorticoids, Denmark, 2001-2011

Cause of death	No glucocorticoid use 1968 deaths, n (%)	Any glucocorticoid use 751 deaths, n (%)	Prevalence rate ratio (95% CI)
Cancer	501 (25.5)	192 (25.6)	1.00 (0.86, 1.16)
Infections	261 (13.3)	97 (12.9)	0.98 (0.78, 1.22)
Heart disease	224 (11.4)	73 (9.7)	0.87 (0.67, 1.12)
Circulatory disease	88 (4.5)	34 (4.5)	1.01 (0.69, 1.49)
Respiratory disease	177 (9.0)	97 (12.9)	1.39 (1.10, 1.75)
Gastrointestinal disease	9 (0.5)	5 (0.7)	1.45 (0.49, 4.32)
Urogenital disease	39 (2.0)	22 (2.9)	1.46 (0.87, 2.45)
Other	486 (24.7)	192 (25.6)	1.02 (0.89, 1.19)
Missing	183 (9.3)	39 (5.2)	0.58 (0.41, 0.81)

5.3 Study lll: Postoperative anastomotic leakage

5.3.1 Colon cancer patients

5.3.1.1 Characteristics of the study cohort

We identified 18 190 colon cancer patients that had a primary anastomosis after resection. Almost 12% of study subjects had at least one prescription for glucocorticoids within 1 year before their surgery date. Glucocorticoid users were more likely than never-users to be female and elderly (median age 74 years vs. 71 years) (Table 5.6). Compared with never users, severe comorbidity and a high ASA score were almost twice as prevalent among glucocorticoid users; however, we noted that 34.9% of users had a CCI score of 0. Prescriptions for NSAIDs and COPD agents were also more prevalent among these patients.

5.3.1.2 Anastomotic leakage after resection

Anastomotic leakage occurred in 1184 colon cancer patients (6.5%). Glucocorticoid users accounted for 287 cases (24.2%), yielding an overall absolute risk of leakage of 6.9% versus 6.4% among never-users (Table 5.7). Absolute risk did not differ substantially among subgroups of oral, inhaled, intestinal-acting, or mixed glucocorticoid users.

Compared with never-users, use of any glucocorticoids was not associated with an increased relative risk of anastomotic leakage (Table 5.7). Although estimates were imprecise, adjusted relative risk was modestly increased among current (OR=1.24, 95% CI: 0.82-1.88) and recent (OR=1.43, 95% CI: 0.87-2.34) users of oral glucocorticoids, as well as for users of intestinal-acting glucocorticoids (OR=1.47, 95% CI: 0.56-3.84). We observed no associations between the use of inhaled glucocorticoids and anastomotic leakage.

Table 5.6. Characteristics of patients that underwent resection for colon or rectal cancer, by use and never-use of any glucocorticoids, Denmark, 2001-2011

Characteristics	Colon cancer		Rectal cancer	
	No glucocorticoid use N=14 041, N (%)	Glucocorticoid use N=4149, N (%)	No glucocorticoid use N=4317, N (%)	Glucocorticoid use N=967, N (%)
Sex				
Female	7122 (50.7)	2369 (57.1)	1737 (40.2)	463 (47.9)
Male	6919 (49.3)	1780 (42.9)	2580 (59.8)	504 (52.1)
Age, years				
<60	2399 (17.1)	482 (11.6)	1187 (27.5)	224 (23.3)
60-69	3841 (27.4)	949 (22.9)	1617 (37.5)	321 (33.2)
70-79	4688 (33.4)	1582 (38.1)	1152 (26.7)	326 (33.7)
80+	3113 (21.2)	1136 (27.4)	361 (8.4)	96 (9.9)
Year of resection				
2001-2004	4767 (34.0)	1074 (25.9)	1418 (32.9)	272 (28.1)
2005-2008	5327 (37.9)	1642 (39.6)	1651 (38.2)	372 (38.5)
2009-2011	3947 (28.1)	1433 (34.5)	1248 (28.9)	323 (33.4)
Stage				
Localized	7192 (51.2)	2261 (54.5)	2460 (57.0)	557 (57.6)
Non-localized	6510 (46.4)	1785 (43.0)	1775 (41.1)	390 (40.3)
Unknown	339 (2.4)	103 (2.5)	82 (1.9)	20 (2.1)
CCI score				
0	8557 (60.9)	1448 (34.9)	3131 (72.5)	490 (50.7)
1-2	4074 (29.0)	1812 (43.7)	970 (22.5)	355 (36.7)
3+	1410 (10.0)	889 (21.4)	216 (5.0)	122 (12.6)
ASA score				
≤2	10 616 (75.6)	2575 (62.1)	3827 (88.3)	766 (79.9)
>2	2812 (20.0)	1420 (34.2)	432 (10.0)	181 (18.7)
Unknown	613 (4.4)	154 (3.7)	77 (1.8)	23 (2.4)
Inflammatory bowel disease	91 (0.7)	108 (2.6)	25 (0.6)	6 (0.8)
Autoimmune disorders or immunosuppressive drug use	90 (0.6)	256 (6.2)	26 (0.6)	50 (5.2)
Obesity	405 (2.9)	208 (5.0)	77 (1.8)	29 (3.0)
Alcoholism	488 (3.5)	159 (3.8)	160 (3.7)	34 (3.5)
Tobacco use				
Current use	2088 (14.9)	563 (13.6)	819 (19.0)	182 (18.8)
Former use	4159 (29.6)	1429 (34.4)	1529 (35.4)	359 (37.1)
Never use	3569 (25.4)	898 (21.6)	1155 (26.8)	244 (25.2)
Unknown	4225 (30.1)	1259 (30.3)	814 (18.9)	182 (18.8)
NSAIDs	3337 (23.8)	1180 (28.4)	806 (18.7)	222 (23.0)
COPD medications	1,547 (11.0)	2404 (57.9)	403 (9.3)	550 (56.9)
Surgical urgency				
Planned	12 140 (86.5)	3617 (87.2)	4295 (99.5)	963 (99.6)
Acute	1894 (13.5)	532 (12.8)	22 (0.5)	4 (0.4)
Unknown	7 (0.1)	0 (0.0)	7 (0.1)	0 (0.0)
Surgical approach				
Laparoscopy	3446 (24.5)	1111 (26.8)	972 (22.5)	239 (24.7)
Laparotomy	10 595 (75.5)	3038 (73.2)	3345 (77.5)	728 (75.3)
Surgical Procedure				
Ileocecal resection	45 (0.3)	8 (0.2)	-	-
Right-sided hemicolectomy	6925 (49.3)	2239 (54.0)	-	-
Colon transversum resection	356 (2.5)	101 (2.4)	-	-
Left-sided hemicolectomy	1546 (11.0)	447 (10.8)	-	-
Sigmoid colon resection	4791 (34.1)	1238 (29.8)	-	-
Other resections	15 (0.1)	8 (0.2)	-	-
Colectomy and IRA	363 (2.6)	108 (2.6)	-	-
Rectal resection	-	-	4317	967
Perioperative blood transfusion				
Yes	3312 (23.6)	1120 (27.0)	830 (19.2)	189 (19.5)
No	10 611 (75.6)	2999 (72.3)	3465 (80.3)	774 (80.0)
Missing/Unknown	118 (0.8)	30 (0.7)	22 (0.5)	4 (0.4)

Table 5.7. Absolute and relative risk (odds ratios [ORs]) associating use of glucocorticoids and anastomotic leakage after colon cancer resection, Denmark, 2001-2011

Glucocorticoid use	Study population N=18 190, n (%)	Leakage N=1184, n (%)	Leakage risk % (95% CI)	Risk difference, % (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No use	14 041 (77.2)	897 (75.8)	6.4 (6.0-6.8)	Referent	Referent	Referent
Any use	4149 (22.8)	287 (24.2)	6.9 (6.0-6.8)	0.5 (-0.3-1.4)	1.09 (0.95-1.25)	1.05 (0.89-1.23)
Oral use						
Current use	345 (1.9)	26 (2.2)	7.5 (5.1-10.7)	1.1 (-1.7-4.0)	1.19 (0.80-1.79)	1.24 (0.82-1.88)
Recent use	207 (1.1)	18 (1.5)	8.7 (5.4-13.1)	2.3 (-1.6-6.2)	1.40 (0.86-2.27)	1.43 (0.87-2.34)
Former use	948 (5.2)	53 (4.5)	5.6 (4.3-7.2)	-0.8 (-2.3-0.7)	0.87 (0.65-1.15)	0.90 (0.67-1.20)
Inhaled use						
Current use	434 (2.4)	32 (2.7)	7.4 (5.2-10.1)	1.0 (-1.5-3.5)	1.17 (0.81-1.68)	1.04 (0.70-1.53)
Recent use	252 (1.4)	16 (1.4)	6.3 (3.8-9.9)	-0.0 (-3.1-3.0)	0.99 (0.60-1.66)	0.96 (0.57-1.62)
Former use	742 (4.1)	51 (4.3)	6.9 (5.2-8.9)	0.5 (-1.4-2.3)	1.08 (0.81-1.45)	1.06 (0.78-1.44)
Intestinal-acting use	54 (0.3)	5 (0.4)	9.3 (3.6-19.1)	2.9 (-4.9-10.6)	1.50 (0.59-3.76)	1.47 (0.56-3.84)
Mixed use	1167 (6.4)	86 (7.3)	7.4 (6.0-9.0)	1.0 (-0.6-2.5)	1.17 (0.93-1.47)	1.02 (0.78-1.35)

5.3.1.3 Stratified analyses

With the exception of alcoholism (OR=2.58, 95% CI: 1.23-5.39), the association the association between any glucocorticoid use and anastomotic leakage did not differ materially across strata of covariates (Appendix, Figure 2).

5.3.1.4 Colon cancer patients; sensitivity analyses

In sensitivity analyses in which the time window for the definition of current use was changed to 60/120 days before surgery, results were close to those presented in Table 5.7 using either cutoff point (data not shown). When we restricted analyses to anastomotic leakages that required surgical intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown). In addition, imputation of missing values on surgical procedures and covariates did not change the observed associations (data not shown).

5.3.2 Rectal Cancer Patients

5.3.2.1 Characteristics of the study cohort

Of the 5284 rectal cancer patients resected, 458 patients (9%) used glucocorticoids within the year before surgery. As for colon cancer patients, glucocorticoid users were more likely than never-users to be female and elderly (median age 68 years vs. 66 years), to present with severe comorbidity and high ASA score, and to fill prescriptions of NSAIDs and COPD

agents (Table 5.6). Again, we noted that a large proportion of glucocorticoid users had a CCI score of 0 (50.7%).

5.3.2.2 Anastomotic leakage after resection

Anastomotic leakage occurred in 695 rectal cancer patients (13.2%) (Table 5.8). Overall, the absolute risk of leakage among glucocorticoid users was 14.6%, versus 12.8% among never-users. Absolute risks among current, recent, and former users of oral glucocorticoids were: 15.9%, 13.0%, and 16.3%, respectively. Current users of inhaled glucocorticoids had the highest absolute risk (17.7%); recent users of inhaled glucocorticoids (11.1%) and those using mixed glucocorticoids (11.7%) had the lowest risks. Anastomotic leakage occurred among 16.7% of users of intestinal-acting glucocorticoids.

Compared with never-users, glucocorticoid users had an adjusted relative risk of anastomotic leakage after rectal cancer resection of 1.36 (95% CI: 1.08-1.72) (Table 5.8). Relative risks were modestly increased in all subgroups of oral glucocorticoid users (current use: OR=1.28, 95% CI: 0.64-2.56; recent use: OR=1.24, 95% CI: 0.51-2.92; and former use: OR=1.42, 95% CI: 1.00-2.01). Among users of inhaled glucocorticoids, current users had the highest risk (OR=1.91, 95% CI: 1.11-3.30). Estimates for use of intestinal-acting and mixed glucocorticoids demonstrated no strong associations.

Table 5.8. Absolute and relative risk (odds ratios [ORs]) associating use of glucocorticoids and anastomotic leakage after rectal cancer resection, Denmark, 2001-2011

Glucocorticoid use	Study population N=5284, N (%)	Leakage N=695, N (%)	Leakage risk, % (95% CI)	Risk difference, % (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No use	4317 (81.7)	554 (79.7)	12.8 (11.9-13.9)	Referent	Referent	Referent
Any use	967 (18.3)	141 (20.3)	14.6 (12.5-16.9)	1.7 (-0.7-4.2)	1.16 (0.95-1.42)	1.36 (1.08-1.72)
Oral use						
Current use	63 (1.2)	10 (1.4)	15.9 (8.5-26.3)	3.0 (-6.0-12.1)	1.28 (0.65-2.53)	1.28 (0.64-2.56)
Recent use	46 (0.9)	6 (0.9)	13.0 (5.6-24.9)	0.2 (-9.6-10.0)	1.02 (0.43-2.41)	1.22 (0.51-2.92)
Former use	258 (4.9)	42 (6.0)	16.3 (12.2-21.1)	3.4 (-1.2-8.1)	1.32 (0.94-1.86)	1.42 (1.00-2.01)
Inhaled use						
Current use	113 (2.1)	20 (2.9)	17.7 (11.5-25.5)	4.9 (-2.2-12.0)	1.46 (0.89-2.39)	1.91 (1.11-3.30)
Recent use	45 (0.9)	5 (0.7)	11.1 (4.4-22.7)	-1.7 (-11.0-7.5)	0.85 (0.33-2.16)	1.04 (0.40-2.71)
Former use	190 (3.6)	28 (4.0)	14.7 (10.2-20.3)	1.9 (-3.2-7.0)	1.17 (0.78-1.77)	1.39 (0.89-2.17)
Intestinal-acting use	12 (0.2)	2 (0.3)	16.7 (3.6-43.6)	3.8 (-17.3-24.9)	1.36 (0.30-6.22)	1.27 (0.27-5.95)
Mixed use	240 (4.5)	28 (4.0)	11.7 (8.1-16.2)	-1.2 (-5.3-3.0)	0.90 (0.60-1.34)	1.15 (0.72-1.84)

5.3.2.3 Stratified analysis

Our stratified analysis revealed no major changes of the relative association between the overall category of glucocorticoid use and postoperative anastomotic leakage (Appendix, Figure 3).

5.3.2.4 Sensitivity analysis

After changing the definition of current use to a 60-day window before surgery, ORs were somewhat higher for current use of oral glucocorticoids (OR=1.63, 95% CI: 0.77-3.46) and somewhat lower for recent users (OR=0.97, 95% CI: 0.44-2.17). However, the 95% CIs for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cutoff-point (data not shown). When we restricted analyses to anastomotic leakages that required reoperation, we observed 215 (31%) fewer outcomes. However, results did not differ materially (data not shown). Likewise, imputation of missing values on surgical procedures and covariates did not change the observed associations (data not shown).

6. Discussion

6.1 Main conclusions

6.1.1 Study I: Risk of colorectal cancer

In this population-based case-control study, we found no evidence of an association between use of systemic glucocorticoids and CRC risk. The timing of use did not affect risk; nor did duration of use and dose. We noted that long-term, high-dose systemic glucocorticoid use was associated with a slightly increased risk of localized colorectal cancer and a slightly decreased risk of metastatic cancer. Although we cannot exclude the possibility that these associations were causal, it seems likely that heightened medical surveillance among glucocorticoid users influenced our findings.

6.1.2 Study II: Risk of postoperative mortality

In this population-based cohort study of patients undergoing CRC surgery, current users of oral glucocorticoids had an increased 30-day mortality compared with never users. Mortality was almost 2-fold higher among new users than among non-users. We found that respiratory diseases were a cause of death among glucocorticoid users more often than non-users. Although we were unable to disentangle whether glucocorticoids themselves or underlying disease activity contributed to postoperative mortality, clinicians should be aware of the association in order to refine preoperative risk assessment, surgical treatment, and perioperative care.

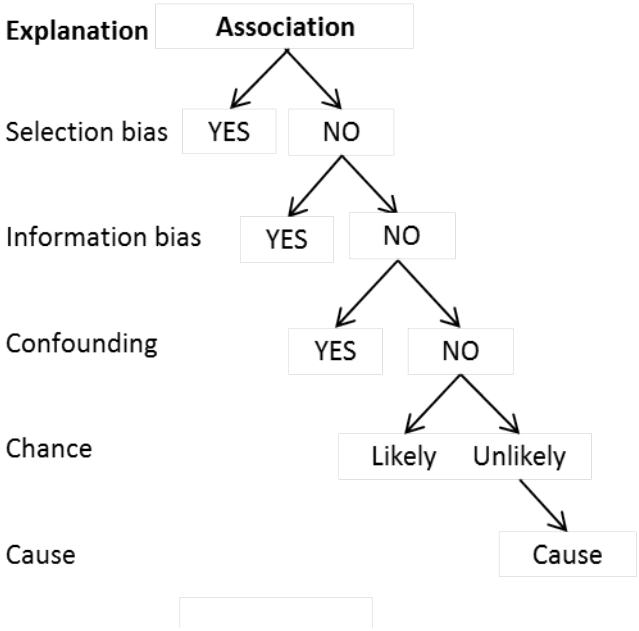
6.1.4 Study III: Risk of postoperative anastomotic leakage

In this population-based cohort study of patients that underwent a colonic or rectal cancer resection and had a primary anastomosis, we found that preadmission glucocorticoid use increased the risk of anastomotic leakage mainly after rectal cancer resection. However, differences in absolute risk were small, and glucocorticoids per se should probably not contraindicate a primary anastomosis.

6.2 Methodological considerations

Studies in this dissertation examined potential causal relations between glucocorticoid use and CRC development and postoperative outcomes, respectively. Estimates in each study represent the product of the study design, study conduct, and data analysis.[142] Ideally, this process should lead to valid and precise estimates of the associations between glucocorticoid exposure and the three outcomes. Valid estimates have few systematic errors (commonly referred to as bias), while precise estimates have few random errors. In our studies, systematic errors in particular may violate internal validity (i.e., the degree of accurate results for our study populations).[143] External validity (or generalizability) is the degree to which the associations hold true outside our defined study populations. Given the population-based design in the setting of a health care system that guarantees free access to uniform health care, we consider the generalizability of our studies to be high. Before inferring causal relationships or their absence, we must consider whether systematic errors, classified into categories of selection bias, information bias or confounding, and random errors (chance), influenced our results[144] (Figure 6.1). While selection bias and information bias stem from the study design and can only be prevented during this phase, confounding can be handled both during the study design and during the statistical analysis. Chance is the component of overall error that cannot be predicted but can be quantified using statistical distributions.[145]

Figure 6.1. Association and cause, adapted from *Fletcher*[144]



6.2.1 Selection bias

Selection bias is usually defined as a systematic error that stems from the procedures used to select study subjects and from factors that influence study participation.[128] The bias arises when the effect of exposure differs for study participants versus non-participants.

All studies in this dissertation were conducted in well-defined populations that encompassed almost all incident CRC patients in Denmark.[4,118] In addition, we had complete follow-up of the study populations.[117] These features minimized the risk of selection bias. Nevertheless, in Study I, increased medical follow-up among glucocorticoid users may have led to the detection of CRC at earlier stages than among non-users,[146] thereby affecting the selection of cases for our secondary outcome. In this context, we would expect fewer patients with metastatic CRC at the time of diagnosis. Our findings supported this assumption. In Study III, exclusion of the 905 patients with incompatible or missing data on surgical approach, procedures or anastomotic leakage might have introduced selection bias. However, we have no reason to believe that the associations observed among study participants would be different among non-participants.

6.2.2 Information bias

Erroneous information about exposure or outcome may introduce information bias. In our studies, glucocorticoid use or the outcomes were considered in categories, and any error

would result in misclassification.[43] For both glucocorticoid use and the outcomes, this misclassification could be differential or non-differential based on the relation with the presence or absence of its counterpart. Differential misclassification biases the estimate in an unpredictable manner, while non-differential misclassification of a dichotomous exposure (or outcome) biases the estimate towards a null effect.[43] However, when the exposure is measured in more than two categories, an exaggeration of an association can occur.[142]

In Studies I-III, misclassification of exposure was possible. We used filled prescriptions as a proxy for drug use, and any misclassification of non-adherence would most likely bias our estimates towards the null when comparing glucocorticoid users with non-users. Given the copayment requirements and the beneficial effects to serious symptoms, we feel confident that filled prescriptions reflect actual use. In addition, a recent Danish study reported complete correspondence between glucocorticoid treatment reported by general practitioners and time of prescription dispensation within 3 months of a set index date.[147] In Studies II and III, patients that filled their prescription more than 90 days before the surgery date that were still taking the drug beyond this cutoff point (i.e., current users incorrectly classified as recent users) could bias the estimates for recent users away from the null, assuming that the misclassification was non-differential and that current users are at greater risk for postoperative adverse outcomes. Finally, because glucocorticoids dispensed during hospitalizations are not logged, glucocorticoid users with numerous hospitalizations may have filled fewer or even no prescriptions, and this situation could be related to both CRC detection and postoperative mortality or anastomotic leakage, thereby causing differential misclassification. The impact of this underestimation of use on the outcomes is unpredictable.

With respect to outcome misclassifications, recording of death is essentially without errors in the CRS [117] (Study II). However, inaccurate coding of causes of death may have influenced our findings, although such misclassification is unrelated to glucocorticoid exposure and would thus bias the estimates towards the null. Data from the DCDR are not regularly validated, and the reproducibility of diagnoses appearing on death certificates during the study period is unclear.[125]

Misclassification of anastomotic leakage (Study lll) is difficult to assess, because no clear standard exists for the recording of anastomotic leakage.[148] Therefore, the recording of anastomotic leakage may not be complete and valid in either the DCCG database or the DNRP. To enhance complete capture of leakage cases, we included those recorded in both registries, which increased the number of cases identified in the DCCG database by 9%. Furthermore, we restricted to those requiring reoperation in order to increase the validity of the outcome, which did not change the observed associations materially.

6.2.3. Confounding

Confounding is an essential issue in studies of causation. Confounding can be considered as a mixing of the effect under study with the effect of another risk factor. To be a confounder, the factor must fulfill three criteria: The factor must be: (1) a cause of the outcome or a proxy or marker of the cause; (2) imbalanced across exposure categories; and (3) not a part of the causal pathway.[142] Confounding can be addressed in the study design through randomization, restriction, and matching, or during the statistical analysis through adjustment, stratification, and standardization.[128]

Confounding by indication is a special type of confounding that could occur in our pharmaco-epidemiologic studies of adverse effects of glucocorticoids. Confounding by indication could arise from the fact that individuals that were prescribed glucocorticoids were inherently different from those not prescribed glucocorticoids, because they had an indication that led to prescription of the drug. The resultant imbalance in the underlying risk profile between glucocorticoid users and non-users might therefore generate biased results.[149] Unfortunately, the prescription databases do not provide information about the indication for the prescription. Controlling for comorbidities was one way to handle this bias. However, recording of comorbidity may be incomplete;[130] even though we used comorbidity-related drug use as its proxy, confounding by indication cannot be excluded.

In Study l, we matched cases and control with respect to age, sex and calendar period. In the analysis, we handled confounding by adjusting and stratifying with respect to various comorbidities and medications, as previously described. We had no data regarding over-the-counter NSAIDs, which account for an estimated 14% of total use in Denmark.[150] These drugs

may be associated with both glucocorticoid use and CRC development.[151] Therefore, our adjustment for this potential confounder may be imperfect.

In Study ll, we handled confounding by adjusting for and stratifying by comorbidities and medications. Unexpectedly, we observed that almost one-third of glucocorticoid users had no recordings of comorbidity (CCI=0), which called into question the completeness of recording in the DNRP. In our stratified analysis, we observed a significant effect of glucocorticoids for patients with CCI=0 that vanished for patients with CCI scores >0, which may reflect either the effects of glucocorticoids among those with less severe diseases (i.e., patients treated solely by general practitioners whose files are not logged in the DNRP) or the effects of comorbidity not captured in the DNRP. Of note, current use (particularly new use, but not recent or former use) of oral glucocorticoids was associated with postoperative mortality, suggesting that treatment initiation or disease onset rather than accumulated underlying medical indications for glucocorticoids led to the increase in mortality. Finally, we had incomplete data on lifestyle factors, such as smoking, alcohol use, and obesity. However, adjustment for associated diseases accounted for at least some of the effect of these factors. Again, mortality was not elevated in recent or former users of oral glucocorticoids, who are likely to have lifestyles relatively similar to those of current users.

In Study lll, we dealt with potential confounding through adjustment and stratification, acknowledging limitations by incomplete recording of comorbidities as discussed. Also, we cannot exclude the possibility of some uncontrolled confounding by lifestyle factors. Data regarding smoking were incomplete (27% missing) and might suffer from underreporting. Although, we adjusted for smoking and associated diseases/COPD agents as proxies, confounding could contribute to the apparent association between inhaled glucocorticoids and anastomotic leakage in rectal cancer patients. Based on their limited bioavailability, we would not expect an association for inhaled glucocorticoids to exceed the association for oral glucocorticoids.[152]

6.2.4 Chance

Chance seems unlikely to explain our findings in Study l, as demonstrated by statistically precise estimates with narrow 95% confidence intervals. However, in Studies ll-lll, the

number of outcomes available for analysis was small within some categories of glucocorticoid exposure. The resultant estimates with wide CIs are difficult to interpret.

6.3 Comparison with the existing literature

6.3.1 Study I: Risk

To the best of our knowledge, no prior study has conducted a detailed analysis of glucocorticoid use in a general population with respect to the risk of developing CRC. Although one US-based case-control study revealed an increased CRC among glucocorticoid users, in the context of glucocorticoid exposure the study had inherent limitations, as previously discussed in Section 2.4.1.2.[64] Different from our findings, several studies on IBD patients revealed inverse associations between glucocorticoids and CRC risk.[66-70] However, the comparison of studies is challenging because of differences in both study populations (high-risk IBD patients vs. the general population) and definitions of glucocorticoid exposure. Moreover, study periods varied from 3 to 35 years.[66-70] Given a 10- to 15-year delay between the initiation of adenoma development and CRC detection,[73] we would expect the induction (i.e., the time span from the causal action of glucocorticoids to irreversible CRC occurrence) and subsequent latency (i.e., the time span from CRC occurrence to disease detection) periods[153] to spread over several years.

Previous studies suggest that immunosuppression by glucocorticoids increases the risk of non-Hodgkin lymphomas, non-melanoma skin cancer, and cancers of the bladder and prostate.[55,57,59,60,62] Still, no association was observed between glucocorticoid therapy and risk of non-Hodgkin lymphomas in a meta-analysis of eight population-based case-control studies (1992-2006),[61] or regarding breast cancer risk in two Danish population-based studies.[54,56 54,56] Even inverse relations between glucocorticoids and lung cancer have been reported.[63] A plausible explanation for this association might be that inhaled glucocorticoids reduced airway inflammation, cell turnover, and propagation of genetic errors, leading to subsequent reduction in lung cancer risk.[63] Protective effects of glucocorticoids on melanomas[58] have also been reported, although the estimates were based on few exposed cases. Overall, our review of the literature suggests that reported associations between

glucocorticoids and cancer risk are disparate and may indicate complex interactions between glucocorticoids, indications for their use, and unknown factors.

6.3.2 Study ll: Postoperative mortality

In our population-based study, we demonstrated that postoperative mortality was substantially higher among current users of oral glucocorticoids than among non-users, whose mortality corresponded with previous international reports.[4,38,154] The pathophysiologic mechanisms underlying our findings are not clear, but may include reduced immune activity, proliferation, and protein synthesis, and altered metabolism and endocrine systems,[10] all of which interfere with postoperative healing processes and recovery. We observed no evidence that inhaled or intestinal-acting glucocorticoids influenced mortality, consistent with their limited systemic bioavailability.[152,155]

None of the few single-centre studies that evaluated glucocorticoids and postoperative mortality were restricted to CRC patients.[78,83,84] Studies are difficult to compare because such patients may differ substantially from those undergoing surgery for non-malignant indications in terms of the extent of the operation, older age, and higher level of comorbidity.[156] Overall, as indicated previously, the identified studies had flaws that precluded further interpretation.

6.3.3. Study lll: Postoperative anastomotic leakage

A recent review comprising 12 studies on glucocorticoids and anastomotic leakage after colorectal surgery provided a summary estimate for the cumulative incidence of leakage among glucocorticoid users.[109] Apparently, overall risk was higher in our cohort of colon and rectal cancer patients. Several explanations may exist for this disparity. First, the lack of a standard definition of anastomotic leakage most likely plays a role.[148] Second, differences in study populations, sample sizes, indications for resection (benign vs. malignant disease) and surgical procedures performed may also lead to variations in results. For example, one single-centre study that was included was not limited to patients that underwent resection; it also included patients treated with stricturoplasty.[157] Finally, differences in the definition of glucocorticoid use varied substantially between studies in the review and our studies. Thus, a randomized clinical trial considered intravenous high-dose glucocorticoids administered 90

minutes prior to colon cancer resection as primary exposure,[158] while others examined effects of glucocorticoids used for >1 month before the surgery.[78,99]

Although they provided evidence about predictors of anastomotic leakage, no previous studies examined causal effects of glucocorticoids on anastomotic leakage after CRC in a population-based setting. Therefore, our study provides novel insight into the role of glucocorticoids as a prognostic factor for leakage. We included a considerably larger sample size than any previous study and provided detailed data about different types of glucocorticoids and the timing of their use. We also analyzed colon and rectum cancer patients separately.

7. Perspectives

This thesis adds to current evidence regarding CRC risk and prognosis among individuals that have been prescribed glucocorticoids. We were unable to demonstrate harmful effects of glucocorticoid use on CRC occurrence; however, we found that initiation of therapy was associated with an increased risk of short-term mortality after CRC surgery. To better understand the clinical course, we explored the potential risk of anastomotic leakage (as an intermediate step from glucocorticoid use to mortality). We found that preadmission glucocorticoids increased risk of leakage mainly after rectal cancer resection. However, absolute risk differences were small and glucocorticoids per se should probably not contraindicate a primary anastomosis.

However, this thesis does raise the following questions:

- Given the 10- to 15-year delay between adenoma development and the manifestation of CRC, would a longer study period and unlimited prescription history change our null result in Study I?
- Glucocorticoid users comprise a heterogeneous cohort of patients, all of whom have one or more medical conditions. What is the impact of polypharmacy on CRC risk and postoperative outcomes?
- What are the causal mechanisms behind our findings in Study II? What is the role of glucocorticoid use, particularly drug initiation per se? Does glucocorticoid use influence medical or surgical postoperative adverse outcomes (e.g., infections, myocardial infarction or perioperative bleeding), thereby increasing the risk of mortality?
- Can we improve the identification of glucocorticoid users at high risk of adverse postoperative outcomes before the CRC surgery, and thereby reduce risk by tailoring perioperative requirements?
- What is the impact of in-hospital glucocorticoid use on CRC risk and postoperative outcomes?

Harmful effects of glucocorticoids cannot be tested in a randomized trial, and CRC patients that are burdened with comorbidity are generally ineligible for clinical trials. Pharmacoepidemiological studies offer a valuable alternative with the advantages of large-

scale population-based investigations, as demonstrated in this thesis. The Danish registries provide a unique opportunity to further study effects of glucocorticoids on CRC risk and outcomes. The availability of unambiguous individual-level linkage facilitates accurate data regarding prescribed medications, hospital diagnoses, and some postoperative outcomes in study subjects. Beginning in 2014, the DCCG has enforced the registration of anastomotic leakage according to a standardized definition and grading system, as proposed by the International Study Group of Rectal Cancer. The introduction of this system may enhance the validity of leakage recordings and comparability between studies. Also, with the introduction of the electronic patient journal in Denmark, detailed data regarding (for example) in-hospital medications, severity of comorbidity, and complications may supplement available data from the administrative registries and clinical databases and eventually strengthen the validity of our non-experimental research.

8. Summary

Worldwide, CRC ranks as the third most common malignancy. More than two-thirds of CRC patients are diagnosed after the age of 65 years. Consequently, age-related comorbidities and polypharmacy are prevalent among these patients, and knowledge is urgently required regarding interactions between drug effects and CRC risk and prognosis.

Glucocorticoids are standard treatment for disorders that share an inflammatory or immunological basis. Each year in Denmark, 8% of the population aged 65 years or older is prescribed systemic glucocorticoids. Glucocorticoids have potent immunologic and metabolic effects that may influence CRC development and prognosis.

This thesis was founded on three clinical epidemiological studies: one nested population-based case-control study in Northern Denmark and two nationwide cohort studies. We used the unique civil registration number to link data from Danish population-based administrative and medical registries, facilitating complete study populations, accurate prescription history, and adjustment for important confounding factors.

The aims of this thesis were to examine associations between glucocorticoids and CRC risk, overall and by stage (Study I); and to examine associations between preadmission glucocorticoid use and 30-day mortality and risk of anastomotic leakage after CRC surgery, respectively (Studies II, III).

Study I included 14 158 patients diagnosed with CRC during 1991-2010 and 141 580 matched population controls. We were unable to demonstrate an association between ever-use or long-term high-dose use (prescription history exceeding 5 years and 5500 mg, respectively) of systemic glucocorticoids and CRC risk. When we examined CRC risk by stage, long-term use of medium-dose (350-5500 mg) or high-dose systemic glucocorticoids was associated with a slightly increased risk of localized CRC and a decreased risk of non-localized cancer. However, this finding might have been influenced by the increased surveillance of glucocorticoid users.

Study II included 34 641 patients that underwent CRC surgery between 2001 and 2011. More than 10% of CRC patients had filled at least one glucocorticoid prescription within 1 year before their surgery date. Glucocorticoid users were more likely to be elderly and to present

with a higher level of comorbidity. Thirty-day mortality among current users of oral glucocorticoids (most recent prescription filled within 90 days before the surgery date) was 15.0% versus 7.3% among non-users, corresponding to a 28% increase in the relative risk. Among new users (first ever prescription filled within 90 days before the surgery date), the relative risk increased by almost 2-fold. No associations were observed for recent or former use (most recent prescription filled within 91-365 days or >365 days before the surgery date), suggesting that treatment initiation or disease onset rather than accumulated underlying medical indications for glucocorticoids led to the increase in mortality.

Study lll included 18 900 colon and 5284 rectal cancer patients that had a tumor resection and a primary anastomosis. When we employed never-use as reference, we found that current and recent users of oral glucocorticoids exhibited a modest increase in the relative risk of anastomotic leakage after colon cancer resection, but estimates were imprecise. No associations were observed for other categories of oral, inhaled, or intestinal-acting glucocorticoids. Among rectal cancer patients, relative risk increased for almost any subgroup of glucocorticoid use, greatest for current use of inhaled glucocorticoids (almost by 2-fold). For both cancers, however, differences in absolute risk among users versus never users were small, and the clinical impact of their use might therefore be limited.

The most important methodological considerations are related to the observational study design and the use of administrative databases. Therefore, selection, information, and confounding bias might influence our findings; the latter two types are the most likely. However, we find it implausible that the effects of these biases alone fully explain our observations.

9. Dansk resume

På verdensplan er colorectal cancer (CRC) den tredje hyppigste kræftsygdom og den fjerde hyppigste årsag til kræftrelateret død. Mere end to tredjedele af CRC tilfældene diagnosticeres efter 65 års alderen. Aldersrelaterede sygdomme og polyfarmaci vil derfor være udbredt blandt disse patienter, og viden om interaktioner mellem farmaka og CRC risiko og prognose er vigtig.

Glukokortikoider er standard behandling ved en række inflammatoriske tilstande og udskrives årligt til 8% af den danske befolkning over 65 år. Glukokortikoider har potente immunologiske og metaboliske effekter som potentielt kan påvirke udvikling af CRC og forløbet efter kirurgisk behandling af sygdommen.

Denne afhandling er baseret på tre klinisk epidemiologiske studier; et nested case-control studie i det tidligere Aarhus og Nordjyllands Amt og to cohorte studier i Danmark. Data fra eksisterende danske registre blev koblet ved hjælp af CPR nummeret, hvilket bidrog til komplette studiepopulationer og præcis medicinhistorie. I alle studier tog vi hånd om vigtige confoundere, herunder komorbiditet.

Formålet med afhandlingen var at undersøge (1) associationen mellem brug af glukokortikoider og risiko for udvikling af CRC, herunder også sygdomsstadie ved diagnosen, (2) associationen mellem glukokortikoider og 30-dages mortalitet efter CRC kirurgi, og (3) risikoen for anastomoselækage efter CRC resektion blandt glukokortoidbrugere sammenlignet med ikke-brugere.

Studie l omfattede 14 158 CRC patienter diagnosticeret i 1991-2010 og 141 580 matchede kontrolpersoner. Vi fandt ingen sammenhæng mellem brug af systemiske glukokortikoider og risiko for CRC, uanset timing, varighed og dosis af glukokortikoider. Analyse af stadiefordelingen af CRC viste at lang recepthistorie med medium (350-5500 mg) eller høj (>5000 mg) kumuleret dosis øgede risikoen for lokaliseret sygdom og reducerede risikoen for regional/metastatisk sygdom. Vi kan ikke udelukke en effekt af hyppig kontrol af disse patienter.

Studie ll omfattede 34 641 opererede CRC patienter. Mere end 10% havde indløst mindst en recept på glukokortikoider i året op til operationen. Høj alder og svær komorbiditet mere

prævalent blandt glukokortikoidbrugere end ikke-brugere. Tredive-dages mortalitet efter indgrebet var 15% hos aktuelle brugere (seneste recept indløst ≤90 dage før operationen) mod 7% hos ikke-brugere, svarende til en 28% øget relativ risiko. Hos nye brugere (første recept indløst ≤90 dage før operationen) var den relative risiko næsten fordoblet. Vi fandt ingen sammenhænge for nylige eller tidligere brugere (seneste recept indløst 91-365 dage eller >365 dage før operationen, henholdsvis). Resultaterne indikerer, at behandlingsstart eller sygdomsopblussen snarere end underliggende komorbiditet førte til stigningen i mortalitet.

I studie 3 indgik 18 900 colon og 5284 rectum cancer patienter som fik en primær anastomose i forbindelse med deres tumorresektion. Som i studie ll fandt vi at høj alder og svær komorbiditet var mere prævalent blandt glukokortikoidbrugere end ikke-brugere. Vi fandt at aktuelle og nylige brugere af orale glukokortikoider havde en let øget relativ risiko for anastomoselækage efter colon cancer resektion, omend resultaterne var upræcise. Blandt rectum cancer patienter sås en let øget relativ risiko for lækage for næsten alle undersøgte ekponeringsgrupper. For begge cancere var forskellene i de absolutte risikoestimater små. Resultaterne antyder, at den kliniske betydning af glukokortikoider forud for CRC resektion med primær anastomose formentlig er begrænset.

De væsentligste metodemæssige problemer ved de 3 studier relaterer sig til det observationelle design og anvendelsen af eksisterende data. Resultaterne kan være påvirket af selektion, information og confounding bias, hvoraf de to sidstnævnte er de væsentlige. Vi finder det mindre sandsynligt at effekter af bias alene forklarer vores resultater.

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Appendix (Thesis)

Figure 1. Subgroup analysis associating current use of oral glucocorticoids and 30−day mortality after colorectal cancer surgery compared to non−use, Denmark, 2001−2011.

Characteristics	Adjusted OR (95% CI)
Overall	1.28 (1.03 − 1.58)
Sex	
Male	1.34 (0.99 − 1.82)
Female	1.22 (0.91 − 1.65)
Age (years)	
<50	–
50−59	3.31 (0.75 − 14.01)
60−69	1.36 (0.71 − 2.60)
70−79	1.34 (0.93 − 1.93)
80+	1.17 (0.87 − 1.57)
Cancer site	
Colon	1.21 (0.95 − 1.51)
Rectum	1.54 (0.95 − 2.51)
Stage	
Localized	1.30 (0.90 − 1.88)
Non−localized	1.37 (0.98 − 1.91)
Unknown	1.19 (0.78 − 1.81)
CCI score	
0	2.06 (1.35 − 3.15)
1−2	1.17 (0.83 − 1.64)
3+	1.11 (0.77 − 1.59)
ASA score	
I−II	1.57 (1.06 − 2.32)
III−V	1.21 (0.93 − 1.58)
Unknown	2.22 (1.04 − 4.73)
Smoking	
Current	1.64 (0.87 − 3.10)
Former	1.82 (1.10 − 3.00)
Never	1.58 (0.86 − 2.89)
Unknown	1.10 (0.83 − 1.45)
Alcohol intake	
None	2.04 (1.24 − 3.36)
41640	1.59 (0.96 − 2.64)
>14	0.44 (0.05 − 3.23)
Unknown	1.14 (0.87 − 1.50)
Surgical urgency	
Planned	1.43 (1.09 − 1.86)
Acute	1.19 (0.83 − 1.70)
Unknown	–
Surgical approach	
Laparoscopy	1.62 (0.86 − 3.07)
Laparotomy	1.26 (0.99 − 1.59)
Missing	–

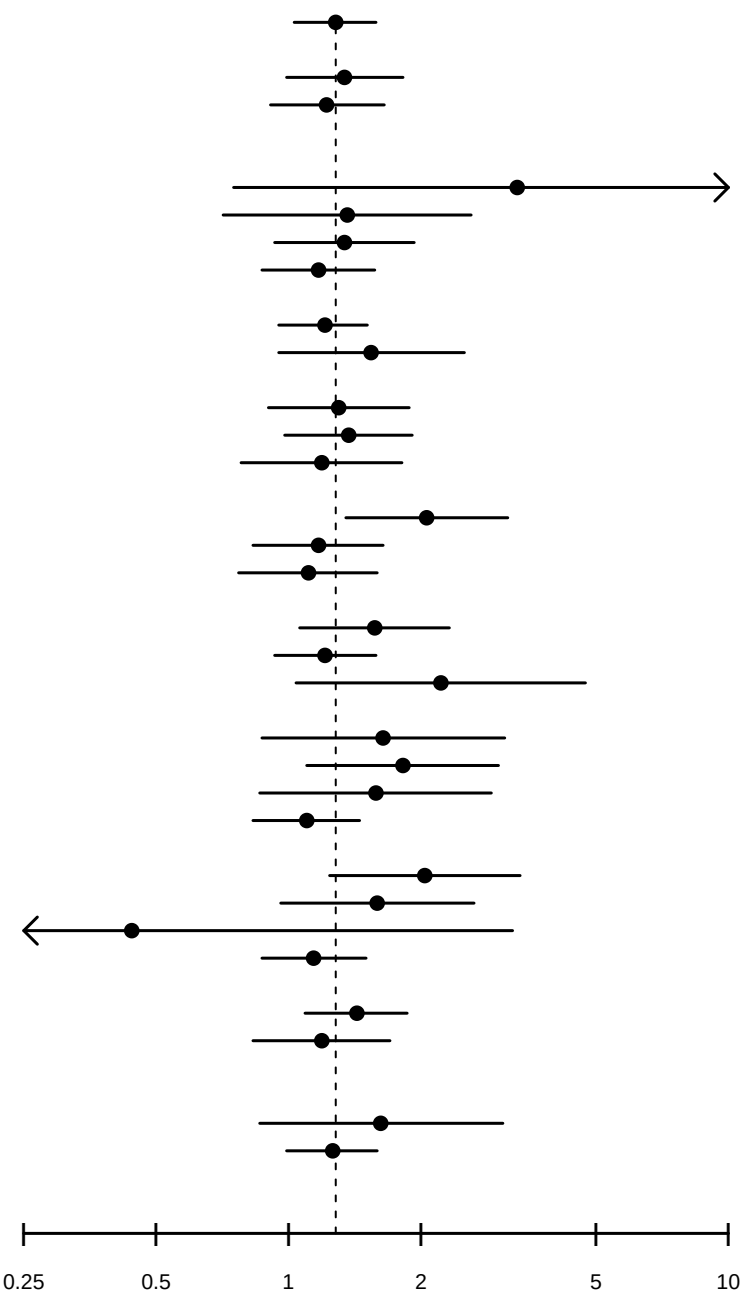


Figure 2. Subgroup analysis associating any use of glucocorticoids and postoperative anastomotic leakage after colon cancer resection compared to non−use, Denmark, 2001−2011.

Characteristics	Adjusted OR (95% CI)
Overall	1.05 (0.89 − 1.23)
Sex	
Male	1.04 (0.84 − 1.30)
Female	1.04 (0.82 − 1.32)
Age (years)	
<60	1.23 (0.79 − 1.91)
60−69	1.14 (0.83 − 1.58)
70−79	1.07 (0.83 − 1.39)
80+	0.81 (0.57 − 1.16)
Year of surgery	
2001−2004	1.38 (1.02−1.86)
2005−2008	0.92 (0.71−1.20)
2009−2011	0.92 (0.69−1.24)
Stage	
Localized	1.10 (0.88 − 1.37)
Non−localized	0.99 (0.77 − 1.28)
Unknown	0.77 (0.27 − 2.19)
CCI score	
0	1.06 (0.83 − 1.36)
1−2	0.93 (0.71 − 1.20)
3+	1.31 (0.88 − 1.95)
ASA score	
I−II	1.04 (0.84 − 1.29)
III−V	1.08 (0.83 − 1.42)
Unknown	0.67 (0.28 − 1.61)
Smoking	
Current	1.17 (0.77 − 1.76)
Former	0.83 (0.61 − 1.11)
Never	1.45 (0.99 − 2.11)
Unknown	1.04 (0.80 − 1.37)
Alcoholism	2.58 (1.23 − 5.39)
Surgical urgency	
Planned	1.10 (0.92 − 1.30)
Acute	0.76 (0.48 − 1.22)
Surgical approach	
Open	1.07 (0.89 − 1.30)
Laparoscopic	0.99 (0.72 − 1.36)
Perioperative blood transfusion	
Yes	1.15 (0.91−1.45)
No	0.97 (0.75−1.24)
Missing/unknown	0.08 (0.01−0.66)

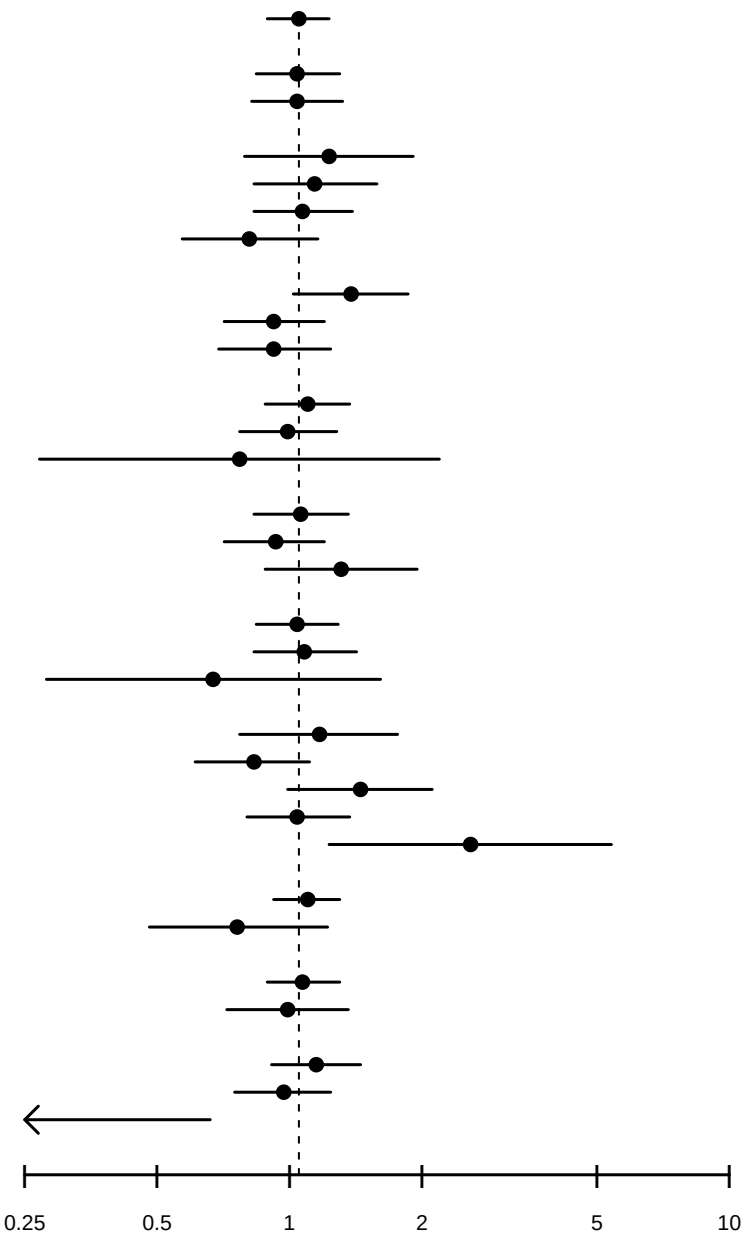
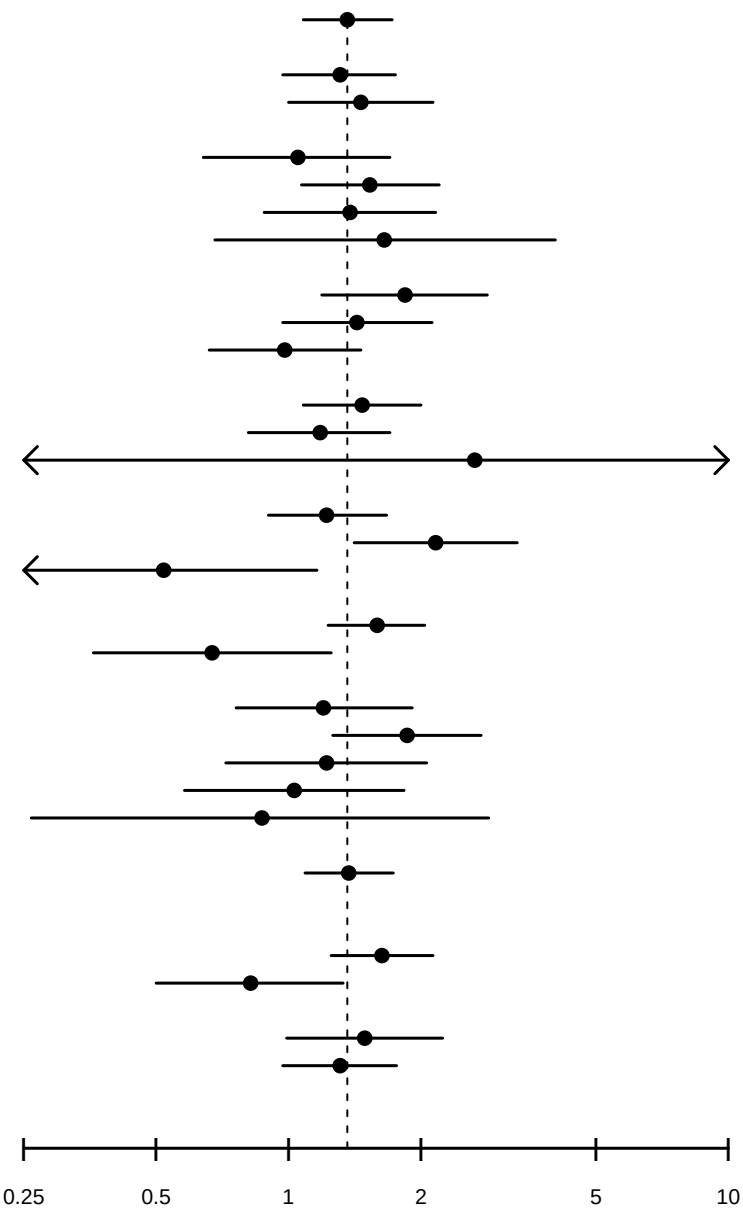


Figure 3. Subgroup analysis associating any use of glucocorticoids and postoperative anastomotic leakage after rectal cancer resection compared to non−use, Denmark, 2001−2011.

Characteristics	Adjusted OR (95% CI)
Overall	1.36 (1.08 − 1.72)
Sex	
Male	1.31 (0.97 − 1.75)
Female	1.46 (1.00 − 2.13)
Age (years)	
<60	1.05 (0.64 − 1.70)
60−69	1.53 (1.07 − 2.20)
70−79	1.38 (0.88 − 2.16)
80+	1.65 (0.68 − 4.04)
Year of surgery	
2001−2004	1.84 (1.19−2.83)
2005−2008	1.43 (0.97−2.12)
2009−2011	0.98 (0.66−1.46)
Stage	
Localized	1.47 (1.08 − 2.00)
Non−localized	1.18 (0.81 − 1.70)
Unknown	2.65 (0.19 − 36.80)
CCI score	
0	1.22 (0.90 − 1.67)
1−2	2.16 (1.41 − 3.31)
3+	0.52 (0.24 − 1.16)
ASA score	
I−II	1.59 (1.23 − 2.04)
III−V	0.67 (0.36 − 1.25)
Smoking	
Current	1.20 (0.76 − 1.91)
Former	1.86 (1.26 − 2.74)
Never	1.22 (0.72 − 2.06)
Unknown	1.03 (0.58 − 1.83)
Alcoholism	0.87 (0.26 − 2.85)
Surgical urgency	
Planned	1.37 (1.09 − 1.73)
Acute	−
Surgical approach	
Open	1.63 (1.25 − 2.13)
Laparoscopic	0.82 (0.50 − 1.33)
Perioperative blood transfusion	
Yes	1.49 (0.99−2.24)
No	1.31 (0.97−1.76)
Missing/unknown	−



Paper I

AP&T Alimentary Pharmacology and Therapeutics

Use of systemic glucocorticoids and the risk of colorectal cancer

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SUMMARY

Background
Systemic glucocorticoids are potent immunosuppressants, potentially facilitating carcinogenesis. Studies examining glucocorticoids and colorectal cancer risk are few.

Aim
To investigate the association between use of systemic glucocorticoids and colorectal cancer risk, both overall and by cancer stage (localised versus metastatic).

Methods
We conducted a nested population-based case–control study in Northern Denmark (1.8 million people) using medical registries. The study included 14 158 patients with a first-time diagnosis of colorectal cancer from 1991 through 2010. Using risk set sampling, we identified 141 580 population controls, matched on age and gender. Logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for covariates.

Results
Frequent use of systemic glucocorticoids (defined as >2 prescriptions) was not associated with overall colorectal cancer risk [adjusted OR (aOR) = 0.93 (95% CI: 0.85–1.00)], compared with never/rare use (≤2 prescriptions). Associations according to duration of use and doses (quartiles of cumulative prednisolone equivalents) were also near the null. Examining colorectal cancer by stage, no substantial associations were found between long-term use (>5 years) of high-dose (>5500 mg) systemic glucocorticoids and localised [aOR = 1.12 (95% CI: 0.81–1.55)] or metastatic [aOR = 0.82 (95% CI: 0.59–1.14)] cancer.

Conclusion
Despite immunological and metabolic effects of frequent use of systemic glucocorticoids, which would be expected to increase colorectal cancer risk, we found no substantial association between the two.

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INTRODUCTION

Colorectal cancer is the third most common malignancy worldwide[1] and the disease has a serious prognosis. Synthetic glucocorticoids are widely used in the treatment of chronic and acute inflammatory diseases due to their potent immunosuppressive effects. In Denmark, 3.3% of the population was treated with systemic glucocorticoids in 2010.[2] Concerns have been raised that prolonged therapy may increase cancer risk.[3–7] Use of glucocorticoids could possibly affect the risk of colorectal cancer through several mechanisms. Glucocorticoids are involved in the regulation of metabolism, cell growth, proliferation, apoptosis and immune function,[8] which all play major roles in the prevention of cancer development and spread.[9, 10] As glucocorticoids are potent inhibitors of immunosurveillance, they may facilitate carcinogenesis and rapid progression of colorectal cancer. Moreover, insulin resistance, a well-known side effect of glucocorticoids,[11] has been suggested to increase colorectal cancer risk.[12] In contrast, glucocorticoids exert antiproliferative and proapoptotic effects,[8] and could thereby even facilitate chemoprevention. In addition, glucocorticoids belong to the same steroid superfamily as oestrogen and progesterone, which appear inversely associated with risk of colorectal cancer.[13]

Although glucocorticoids are commonly prescribed in clinical practice, an association with colorectal cancer development is unclear and existing epidemiological data are few. Previous studies evaluating glucocorticoid therapy and colorectal cancer risk all were restricted to patients with inflammatory bowel disease, who *a priori* have an increased risk of cancer.[14] Moreover, glucocorticoid use was not the main exposure of interest in any of the studies, and their results were conflicting. We therefore conducted a large prospective population-based case–control study examining the association between glucocorticoid use and colorectal cancer risk, both overall and according to cancer stage.

MATERIALS AND METHODS

Source population

We conducted this nested population-based case–control study in Northern Denmark, covering a population of 1.8 million inhabitants.[15] The Danish National Health Service guarantees free access to medical care provided by general practitioners and hospitals, and partial reimbursement of the costs of most prescribed drugs. Health-related services are recorded for individual patients using the unique civil registration number assigned to each Danish citizen at birth and to residents upon immigration. The civil registration number encodes age and gender, and allows unambiguous linkage of data from different medical registries. From the source population, we excluded persons with any cancer diagnosis (except for nonmelanoma skin cancer) before their index date (as defined below). Also, to ensure at least 2 years of prescription history for each case and control, we restricted the study to persons who resided in the study area for at least 2 years prior to the index date.

Patients with colorectal cancer

We used the Danish Cancer Registry to identify patients with a first-time colorectal cancer diagnosis between 1 January 1991 and 31 December 2010 (see Appendix S1 for diagnosis codes). The Danish Cancer Registry has recorded cases of incident cancer since 1943.[16, 17] During the 1991–2010 period, cancers were classified in this registry according to the 10th revision of the International Classification of Diseases. Recorded data include civil registration number, date of cancer diagnosis, cancer type and cancer stage at time of diagnosis [according to the Dukes classification system until the end of 2003 and the Tumor Node Metastasis (TNM) classification thereafter].[18] We defined localised cancer as Dukes A or B and associated TNM classification codes and metastatic cancer as Dukes C or D and associated TNM classification codes (see Appendix S1, published online).

Population controls

For each colorectal cancer case, we used the Danish Civil Registration System[19] to select 10 population controls matched on age and gender. Risk set sampling was applied, i.e. controls had to be alive and at risk of colorectal cancer at the time the corresponding case was diagnosed (index date). The Civil Registration System contains data on civil registration number, vital status, residence, migration, and date of death from 1968 onwards.

Prescription data

All pharmacies in Northern Denmark are equipped with an electronic accounting system that records the customer's civil registration number, type and amount of drug prescribed according to the Anatomical Therapeutic Chemical classification system, and the prescription redemption date. Prescription data on reimbursable medicines have been transferred from pharmacies in the study area to a research database at Aarhus University since 1989, with complete coverage from 1998

onwards.[20] In Denmark, glucocorticoids are dispensed by prescription only, except for a few nasal medications sold over the counter (see Appendix S2 published online for codes).

Use of systemic glucocorticoids

For each case and control, we identified all dispensed prescriptions of glucocorticoids prior to the index date. The exposure of interest was the use of systemic glucocorticoids. As a number of subjects were expected to use both systemic and locally acting glucocorticoids, we categorised exposure based on (i) never/rare use of systemic glucocorticoids (defined as two or fewer prescriptions filled prior to the index date); (ii) frequent use of systemic glucocorticoids (more than two prescriptions); and (iii) combined use (including systemic and locally acting or locally acting glucocorticoids alone, the latter including inhaled glucocorticoids and those acting locally in the intestines). For frequent systemic glucocorticoid use, we further defined subgroups based on timing of use, duration and dose. Time of treatment was categorised as recent use (most recent prescription filled 3 years or less prior to the index date) or former use (most recent prescription filled four or more years prior to the index date). Duration and dose were combined to identify the intensity of frequent systemic glucocorticoid use. The duration of use was grouped into short-term use (less than 5 years elapsing between the first and the most recent prescription) or long-term use (five or more years between the first and the most recent prescription) use. Within duration groups, we defined three categories according to cumulative prednisolone-equivalent doses [21, 22] used by cases and controls: low dose (lowest quartile), medium dose (middle quartiles) and high dose (highest quartile) (see Appendix S3, published online, for equivalence calculations). To minimise the risk of detection bias associated with glucocorticoid use due to regular medical follow-ups, we disregarded glucocorticoid prescriptions filled within 1 year prior to the index date in the main analysis. Also, glucocorticoid exposure during that period was unlikely to play an aetiological role in colorectal cancer incidence.

Potential confounders

A number of covariates were included in the study as potential confounders, based on their clinical relevance for, and known association with, both colorectal cancer risk and glucocorticoid exposure. To address the issue of confounders, we used the Danish National Registry of Patients. This registry contains records of nonpsychiatric discharges from Danish hospitals since 1977 and outpatient hospital contacts since 1995.[23] Data include the patient's civil registration number, dates of admission and discharge, surgical and diagnostic procedures and up to 20 discharge diagnoses, coded by physicians according to the 8th revision of the International Classification of Diseases until the end of 1993, and the 10th revision thereafter. We retrieved information from the Danish National Registry of Patients and the prescription database on diagnoses of diabetes/use of antidiabetic drugs, alcoholism/use of disulfiram, pulmonary diseases/use of beta-agonists, inflammatory bowel diseases and rheumatoid arthritis. In addition, we obtained information on use of prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin (75 or 150 mg tablets), high-dose aspirin (500 mg tablets) and immunosuppressants. The corresponding codes are provided in Appendix S4 published online.

Statistical analysis

We calculated the frequency and proportion of colorectal cancer cases and population controls within categories of systemic glucocorticoid use, demographic variables and potential confounders. In addition, we calculated mean duration of frequent systemic glucocorticoid use (time between first and last prescription redemption) among cases and controls. We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) associating systemic glucocorticoid use and colorectal cancer risk. Given the risk set sampling of controls, these ORs represent unbiased estimates of the corresponding incidence rate ratios. As two outcomes were associated with cancer stage distribution, we estimated the ORs using unconditional polytomous logistic regression,[24] adjusting for potential confounding covariates. In all analyses, the reference category was never/rare use of systemic glucocorticoids.

Additional subanalyses were performed to explore observed associations. We examined the association between glucocorticoid use and colorectal cancer risk across strata of comorbidity and drug use. Also, we stratified by time period (1991–2002 and 2003–2010) to provide at least 5 years of prescription history for patients diagnosed during 2003–2010. For cases and controls in the 2003–2010 period, left truncation of prescription data thus would be less likely to influence the results. Furthermore, in a sensitivity analysis, we repeated all analyses, including prescriptions of glucocorticoids within the year before the index date to explore whether the most recent exposure would affect the risk estimates.

Statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Protection Agency (record number 2011-41-6151).

RESULTS

We identified 14 158 colorectal cancer cases and 141 580 population controls during the study period, of which 782 (5.5%) and 8434 (6.0%), respectively, were frequent users of systemic glucocorticoids (Table 1). More men (52.5%) than women (47.5%) had colorectal cancer, and most patients were diagnosed between the ages of 70 and 79 years (32.6%). The distribution of potential confounders was nearly the same for cases and controls.

Among frequent users of systemic glucocorticoids, each subject filled 11 prescriptions on average, ranging from 3 to 311, during a mean period of 4.4 years. The mean cumulative prednisolone-equivalent dose prescribed was 4295 mg, ranging from 75 to 87 550 mg. Grouped according to quartiles, low, medium and high doses were 75–350 mg, 350–5500 mg, and more than 5500 mg, respectively.

We found no association between frequent use of systemic glucocorticoids and overall risk of colorectal cancer [aOR = 0.93 (95% CI: 0.85–1.00)]. Recent vs. former use did not affect this overall OR (data not shown). Table 2 outlines the ORs according to duration of use and dose. The results are virtually identical to the overall OR, although short-term high-dose systemic glucocorticoid use was associated with a slightly lower aOR of 0.74 (95% CI: 0.59–0.94). In the analysis by colorectal cancer stage, associations between long-term use of medium-dose [aOR = 1.16 (95% CI: 0.89–1.53)] or high-dose [aOR = 1.12 (95% CI: 0.81–1.55)] systemic glucocorticoids and localised cancer were near the null (Table 3). Corresponding associations for metastatic cancer were also almost null [aOR = 0.79 (95% CI: 0.59–1.05) and aOR = 0.82 (95% CI: 0.59–1.14)].

Subanalyses across strata of comorbidities and drug use did not change the association between frequent use of systemic glucocorticoids and overall colorectal cancer risk, except for use of NSAIDs [aOR = 0.89 (95% CI: 0.81–0.97)]. The sensitivity analysis stratified by time period (1991–2002 and 2003–2010) also yielded results near the null (data not shown). Results of our sensitivity analyses, including glucocorticoid prescriptions filled within 1 year before the index date, were not substantially different from the results of the main analysis (data not shown).

Table 1 | Characteristics of colorectal cancer cases and matched population controls, Northern Denmark, 1991–2010

Characteristics	Cases N (%)	Controls N (%)
Glucocorticoid use		
Never/rare systemic use	12 122 (85.6)	121 271 (85.7)
Frequent systemic use	782 (5.5)	8434 (6.0)
Combined use*	1254 (8.9)	11 875 (8.4)
Gender		
Female	6727 (47.5)	67 270 (47.5)
Male	7431 (52.5)	74 310 (52.5)
Age at diagnosis, years		
<50	749 (5.3)	7505 (5.3)
50–59	1910 (13.5)	19 260 (13.6)
60–69	3668 (25.9)	36 404 (25.7)
70–79	4596 (32.5)	46 206 (32.6)
80+	3235 (22.9)	32 205 (22.8)
Time period†		
1991–1995	1391 (9.8)	13 910 (9.8)
1996–2000	2672 (18.9)	26 720 (18.9)
2001–2005	4777 (33.7)	47 770 (33.7)
2006–2010	5318 (37.6)	53 180 (37.6)
Diagnoses or related medication before index date		
Diabetes‡	1203 (8.5)	10 176 (7.2)
Obesity	352 (2.5)	3040 (2.2)
Alcoholism§	366 (2.6)	3398 (2.4)
Pulmonary diseases¶	2191 (15.5)	20 868 (14.7)
In□ammatory bowel diseases	107 (0.8)	1036 (0.7)
Rheumatoid arthritis	154 (1.1)	1593 (1.1)
Medication before index date		
NSAIDs	8230 (58.1)	83 257 (58.9)
Low-dose aspirin**	4038 (28.5)	40 180 (28.4)
High-dose aspirin†	68 (0.5)	942 (0.7)
Immunosuppressants	176 (1.2)	1727 (1.2)

NSAIDs, nonsteroidal anti-in□ammatory drugs.

* Systemic and locally acting or locally acting glucocorticoids alone.

† Number of cases according to availability of prescription data.

‡ Diabetes/antidiabetic agents (single variable).

§ Alcoholism/disul□ram (single variable).

¶ Pulmonary diseases/beta-2 agonists (single variable).

** 75, 100 or 150 mg tablets.

†† 500 mg tablets.

DISCUSSION

In this large population-based case–control study, we found no evidence of an overall association between

Table 2 | Associations between systemic glucocorticoid use and overall risk of colorectal cancer

Systemic glucocorticoids	Cases N (%)	Controls N (%)	OR (95% CI)	aOR* (95% CI)
Never/rare use	12 122 (85.6)	121 271 (85.7)	1.0 (referent)	1.0 (referent)
Combined use†	1254 (8.9)	11 875 (8.4)	1.06 (0.99–1.12)	1.02 (0.95–1.10)
Short-term use				
Low dose‡	142 (1.0)	1553 (1.1)	0.91 (0.77–1.09)	0.92 (0.78–1.10)
Medium dose§	276 (2.0)	2835 (2.0)	0.97 (0.86–1.10)	0.97 (0.85–1.10)
High dose¶	79 (0.6)	1044 (0.7)	0.76 (0.60–0.95)	0.74 (0.59–0.94)
Long-term use				
Low dose	54 (0.4)	666 (0.5)	0.81 (0.61–1.07)	0.81 (0.62–1.08)
Medium dose	133 (0.9)	1318 (0.9)	1.01 (0.84–1.21)	1.01 (0.84–1.21)
High dose	98 (0.7)	1018 (0.7)	0.96 (0.78–1.19)	0.95 (0.76–1.17)

aOR, adjusted odds ratio; CI, con□dence interval; OR, odds ratio.

* Adjusted for diabetes, obesity, alcoholism, pulmonary diseases, in□ammatory bowel diseases, rheumatoid arthritis, and use of nonsteroidal anti-in□ammatory drugs, low-dose aspirin, high-dose aspirin or immunosuppressants.

† Systemic and locally acting or locally acting glucocorticoids alone.

‡ Low dose: cumulative prednisone equivalent dose from 75 mg to 350 mg.

§ Medium dose: cumulative prednisone equivalent dose from 350 mg to 5500 mg.

¶ High dose: cumulative prednisone equivalent dose more than 5500 mg.

Table 3 | Associations between systemic glucocorticoid use and risk of colorectal cancer by stage*

	Localised colorectal cancer			Metastatic colorectal cancer		
Systemic glucocorticoids	N	OR (95% CI)	aOR† (95% CI)	N	OR (95% CI)	aOR (95% CI)
Never/rare use	4635	1.0 (referent)	1.0 (referent)	6136	1.0 (referent)	1.0 (referent)
Combined use‡	542	1.19 (1.09–1.31)	1.17 (1.04–1.31)	527	0.88 (0.80–0.96)	0.88 (0.79–0.99)
Short-term use						
Low dose	45	0.76 (0.56–1.02)	0.77 (0.57–1.03)	80	1.02 (0.81–1.28)	1.05 (0.84–1.32)
Medium dose	116	1.07 (0.89–1.29)	1.09 (0.90–1.31)	116	0.81 (0.67–0.98)	0.84 (0.70–1.02)
High dose	30	0.75 (0.52–1.08)	0.76 (0.53–1.10)	39	0.74 (0.54–1.02)	0.77 (0.56–1.07)
Long-term use						
Low dose	17	0.67 (0.41–1.08)	0.70 (0.43–1.14)	31	0.92 (0.64–1.32)	0.96 (0.67–1.37)
Medium dose	55	1.09 (0.83–1.43)	1.16 (0.89–1.53)	50	0.75 (0.56–1.00)	0.79 (0.59–1.05)
High dose	41	1.05 (0.77–1.44)	1.12 (0.81–1.55)	40	0.78 (0.57–1.07)	0.82 (0.59–1.14)

aOR, adjusted odds ratio; CI, con□dence interval; OR, odds ratio.

* 1658 colorectal cancer patients were excluded due to missing stage. Including these patients did not change the estimates (data not shown).

† Adjusted for diabetes, obesity, alcoholism, pulmonary diseases, in□ammatory bowel diseases, rheumatoid arthritis, and use of nonsteroidal anti-in□ammatory drugs, low-dose aspirin, high-dose aspirin or immunosuppressants.

‡ Systemic and locally acting or locally acting glucocorticoids alone.

frequent use of systemic glucocorticoids and colorectal cancer risk. Although results were close to null, long-term use of medium- or high-dose systemic glucocorticoids slightly increased risk of localised colorectal cancer, and decreased risk of metastatic cancer. We cannot exclude the possibility that this association was causal; however, it seems likely that increased surveillance influenced our findings. Systemic glucocorticoids are used for the treatment of various medical conditions and only by prescription. Thus, patients using these drugs may have frequent contacts with physicians. Moreover, glucocorticoids can cause serious side effects, including peptic ulcers, upper gastrointestinal bleeding, and anaemia,[25] which may lead to blood tests, diagnostic endoscopies and early detection

of colorectal neoplasia. In this context, we would expect fewer metastatic colorectal cancers at the time of diagnosis. Our study findings supported this assumption.

To our knowledge, this is the first study to investigate the association between systemic glucocorticoid use and risk of colorectal cancer in the general population. Previous studies suggest that immune suppression by glucocorticoids increases the risk of non-Hodgkin lymphomas, and cancers of the skin, bladder and prostate.[3–7] Still, no association was found between glucocorticoid therapy and risk of breast cancer in a Danish population-based case–control study,[22] and an inverse association was reported for inhaled corticosteroids and lung cancer among patients with chronic obstructive pulmonary disease.[26] Differences in study results may indicate that associations between glucocorticoids and cancer risk depend on where the cancer is located.

Major strengths of our study include its population-based design, encompassing all incident colorectal cancers in the study period. Our study population was identified in registries with complete follow-up.[16, 19] In addition, accurate registry data on prescriptions and diagnoses eliminated recall bias and permitted adjustment for potential confounders.[20, 23]

Our study also has potential weaknesses.[27] Misclassification of both exposure and covariates is a major concern. First, filled prescriptions for medications were used to estimate actual intake, as we lacked information on adherence. However, a recent Danish study reported complete correspondence between corticosteroid treatment reported by general practitioners and time of prescription dispensation within 3 months of a set index date.[28] Second, we lacked data on glucocorticoids dispensed to hospital inpatients, thereby potentially underestimating the actual use of glucocorticoids. However, adjustment and stratification based on hospitalisations and corresponding diagnoses did not change the overall risk estimates. Third, the prescription database does not include over-the-counter NSAIDs, which account for 14% of total NSAID use in Denmark.[29] Also, low-dose aspirin is available without prescription. These drugs are inversely associated with colorectal cancer risk[30] and may also be related to glucocorticoid exposure. We assumed that these drugs were likely to be prescribed when used to treat chronic conditions, to allow patients to get reimbursed. Fourth, left truncation of prescription data could lead to misclassification of users as non-users. However, potential bias due to under-ascertainment of glucocorticoid exposure before establishment of the prescription database cannot explain our findings.

We had no information on the indication for prescription of systemic glucocorticoids. However, we adjusted for relevant diagnoses before the index date and included glucocorticoid dose and duration of use, which are surrogate markers of disease severity. Moreover, our definition of systemic glucocorticoids minimised confounding by the indication for concurrent use of either inhaled glucocorticoids or glucocorticoids acting locally in the intestines (i.e. related to severe underlying conditions).

Finally, unmeasured factors such as smoking, physical activity, and diet could affect colorectal cancer risk. However, confounding by lifestyle factors would have caused an overestimation of the ORs and thus cannot explain a null result or an inverse association.

In conclusion, despite immunological and metabolic effects of frequent use of systemic glucocorticoids, which would be expected to increase colorectal cancer risk, we found no overall association between the two. Associations between frequent use of systemic glucocorticoids and colorectal cancer stage are probably influenced by detection bias, due to increased medical surveillance among these patients.

AUTHORSHIP

Guarantor of the article: EBO takes the responsibility for the integrity of the work as a whole, from inception to published article.

Author contributions: All authors have made substantial contributions to the study design, analysis or interpretation of data, drafted the manuscript or critically revised it for important intellectual content. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Colorectal cancer diagnosis codes and classification codes.

Appendix S2. Anatomical Therapeutic Chemical classification codes for glucocorticoids.

Appendix S3. Equivalency table presenting systemic glucocorticoids and corresponding prednisolone conversion factors.

Appendix S4. Diagnosis codes for potential confounders.

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Paper II

AP&T Alimentary Pharmacology and Therapeutics

Pre-admission use of glucocorticoids and 30-day mortality following colorectal cancer surgery: a population-based Danish cohort study

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SUMMARY

Background
Previous studies indicate that pre-admission glucocorticoids increase the risk of perioperative complications.

Aim
To examine whether pre-admission use of glucocorticoids affects 30-day mortality after colorectal cancer (CRC) surgery.

Methods
We conducted a nationwide population-based cohort study by linking Danish medical registries. All residents in Denmark who underwent CRC surgery from 2001 to 2011 were included. We characterised subjects who filled their most recent glucocorticoid prescription ≤90, 91–365 and >365 days before their surgery date as prevalent, recent and former users, respectively. Prevalent users were subgrouped into new (first-ever prescription ≤90 days before surgery date) and continuing users. We estimated 30-day cumulative mortality by the Kaplan–Meier method and corresponding mortality rate ratios (MRRs) using Cox proportional hazard regression, adjusting for potential confounders.

Results
Of the 34 641 CRC patients included, 3966 (11.5%) had filled one or more prescriptions of glucocorticoids within the year before the surgery date. Thirty-day mortality among prevalent users of oral glucocorticoids was 15.0% vs. 7.3% among non-users [MRR = 1.28; 95% confidence interval (CI): 1.03, 1.58]. Among new users, the 30-day mortality was 17.8% (MRR = 1.92; 95% CI: 1.30, 2.83) while it was 14.2% among continuing users (MRR = 1.13; 95% CI: 0.88, 1.44). No associations were found for recent or former use of oral glucocorticoids nor for use of inhaled, intestinal-acting, and mixed glucocorticoids.

Conclusions
Prevalent use, particulary new use, of oral glucocorticoids was associated with markedly increased 30-day mortality after colorectal cancer surgery compared to patients not exposed to any glucocorticoids.

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INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most common malignancy and the fourth most common cause of cancer-related death.[1] Surgical resection of the tumour is crucial for cure, but inevitably carries a risk. In previous reports, overall 30-day mortality following major CRC resections accounts for 4–8%.[2–4] These rates, however, are strongly influenced by factors such as patient age, comorbidities, cancer stage, and urgency of surgery.[4, 5] Likewise, differences in availability of mortality data, i.e. through population-based registries or in-hospital records may influence reported mortality rates.

Synthetic glucocorticoids are potent immune-suppressive drugs widely used to treat chronic inflammatory diseases and some malignancies.[6] In Denmark, 8% of the population aged 65 years or older are prescribed systemic glucocorticoids[7] and more than two-thirds of CRC diagnoses occur within this age group.[4, 8]

Glucocorticoid use has been associated with severe complications following surgery, including infections[9–13] respiratory, renal and cardiac events,[11] wound healing[14] as well as anastomotic leakage following colorectal resection.[15] Moreover, glucocorticoids cause adrenal suppression, hindering the cortisol response to such stressors as surgery and eventually inducing life-threatening secondary adrenal insufficiency.[16] Glucocorticoids thus may affect mortality following CRC surgery through several mechanisms, however, no data exist for this association.

Given the frequent prescription of glucocorticoids, any association with mortality following CRC surgery has important clinical implications. We therefore conducted a population-based cohort study using data from Danish medical registries to examine 30-day mortality after CRC surgery among patients prescribed glucocorticoids.

MATERIALS AND METHODS

Setting

The Danish National Health Board provides the entire population of Denmark (5.5 million people) with tax-supported health care and partial reimbursement for most prescribed drugs. Health service utilisation is recorded using the unique personal identification number assigned to each Danish citizen at birth and to residents upon immigration, allowing unambiguous individual-level linkage of registries.[17]

CRC patients

This nationwide cohort study included all Danish residents, who underwent surgical treatment following a CRC diagnosis between May 1, 2001 and December 31, 2011, and whose records were submitted to the Danish Colorectal Cancer Group (DCCG) database.[18] Since its establishment in 2001, the DCCG has registered cases of incident colorectal adenocarcinoma diagnosed or treated in surgical departments in Denmark. Data on tumour, treatment and patient characteristics are collected by the DCCG using standardised forms completed by surgeons. Self-reported information on factors related to health and lifestyle, is recorded in patient questionnaires. Completeness of CRC registration in the DCCG ranged from 98% to 100% during the 2001–2010 period.[4] We retrieved data from the DCCG on date of CRC surgery, cancer site and staging information including tumour extent, node involvement, and metastases.[19] We also obtained information on the surgical urgency (acute or planned), approach (laparoscopic or open surgery) and procedure performed, as well as American Society of Anesthesiologists Physical Status Classification (ASA) score, tobacco and alcohol consumption.

Use of glucocorticoids

The National Registry of Medicinal Products (NRMP) records prescriptions dispensed at Danish pharmacies, with complete coverage from 1995 on.[20] The NRMP contains information on the prescription redemption date and the type and amount of dispensed medication according to the *Anatomical Therapeutic Chemical* (ATC) *Classification System*. We used NRMP data to identify all prescriptions of oral, inhaled and intestinal-acting glucocorticoids redeemed before the CRC surgery date (see Appendix for ATC-codes). Data on prescriptions of glucocorticoid injections were not included in the main analysis, as injections are used primarily for local treatment of synovitis and bursitis, or for seasonal allergy. On the basis of the methods used previously,[21] we categorised exposure into five main groups: (i) non-use, (ii) oral glucocorticoid use only, (iii) inhaled glucocorticoid use only, (iv) intestinal-acting glucocorticoid use only and (v) mixed use (i.e. treatment with glucocorticoids from at least two of the foregoing three groups). We further categorised oral and inhaled glucocorticoid use as prevalent use (most recent prescription filled within 90 days prior to the surgery date), recent use (most recent prescription filled within 91–365 days prior to the surgery date), and former use (most recent prescription filled more than 365 days prior to the surgery date). Prevalent use was disaggregated into new use (first-ever prescription filled within 90 days before the surgery date) and continuing use (first-ever

prescription filled more than 90 days before the surgery date and most recent prescription filled within 90 days before the surgery date). Intestinal-acting glucocorticoid use was not divided into subcategories due to paucity of exposed subjects. The definitions of glucocorticoid use are summarised in Table 1.

We defined intensity of oral glucocorticoid use as the prednisolone-equivalent cumulative dose[6, 22] divided by total duration of use in days (i.e. the number of days between the date of the first and last prescription plus the number of pills provided in the last prescription). Intensity was categorised by quartiles: low (lowest quartile), medium (middle quartiles) and high (highest quartile).

Comorbidity

A number of comorbidities or co-medications potentially could confound the association between glucocorticoid use and mortality following CRC surgery. We obtained data on comorbidities from the Danish National Registry of Patients (DNRP). This registry contains records of all nonpsychiatric discharges from Danish hospitals since 1977 and on out-patient clinic and emergency room visits since 1995 coded by physicians according to the 8th revision of the *International Classification of Diseases* (ICD-8) until the end of 1993, and the 10th revision (ICD-10) thereafter.[23] We summarised each patient's medical history from 1977 until the surgery date by searching the DNRP for the diagnoses included in the Charlson Comorbidity Index (CCI).[24] The CCI has been adapted and validated for use with hospital discharge data for predicting short- and long-term mortality,[25] including mortality following colon cancer.[26] After excluding CRC diagnoses from the index (see Appendix for ICD codes defining a modified CCI), we grouped patients according to level of comorbidity, defined as a CCI score of 0 (low), 1–2 (moderate) and 3+ (severe). Inflammatory bowel disease, autoimmune disease and obesity diagnoses are not included in the CCI, and were therefore included as separate variables (see Appendix for ICD codes).

From the NRMP, we also ascertained use of cardiovascular drugs [including angiotensin-converting enzyme inhibitors, β-blocking agents, calcium antagonists and other anti-hypertensives, diuretics, nitrates, statins and low-dose (75–150 mg tablets aspirin), nonsteroidal anti-inflammatory drugs (NSAIDs], high-dose aspirin, chronic obstructive pulmonary disease (COPD) agents, anti-diabetics and immuno-suppressants (see Appendix for ATC-codes).

Mortality and causes of death

The Danish Civil Registration System contains data on vital status (dead or alive), date of death, and residence. We followed patients from date of CRC surgery until death, 30 days following surgery, emigration or 30 January 2012, whichever came first. We ascertained causes of death from the Danish Cause of Death Registry (DCDR). Since 1970, all deaths in Denmark have been recorded in this registry.[27] Information includes the underlying cause of death and a chain of one to four contributing conditions that led to death, coded according to ICD-10. We defined the cause of death as the first recorded contributing condition (i.e. the immediate event that led to death). We categorised causes of deaths as cancer, infections, as well as cardiovascular, respiratory,

Table 1 | Glucocorticoid exposure definitions

Non-users	Patients with no redemptions of any prescribed glucocorticoids (oral, inhaled, or intestinal-acting) before the surgery date
Users of oral or inhaled glucocorticoids*	Patients who filled one or more prescriptions for a particular glucocorticoid type but no prescriptions for the other two types of glucocorticoids before the surgery date
Prevalent users	Patients who filled their most recent prescription within 90 days before the surgery date
New users	First-ever prescription filled within 90 days before the surgery date
Continuing users	First-ever prescription filled more than 90 days before the index date, but most recent prescription within 90 days before the surgery date
Recent users	Patients who filled their most recent prescription within 91–365 days before the surgery date
Former users	Patients who filled their most recent prescription more than 365 days before the surgery date
Users of intestinal-acting glucocorticoids	Patients who filled one or more prescriptions for intestinal-acting glucocorticoids before the surgery date
Users of mixed glucocorticoids	Patients who filled prescriptions for more than one type of glucocorticoid before the surgery date

* Categories of glucocorticoid users were defined for both oral and inhaled glucocorticoids.

gastrointestinal, and urogenital diseases (see Appendix for ICD-10 codes).

Statistical analysis

We tabulated frequencies of glucocorticoid use and non-use within categories of demographic and study variables. Using the Kaplan–Meier method,[28] we estimated 30-day cumulative mortality for patients according to our pre-defined glucocorticoid exposures. We then estimated mortality rate ratios (MRRs) and 95% confidence intervals (CIs) associating mortality following CRC surgery and glucocorticoid exposure in crude and adjusted Cox regression models, including the following potential confounders: sex, age, year of surgery, cancer site, stage, CCI score, ASA score, inflammatory bowel disease, auto-immune disease or use of immune-suppressive drugs (single variable), obesity, alcoholism or use of disulfiram (single variable) and use of tobacco, cardiovascular drugs, NSAIDs, high-dose aspirin, COPD agents and anti-diabetics. In a subsequent analysis, we assessed crude and adjusted MRRs according to the intensity of oral glucocorticoid use.

To examine variations in post-operative mortality in the presence of associated risk factors, MRRs were calculated by sex, age groups, cancer site, cancer stage, CCI score, ASA score, as well as surgical urgency, approach and procedure. Non-use of any glucocorticoids served as the comparison cohort in all analyses. The assumption of proportional hazards was assessed graphically using log-log plots and found appropriate.

We then calculated frequencies of glucocorticoid users and non-users within causes of death. For comparison purposes we calculated prevalence proportion ratios, using non-users as the reference.

Finally, in a sensitivity analysis, we first restricted to patients who had a CRC resection. Second, we included prescriptions of glucocorticoids injections together with oral use and redefined this group as systemic glucocorticoid users.

Statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record number 2011-41-6151).

RESULTS

Characteristics of the study cohort

We identified 34 641 patients undergoing CRC surgery between 2001 and 2011, of whom 3966 (11.5%) had

Table 2 | Characteristics of patients undergoing surgery for colorectal cancer, by use and non-use of any glucocorticoids, Denmark, 2001–2011

Characteristics	No glucocorticoid use, *N* = 27 011 *N* (%)	Any glucocorticoid use, *N* = 7630 *N* (%)
Sex		
Female	12 447 (46.1)	4016 (52.6)
Male	14 564 (53.9)	3614 (47.4)
Age (years)		
<50	1284 (4.8)	269 (3.5)
50–59	3722 (13.8)	766 (10.0)
60–69	7665 (28.4)	1837 (24.1)
70–79	8587 (31.8)	2821 (37.0)
80+	5753 (21.3)	1937 (25.4)
Year of surgery		
2001–2004	9369 (34.7)	2047 (26.8)
2005–2008	10 195 (37.7)	3028 (39.7)
2009–2011	7447 (27.6)	2555 (33.5)
Cancer site		
Colon	17 950 (66.5)	5336 (69.9)
Rectum	9061 (33.5)	2294 (30.1)
Stage		
Localised	12 599 (46.6)	3702 (48.5)
Non-localised	11 252 (41.7)	2929 (38.4)
Unknown	3160 (11.7)	999 (13.1)
Charlson Comorbidity Index score		
0	16 713 (61.9)	2764 (36.2)
1–2	7542 (27.9)	3213 (42.1)
3+	2756 (10.2)	1653 (21.7)
ASA score		
≤2	20 130 (74.5)	4629 (60.7)
>2	5693 (21.1)	2700 (35.4)
Unknown	1188 (4.4)	301 (3.9)
IBD	186 (0.7)	224 (2.9)
Auto-immune disorders or immunosuppressive drug use	724 (2.7)	740 (9.7)
Obesity	686 (2.5)	351 (4.6)
Alcohol (drinks per week)		
0	3931 (14.6)	1357 (17.8)
1–14	10 258 (38.0)	2745 (36.0)
>15	3188 (11.8)	782 (10.3)
Unknown	9634 (35.7)	2746 (36.0)
Tobacco		
Prevalent use	4280 (15.9)	1095 (14.4)
Former use	7733 (28.6)	2497 (32.7)
Never use	6486 (24.0)	1575 (20.6)
Unknown	8512 (31.5)	2463 (32.3)
Cardiovascular drugs	16 694 (61.8)	5759 (75.5)
NSAIDs	17 888 (66.2)	6015 (78.8)
High-dose aspirin	414 (1.5)	203 (2.6)
COPD agents	2827 (10.4)	4382 (57.4)
Anti-diabetic drugs	2334 (8.6)	760 (10.0)
Surgical urgency		
Elective	23 117 (85.6)	6555 (85.9)

Table 2 | (Continued)

Characteristics	No glucocorticoid use, *N* = 27 011 *N* (%)	Any glucocorticoid use, *N* = 7630 *N* (%)
Acute	3885 (14.4)	1075 (14.11)
Unknown	9 (0.0)	0 (0.0)
Surgical approach		
Laparoscopy	5564 (20.6)	1737 (22.8)
Laparotomy	20 184 (74.7)	5437 (71.3)
Endoscopy	1262 (4.7)	456 (6.0)
Unknown	1 (0.0)	0 (0.0)
Surgical procedure		
Resection	24 031 (89.0)	6678 (87.5)
Other	2727 (10.1)	894 (11.7)
Missing	253 (0.9)	58 (0.8)

IBD, inflammatory bowel disease; ASA, American Society of Anesthesiologists Physical Status Classification; NSAIDs, non-steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

filled at least one prescription for oral, inhaled or intestinal-acting glucocorticoids within the year before their surgery date. Glucocorticoid users were more likely than non-users to be women, elderly, to have comorbid conditions (although we noted that 36.2% of users had a CCI score of 0) and to present with a high ASA score (Table 2). Accordingly, compared with non-users, a larger proportion of glucocorticoid users had prescriptions for cardiovascular drugs, NSAIDs and COPD agents.

Thirty-day mortality following CRC surgery

Thirty-day mortality among prevalent users and subcohorts of new users and continuing users of oral glucocorticoids was 15.0%, 17.8% and 14.2%, respectively (Table 3). Death occurred in 7.3% of non-users, a rate close to that for recent and former oral glucocorticoid users. Also, subgroups of patients prescribed inhaled glucocortiocids showed mortality rates similar to non-users. Only 2.7% of users of intestinal-acting glucocorticoids died within 30 days post-operatively. However, the number of deaths in this subgroup was very low. Among users of mixed glucocorticoids, 30-day mortality was 12.1%.

Compared with non-users, prevalent users of oral glucocorticoids had increased 30-day mortality after CRC surgery (aMRR = 1.28; 95% CI: 1.03, 1.58); among new users, the aMRR was 1.92 (95% CI: 1.30, 2.83) and among continuing users, the aMRR was 1.13 (95% CI: 0.88, 1.44). No increased risk was found among recent or former glucocorticoid users (Table 3). Risk estimates for users of inhaled, intestinal-acting or mixed glucocorticoids were all close to the null. Among the 176

Table 3 | Cumulative mortality rates and mortality rate ratios (MRRs) associating use of glucocorticoids and 30-day mortality following colorectal cancer surgery, Denmark, 2001–2011

Glucocorticoid use	*N* (%)	30-day mortality, *N* (%)	Absolute risk% (95% CI)	Unadjusted MRR (95% CI)	Adjusted* MRR (95% CI)
No use	27 011 (78.0)	1968 (72.4)	7.3 (7.0, 7.5)	Referent	Referent
Any glucocorticoid use	7630 (22.0)	751 (27.6)	9.8 (9.2, 10.5)	1.37 (1.26, 1.49)	1.06 (0.96, 1.17)
Oral use					
Prevalent use	619 (1.8)	93 (3.4)	15.0 (12.4, 18.1)	2.14 (1.74, 2.64)	1.28 (1.03, 1.58)
New use	146 (0.4)	26 (1.0)	17.8 (12.5, 25.0)	2.57 (1.75, 3.79)	1.92 (1.30, 2.83)
Continuing use	473 (1.4)	67 (2.5)	14.2 (11.3, 17.6)	2.01 (1.58, 2.57)	1.13 (0.88, 1.44)
Recent use	377 (1.1)	34 (1.3)	9.0 (6.5, 12.4)	1.25 (0.89, 1.75)	0.92 (0.65, 1.29)
Former use	1809 (5.2)	165 (6.1)	9.1 (7.9, 10.5)	1.26 (1.08, 1.48)	1.03 (0.88, 1.22)
Inhaled use					
Prevalent use	784 (2.3)	69 (2.5)	8.8 (7.0, 11.0)	1.21 (0.95, 1.54)	1.04 (0.81, 1.35)
New use	67 (0.2)	6 (0.2)	9.0 (4.1, 18.9)	1.22 (0.55, 2.73)	0.98 (0.44, 2.19)
Continuing use	717 (2.1)	63 (2.3)	8.8 (6.9, 11.1)	1.21 (0.94, 1.56)	1.05 (0.81, 1.37)
Recent use	416 (1.2)	33 (1.2)	7.9 (5.7, 11.0)	1.09 (0.77, 1.54)	0.88 (0.62, 1.25)
Former use	1334 (3.9)	90 (3.3)	6.8 (5.5, 8.2)	0.92 (0.75, 1.14)	0.97 (0.78, 1.20)
Intestinal-acting use	112 (0.3)	3 (0.1)	2.7 (0.9, 8.1)	0.36 (0.12, 1.11)	0.56 (0.18, 1.76)
Mixed use	2179 (6.3)	264 (9.7)	12.1 (10.8, 13.6)	1.71 (1.50, 1.94)	1.11 (0.95, 1.31)

* Adjusted for sex, age, year of surgery, cancer site, stage, Charlson Comorbidity Index score, American Society of Anesthesiologists Physical Status Classification score, auto-immune disorders or use of immuno-suppressive drugs, inflammatory bowel disease, obesity, use of alcohol, tobacco, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, high-dose aspirin, chronic obstructive pulmonary disorder agents, and anti-diabetics.

prevalent low-intensity users of oral glucocorticoids, the aMRR was 1.53 (95% CI: 1.07, 2.21), compared to non-users. Corresponding aMRRs were 0.93 (95% CI: 0.67, 1.29) for the 292 patients with medium-intensity oral glucocorticoid use, and 1.91 (95% CI: 1.30, 2.82) for the 151 patients with high-intensity use. Risk estimates for recent and former users of oral glucocorticoids were all close to null across strata of intensity (data not shown).

The subgroup analysis revealed no major changes of the relative association between prevalent use of oral glucocorticoids and 30-day mortality (Table 4). However, it was noted that risk estimates tended to be higher among patients with a low CCI and ASA score, respectively.

Cancer, infections and diseases of the heart and respiratory system were the most frequent causes of death among subgroups of both glucocorticoids users and non-users, while gastrointestinal causes of death were less frequent (Table 5). Compared to non-users, we found that respiratory, gastrointestinal and urogenital diseases were more often reported as causes of death among users of glucocorticoids than among non-users, although the latter two results were statistically imprecise.

Results from the sensitivity analysis of patients who had a colorectal resection were virtually identical to those from the main analysis (data not shown). Accordingly, results from the analysis of systemic users, i.e. including prescriptions of glucocorticoid injections together with oral use, did not materially differ from the main analysis of oral use (data not shown).

Table 4 | Subgroup analysis associating prevalent use of oral glucocorticoids and 30-day mortality after colorectal cancer surgery compared to non-use, Denmark, 2001–2011

	Unadjusted MRR (95% CI)	Adjusted MRR (95% CI)*
Sex		
Male	2.40 (1.79, 3.23)	1.34 (0.99, 1.82)
Female	1.97 (1.47, 2.65)	1.21 (1.22, 1.65)
Age at surgery date (years)		
<50	–	–
50–59	3.30 (0.81, 13.46)	3.31 (0.75, 14.01)
60–69	2.34 (1.24, 4.39)	1.36 (0.71, 2.60)
70–79	1.72 (1.21, 2.45)	1.34 (0.93, 1.93)
80+	1.52 (1.14, 2.02)	1.17 (0.87, 1.57)
Cancer site		
Colon	2.02 (1.60, 2.55)	1.21 (0.95, 1.51)
Rectum	2.30 (1.44, 3.69)	1.54 (0.95, 2.51)
Stage		
Localised	2.15 (1.50, 3.08)	1.30 (0.90, 1.88)
Nonlocalised	2.30 (1.65, 3.20)	1.37 (0.98, 1.91)
Unknown	1.72 (1.15, 2.57)	1.19 (0.78, 1.81)
CCI score		
0	2.71 (1.79, 4.10)	2.06 (1.35, 3.15)
1–2	1.40 (1.00, 1.96)	1.17 (0.83, 1.64)
3+	1.39 (0.98, 1.97)	1.11 (0.77, 1.59)
ASA score		
I–II	2.22 (1.51, 3.26)	1.57 (1.06, 2.32)
III–V	1.21 (0.93, 1.58)	1.21 (0.93, 1.58)
Unknown	2.22 (1.04, 4.73)	2.22 (1.04, 4.73)
Surgical urgency		
Planned	2.37 (1.83, 3.08)	1.43 (1.09, 1.86)
Acute	1.76 (1.24, 2.49)	1.19 (0.83, 1.70)
Unknown	–	–
Surgical approach		
Laparoscopy	3.04 (1.65, 5.59)	1.62 (0.86, 3.07)
Laparotomy	2.06 (1.64, 2.60)	1.26 (0.99, 1.59)
Missing	–	–
Surgical procedure		
Resection	2.11 (1.64, 2.70)	1.25 (0.97, 1.61)
Other	2.00 (1.35, 2.97)	1.49 (0.99, 2.24)
Missing	1.36 (0.33, 5.56)	1.64 (0.35, 7.61)

MRR, mortality rate ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification.

* Adjusted for sex, age, year of surgery, cancer site, stage, Charlson Comorbidity Index score, American Society of Anesthesiologists Physical Status Classification score, auto-immune disorders or use of immuno-suppressive drugs, inflammatory bowel disease, obesity, use of alcohol, tobacco, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, high-dose aspirin, chronic obstructive pulmonary disorder agents, and anti-diabetics.

DISCUSSION

In this large population-based nationwide cohort study of patients who underwent CRC surgery, more than one-tenth had filled prescriptions for glucocorticoids within the year before their surgery date. We observed that prevalent users of oral glucocorticoids had markedly increased 30-day mortality compared to patients not exposed to any glucocorticoids. Among new users, mortality was almost twofold higher than among non-users. Risk estimates for users of inhaled, intestinal-acting and mixed glucocorticoids were not increased. We found that respiratory diseases caused death among glucocorticoid users more often than non-users.

The pathophysiological mechanisms underlying our findings are not clear. Glucocorticoids are involved in the regulation of various physiological processes maintaining homeostasis.[6] At supraphysiological doses, glucocorticoids suppress immune activity, proliferation and protein synthesis, and alter metabolism and endocrine systems[29] which may all interfere with postoperative healing processes and recovery. Also,

Table 5 | Immediate cause of death within 30 days after colorectal cancer surgery among users and non-users of any glucocorticoids, Denmark, 2001–2011

Cause of death	No glucocorticoid use 1968 deaths, *N* (%)	Any glucocorticoid use 751 deaths, *N* (%)	Prevalence rate ratio (95% CI)
Cancer	501 (25.5)	192 (25.6)	1.00 (0.86, 1.16)
Infections	261 (13.3)	97 (12.9)	0.98 (0.78, 1.22)
Heart disease	224 (11.4)	73 (9.7)	0.87 (0.67, 1.12)
Circulatory disease	88 (4.5)	34 (4.5)	1.01 (0.69, 1.49)
Respiratory disease	177 (9.0)	97 (12.9)	1.39 (1.10, 1.75)
Gastrointestinal disease	9 (0.5)	5 (0.7)	1.45 (0.49, 4.32)
Urogenital disease	39 (2.0)	22 (2.9)	1.46 (0.87, 2.45)
Other	486 (24.7)	192 (25.6)	1.02 (0.89, 1.19)
Missing	183 (9.3)	39 (5.2)	0.58 (0.41, 0.81)

glucocorticoid therapy may blur symptoms of early post-operative complications requiring intervention, thereby delaying diagnosis and treatment, and subsequently leading to death. We found no evidence that inhaled or intestinal-acting glucocorticoids influenced mortality, consistent with their limited systemic bioavailability.[30, 31]

Our study is the first to provide evidence regarding the association between pre-admission glucocorticoid use and mortality following CRC surgery. We found that post-operative mortality rates were substantial higher among prevalent users of oral glucocorticoids than non-users whose mortality corresponded to previous international reportings.[2–4] None of the few previous studies on glucocorticoids and post-operative mortality restricted to CRC patients.[11, 12, 32] Such patients may differ substantially from those undergoing surgery for nonmalignant indications, in terms of the extent of the operation, older age and higher level of comorbidity[33] and studies are thus difficult to compare. Moreover, mortality was not the main endpoint of interest in any previous study and mortality data were limited by a lack of adjustment in multivariate models[12, 32] and by not including 95% CIs or *P*-values.[11]

Major study strengths include its population-based design, encompassing all CRC patients treated with surgery during the study period. Our cohort was well-defined due to use of computerised registries with complete follow-up.[34, 35] In addition, accurate data on prescriptions and diagnoses eliminated recall bias and allowed adjustment for potential confounders.[20, 23] The availability of information from the DCDR allowed us to explore conditions leading to death.[27]

Several issues should be considered when interpreting our study results. The potential for misclassification is a concern. Because the NRMP contains no information on adherence, misclassification of non-adherant patients as users could occur. However, copayment requirements and beneficial effects on serious medical conditions increase the likelihood that filled prescriptions reflect actual use. Also, we lacked data on glucocorticoids dispensed in hospitals, potentially leading to underestimation of actual use. Still, results of stratified analyses based on hospitalisations and corresponding diagnoses did not differ substantially from results of the main analysis, although some estimates were imprecise. Finally, inaccurate coding of causes of death may influence the prevalence rate ratios. However, such misclassification is unrelated to glucocorticoid exposure and would thus bias the estimates towards the null. Data from the DCDR are not regularly validated and the reproducibility of diagnoses appearing on death certificates during the study period is unclear.[27]

Our nonrandomised study may be vulnerable to uncontrolled confounding, particularly confounding by the indication for glucocorticoid therapy. Unfortunately, the prescription data include no information on the indication for glucocorticoids, however, we adjusted for a range of comorbid conditions and treatments associated with their use. Unexpected, we observed that almost one-third of glucocorticoid users had no recordings of comorbidity (CCI = 0). These patients may have been treated solely by general practitioners whose patients' files are not logged in the DNRP. Although the predictive value of the recording of CCI conditions in the DNRP is high,[36] completeness may be less than 100%. In our stratified analysis, we observed a significant effect of glucocorticoids for patients with CCI = 0 that vanished for patients with CCI score greater than 0, which may reflect effects of therapy among those with less severe disease

(not requiring hospitalisation) or effects of comorbidity not captured in the DNRP. We included intensity of use as a marker of disease severity, but results were inconclusive. Interestingly, prevalent use (merely driven by new use) but not recent or former use of oral glucocorticoids was associated with post-operative mortality, suggesting that treatment initiation or disease onset rather than accumulated underlying medical indications for glucocortiocids led to the increase in mortality.

We had incomplete data on lifestyle factors, such as smoking, alcohol use, and obesity. However, adjustment for associated diseases accounted for at least some of the effect of these factors. Furthermore, mortality was not elevated in recent or former users of systemic glucocorticoids, who are likely to have lifestyles relatively similar to those of prevalent users.

In conclusion, in this large population-based study, prevalent use, particulary new use, of oral glucocorticoids was associated with an increased 30-day mortality after CRC surgery compared to patients not exposed to any glucocorticoids. Although we were not able to disentangle whether glucocorticoids themselves or underlying disease activity contributed to post-operative mortality, clinicians should be aware of the association in order to refine pre-operative risk assessment, surgical treatment and perioperative care.

AUTHORSHIP

Guarantor of the article: Eva Bjerre Ostenfeld.

Author contributions: HTS, RE and EBO designed the study. EBO and AHR was responsible for acquiring the data and conducting the analysis. EBO drafted the first version of the manuscript, but all authors (EBO, RE, AHR, OTU and HTS) contributed to the interpretation of the findings and the critical revision of the draft. All authors approved the final version of the manuscript.

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APPENDIX

Anatomical Therapeutic Classification (ATC) codes and International Classification of Disease (ICD) codes version 8 and 10 used in the present study.

ATC-codes defining glucocorticoids

Glucocorticoids	ATC-codes
Systemic glucocorticoids*	
Betamethasone	H02AB01
Dexamethasone	H02AB02
Methylprednisone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07
Triamcinolone	H02AB08
Hydrocortisone	H02AB09
Cortisone	H02AB10
Inhaled glucocorticoids	
Beclomethason	R03BA01
Budesonide	R03BA02
Flunisolid	R03BA03
Fluticasone	R03BA05
Mometason	R03BA07
Salmeterole	R03AK06
Formoterole	R03AK07
Intestinal-acting glucocorticoids†	
Prednisolone	A07EA01
Hydrocortisone	A07EA02
Prednisone	A07EA03
Betamethason	A07EA04
Tixocortol	A07EA05
Budesonide	A07EA06
Beclometason	A07EA07

* Hereof injections identified by the variable `dosform'!

† Medications with local effects in the intestines, e.g. foam or tablets that release active substances in the intestines.

ICD codes defining a modified Charlson Comorbidity Index

Disease	ICD-8	ICD-10	Score
Myocardial infarction	410	I21; I22; I23	1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
Cerebrovascular disease	430–438	I60–I69; G45; G46	1
Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30	1
Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1	1
Connective tissue disease	712; 716; 734; 446; 135.99	J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Ulcer disease	530.91; 530.98; 531–534	M05; M06; M08; M09;M30;M31	1
Mild liver disease	571; 573.01; 573.04	M32; M33; M34; M35; M36; D86	1
Diabetes type 1/type 2	249.00; 249.06; 249.07; 249.09	K22.1; K25-K28	1
Any tumour	140–194 (excluding 153–154)	C00-C75 (excluding C18–C20)	2
Hemiplegia	250.00; 250.06; 250.07; 250.09	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	2
Moderate to severe renal disease	344	E10.0, E10.1; E10.9	2
Diabetes with end organ damage type 1/type 2	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	E11.0; E11.1; E11.9	2
Moderate/severe liver disease		G81; G82	3
Metastatic solid tumour	195–198; 199	C76-C80	6
AIDS	249.01–249.05; 249.08	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61	6

ICD codes defining comorbidity not included in the Charlson Comorbidity Index

Diseases	ICD-8 codes	ICD-10 codes
Inflammatory bowel disease	563.01, 563.19, 563.99, 569.04	K50, K51 (excl 51.4), M07.4, M07.5
Obesity	277	E65-E66
Autoimmune diseases		
Haematological system		
Autoimmune haemolytic anaemia	283.90	D59.0, D59.1
Ideopatic thrombocytopenic purpura	287.10	D69.3
Endocrine system		
Graves disease	242.00, 242.01, 242.08, 242.09	E05.0
Autoimmune thyroiditis	244.01, 245.03	E06.3
Addison's disease	255.10	E27.1
Central nervous/neuromuscular system		
Multiple sclerosis	340*	G35*
Myasthenia gravis	733.09	G70.0
Gastrointestinal/hepatobilliary system		
Pernicious anaemia	281.00, 281.01, 281.08, 281.09	D51.0
Coelic disease	269.00	K90.0
Primary biliary cirrhosis	571.90	K74.3
Skin		
Vitiligo	709.01	L80
Atopic dermatitis	691.00	L20*
Pemphigus/pemphigoid	694.00–694.03, 694.05	L10.0, L10.1, L10.2, L10.4, L12.0
Dermatitis herpetiformis	693.08, 693.09	L13.0
Psoriasis	696.09, 696.10, 696.19	L40*, M07.0–M07.3

ATC-codes defining medication use

Medication	ACT code
NSAIDs	M01A
Aspirin high-dose 500 mg	N02BA01, N02BA51
Anti-diabetics	A10A, A10B, A10X
Immune suppressants	L01, L04, A07EC01–04
Cardiovascular drugs	
ACE-inhibitors	C09
β-blocking agents	C07
Calcium antagonists	C08D
Other anti-hypertensives	C02
Diuretics	C03
Nitrates	C01DA, C01DX
Statins	C10AA
Aspirin low dose 75–150 mg	B01AC06 N02BA01
Respiratory drugs	R03 exept R03AK06, R03AK07, and R03BA

ICD-10 codes defining causes of death

Cause of death	ICD-10 codes
Cancer	C00–97
Infections	A00–B99, K35–K37, K65, K67, N00–N01, N10–N12, N30, N70–N77
Cardiac conditions	I00–25, I27, I30–I51
Circulatory conditions	I26, I28, I60–I99
Respiratory conditions	J00–J22, J30–J99
Gastrointestinal conditions	K00–K31, K38–K64, K66, K70–K93
Urogenital conditions	N02–N08, N13–29, N31–N64
Other conditions	All other ICD-10 codes

Paper III

Title: Preadmission use of glucocorticoids and anastomotic leakage after colon and rectal cancer resection: a Danish population-based cohort study

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Running head: Glucocorticoids and anastomotic leakage

ABSTRACT

Objective: To examine whether preadmission glucocorticoid use increases the risk of anastomotic leakage after colon or rectal cancer resection.

Background: Glucocorticoids impair wound healing in skin, however, their effect on colorectal anastomoses remains controversial.

Methods: In this population-based cohort study, we identified all patients in Denmark who had a primary anastomosis after a colorectal cancer resection (2001-2011) by linking medical registries. Participants that filled their most recent glucocorticoid prescription ≤90, 91-365, and >365 days before their surgery date were characterized as current, recent, and former users, respectively. We calculated absolute risk of anastomotic leakage within 30 days postoperatively and computed odds ratios (ORs) as a measure of relative risk using logistic regression models, adjusting for potential confounders.

Results: Of the 18,190 colon cancer patients included, anastomotic leakage occurred in 1184 (6.5%). Absolute risk of leakage was 7.5% (OR=1.24, 95% confidence interval [CI]: 0.82-1.88) among current users of oral glucocorticoids and 8.7% (OR=1.43, 95% CI: 0.87-2.34) among recent users, versus 6.4% among never-users. No associations were observed for other categories of oral, inhaled, or intestinal-acting glucocorticoids. Anastomotic leakage occurred in 695 (13.2%) of 5284 rectal cancer patients. Estimates were slightly increased for almost any glucocorticoid category and greatest for current use of inhaled glucocorticoids (absolute risk=17.7%, versus 12.8% among never-users; OR=1.91, 95% CI: 1.11-3.30).

Conclusions: Preadmission glucocorticoids increased the risk of leakage of primary anastomoses mainly after rectal cancer resection. However, differences in absolute risk were small and glucocorticoid use per se should probably not contraindicate a primary anastomosis.

INTRODUCTION

Anastomotic leakage is a serious complication after colorectal cancer (CRC) resection that inevitably increases morbidity, mortality, and hospital resource utilization.[1, 2] Moreover, leakage may negatively affect the risk of local cancer recurrence and long-term survival.[3]

Synthetic glucocorticoids are potent immune-suppressive drugs that are widely used to treat various chronic inflammatory diseases and some malignancies.[4] Although glucocorticoids have been associated with impaired wound healing in skin,[5, 6] their effect on colon and rectal anastomoses is controversial.[7-18] Some animal studies of intestinal anastomoses have demonstrated that glucocorticoids impair healing and reduce the tensile strength of wounds,[7-9] while others have not.[10, 11] Clinical data are also mixed. Several reports have indicated that glucocorticoid use might predict leakage,[12-15] although others have not.[16-18] Unfortunately, identified studies were limited by sparse data (including 0-4 exposed cases)[12-18] and the consideration of colon and rectal surgery together rather than separately.[12-14, 17] It is important to distinguish between colon and rectal procedures because the anatomy and surgical techniques differ, leading to substantial differences in leakage rates: 3-4% after colonic surgery compared with 11-12% after rectal surgery.[19]

Based on available evidence, surgeons may question the safety of primary anastomoses in glucocorticoid users. To address the limitations of earlier studies, we examined associations between glucocorticoid administration and the risk of anastomotic leakage in a large nationwide cohort of colon and rectal cancer patients.

METHODS

Setting

We conducted a cohort study in the setting of the entire Danish population, comprising cumulatively over the study period approximately 6.5 million individuals. The Danish national health care provides free access to tax-supported health services for all residents and refunds parts of patient costs for most prescribed drugs. Health service utilization is registered to

individual patients by use of the personal identification number assigned to each Danish citizen at birth and to residents upon immigration. The use of this system facilitates unambiguous individual-level linkage of nationwide registries.[20]

Colon and rectal cancer patients

We identified all 23,474 residents of Denmark who had a colonic or rectal cancer resection and primary anastomosis between May 1, 2001 and December 31, 2011, and who were reported to the Danish Colorectal Cancer Group (DCCG) database[21] (Figure 1).

Beginning in 2001, the DCCG has registered all patients with an incident colon or rectal adenocarcinoma diagnosed or treated in surgical departments in Denmark. Completeness of cancer registration in the database was 98-100% during 2001-2010.[22] Data regarding patient, tumor, and treatment characteristics, as well as postoperative outcomes including anastomotic leakage (arbitrarily defined as those occurring within 30 days postoperatively) are collected by the DCCG using standardized forms that are completed by physicians.[21] We retrieved the DCCG data regarding pre-operative fitness according to the American Society of Anesthesiologists' (ASA) Physical Status Classification score;[23] cancer site; tumor extent, node involvement, and distant metastases allowing for staging (recorded as localized or non-localized if the cancer involved nodes or distant organs);[24] as well as date of surgery, surgical urgency (planned or acute), approach (laparoscopy or laparotomy), and procedure (type of resection), perioperative blood transfusion, and postoperative anastomotic leakage. Finally, we obtained information regarding smoking status, which is recorded from patient questionnaires.

Use of glucocorticoids

The National Registry of Medicinal Products (NRMP) has automatically recorded prescriptions dispensed at Danish pharmacies with complete coverage since 1995.[25] Each record logs information about the type and quantity of medication dispensed according to the *Anatomical Therapeutic Chemical* (ATC) *Classification System* and the prescription redemption date. We used the NRMP to identify all prescriptions of oral, inhaled, and intestinal-acting glucocorticoids redeemed before the CRC surgery date (see Table, Supplementary Digital Content 1 for ATC codes). Intestinal-acting glucocorticoids included rectally administered formulas, as well as

capsules that release active substances into the ileum or proximal colon. Based on methods used previously,[26] we categorized exposure into the following five main groups: 1) lack of use ("never-use"), 2) oral glucocorticoid use only, 3) inhaled glucocorticoid use only, 4) intestinal-acting glucocorticoid use only, and 5) mixed use (i.e., treatment with glucocorticoids from at least two of the previous three groups). We further categorized oral and inhaled glucocorticoid use according to the timing of use as: current use (most recent prescription filled within 90 days before the surgery date), recent use (most recent prescription filled within 91-365 days before the surgery date), and former use (most recent prescription filled more than 365 days before the surgery date). Intestinal-acting glucocorticoid use was not divided into subcategories owing to the paucity of individuals in the group. The definitions of glucocorticoid use are summarized in Table 1.

Comorbidity and medication

The Danish National Registry of Patients (DNRP) has tracked all non-psychiatric hospitalizations since 1977 and outpatient visits since 1995, including essentially all specialist care in the country.[27] The DNRP records dates of admission and discharge, surgical and diagnostic procedures, and discharge diagnoses coded by physicians according to the 8th revision of the *International Classification of Diseases* (ICD-8) until the end of 1993 and the 10th revision (ICD-10) since then. Using records from the DNRP and the Charlson Comorbidity Index (CCI), we summarized each patient's medical history from 1977 until the surgery date, excluding colon or rectal cancer diagnoses (see Table, Supplementary Digital Content 2 for ICD codes defining a modified CCI).[28] The CCI assigns between one and six points to a range of diseases, which are then summed to obtain an aggregate score. We grouped patients according to their CCI score: 0 (low comorbidity), 1–2 (moderate comorbidity), and 3+ (severe comorbidity). In addition, we obtained recorded diagnoses of inflammatory bowel disease (IBD), autoimmune disease, alcoholism, and obesity because these diagnoses are not included in the CCI (see Table, Supplementary Digital Content 3 for ICD-codes).

Using the NRMP, we also identified filled prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs), medications for chronic obstructive pulmonary disease (COPD) other than glucocorticoids, and immuno-suppressants (see Table, Supplementary Digital Content 4 for ATC-codes).

Patients with anastomotic leakage after colon or rectal cancer resection

We identified patients with anastomotic leakage recorded in the DCCG database or in the DNRP using the ICD codes associated with anastomotic leakage or surgery codes for reoperation of anastomotic leakage (see Table, Supplementary Digital Content 5 for ICD-10 codes).

Statistical analysis

We analyzed colon and rectal cancer patients separately. We tabulated the frequencies of glucocorticoid use with regard to the characteristics of the patient, the tumor, and the surgery. According to our predefined glucocorticoid exposure groups, we estimated absolute risk of anastomotic leakage within 30 days postoperatively and 95% confidence intervals (CIs) using Jeffreys' method.[29] Corresponding risk differences were calculated subtracting the estimate for never-use from those for glucocorticoid users. We computed odds ratios (ORs) as a measure of relative risk and 95% CIs associating anastomotic leakage after colon or rectal cancer surgery with glucocorticoid exposure in crude and adjusted logistic regression models. Based on their associations with both anastomotic leakage risk and glucocorticoid use, we included the following covariates in the model as potential confounders: sex, age, CCI score, ASA score (≤2, >2, unknown), history of IBD, alcoholism/use of disulfiram (single variable), smoking status at the time of the surgery (current, former, never or unknown), and COPD medications as its proxy, as well as non-aspirin NSAID prescriptions filled within 90 days before the surgery date.[30, 31]Missing data (e.g., for smoking) were categorized separately and included in the analysis (see Table 2 for a description of categories within each covariate). To examine variations in postoperative anastomotic leakage, ORs were calculated within subgroups of sex, age, year of surgery, cancer site, cancer stage, CCI score, ASA score, and smoking status, as well as surgical urgency and approach, type of procedure, and perioperative blood transfusion.

In sensitivity analyses, we first changed the time window for filled glucocorticoid prescriptions to 60 and 120 days before the surgery dates. Second, we included patients with prescriptions for both oral and/or injected glucocorticoids as systemic glucocorticoid users, in conformity with the ATC classification of systemic glucocorticoids. Third, we restricted anastomotic leakage to patients who were re-operated upon to heighten the predictive value of our outcome. Finally, to handle missing DCCG data on potential confounders, e.g., smoking status, we used multiple imputations

of missing values[32, 33] generating twenty imputed datasets. ORs were calculated as the average ORs of the twenty datasets, corrected for between- and within-imputation variation.[34-36] The imputation model included surgical procedures, outcomes and all variables from Table 2. Never-use of any glucocorticoids consistently served as the comparison cohort.

Statistical analyses were performed using Stata 12.0 (StataCorp LP, College Station, TX, USA) and SAS 9.2 (SAS Institute Inc., Cary, North Carolina). The study was approved by the Danish Data Protection Agency (record number 2011-41-6151) and the National Board of Health.

RESULTS

Colon Cancer Patients

We identified 18,190 colon cancer patients that had a primary anastomosis after tumor resection during 2001-2011. We found that 2170 study participants (11.9%) had at least one prescription for glucocorticoids within 1 year before their surgery date (Table 2). Glucocorticoid users were more likely than never-users to be female and elderly (median age 74 years versus 71 years). Compared with never-users, severe comorbidity and a high ASA score were almost twice as prevalent among glucocorticoid users, although 34.9% of users had a CCI score of 0. Prescriptions for NSAIDs and COPD agents were also more prevalent among these patients.

Anastomotic leakage occurred in 1184 colon cancer patients (6.5%). Glucocorticoid users contributed 287 cases (24.2%), yielding an overall absolute risk of leakage of 6.9% versus 6.4% among never-users (Table 3a). Absolute risk did not differ substantially among subgroups of users of oral, inhaled, intestinal-acting, or mixed glucocorticoids.

Compared with never-users, any glucocorticoid use was not associated with an increased relative risk of anastomotic leakage (Table 3a). Although estimates were imprecise, relative risk was modestly increased among current (adjusted odds ratio (aOR)=1.24, 95% CI: 0.82-1.88) and recent (aOR=1.43, 95% CI: 0.87-2.34) users of oral glucocorticoids, as well as among users of intestinal-acting glucocorticoids (aOR=1.47, 95% CI: 0.56-3.84). We observed no association for inhaled glucocorticoids. With the exception of alcoholism (aOR=2.58, 95% CI: 1.23-5.39), the association

between glucocorticoid use and anastomotic leakage did not differ materially across strata of covariates (see Figure, Supplementary Digital Content 6).

In sensitivity analyses in which the time window for the definition of current use was changed to 60/120 days before surgery, results were close to those in the main analysis using either cutoff (data not shown). Including prescriptions of glucocorticoid injections together with oral use did not materially change results (data not shown). When we restricted analyses to anastomotic leakages that required surgical intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown). Imputation of missing values on surgical procedures and covariates did not change the associations observed (data not shown).

Rectal Cancer Patients

Of the 5284 rectal cancer patients resected, 458 (9%) used glucocorticoids within 1 year before surgery. Among rectal cancer patients, glucocorticoid users were more likely than never-users to be female and elderly (median age 68 years versus 66 years) (Table 2). Similarly, severe comorbidity, high ASA score, and prescriptions of NSAIDs and COPD agents were more prevalent among patients using glucocorticoids.

Anastomotic leakage occurred in 695 rectal cancer patients (13.2%). Overall, the absolute risk of leakage was 14.6% among glucocorticoid users versus 12.8% among never-users. Absolute risks among current, recent, and former users of oral glucocorticoids were; 15.9%, 13.0, and 16.3%, respectively. Current users of inhaled glucocorticoids had the highest absolute risk (17.7%); recent users of inhaled glucocorticoids and those using mixed glucocorticoids had the lowest risks (11.1% and 11.7%, respectively). Anastomotic leakage occurred among 16.7% of users of intestinal-acting glucocorticoids.

Compared with never-users, glucocorticoid use was associated with an increased risk of anastomotic leakage after rectal cancer resection (aOR=1.36, 95% CI: 1.08-1.72) (Table 3b). Relative risks were modestly increased in all subgroups of oral glucocorticoid users (current use: aOR=1.28, 95% CI: 0.64-2.56; recent use: aOR=1.22, 95% CI: 0.51-2.92; and former use: aOR=1.42, 95% CI: 1.00-2.01). Among users of inhaled glucocorticoids, current users had the highest risk:

aOR=1.91 95% CI: 1.11-3.30. Estimates for the use of intestinal-acting and mixed glucocorticoids showed no strong associations. Our stratified analysis revealed no major difference across strata in the relative association between glucocorticoid use and postoperative rectal anastomotic leakage (see Figure, Supplementary Digital Content 7).

After changing the definition of current use to a 60-day window before surgery, ORs were somewhat higher for current use of oral glucocorticoids (aOR=1.63, 95% CI: 0.77-3.46) and somewhat lower for recent users (aOR=0.97, 95% CI: 0.44-2.17). However, the 95% CIs for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cutoff (data not shown). Including prescriptions of glucocorticoid injections together with oral use did not alter the main analysis of oral use (data not shown). When we restricted analyses to anastomotic leakages that required reoperation, we observed 215 (31%) fewer outcomes. However, results did not differ materially (data not shown). Also, imputation of missing values on surgical procedures and covariates did not change the associations observed (data not shown).

DISCUSSION

In this nationwide population-based study, we found that current and recent users of oral glucocorticoids exhibited a modest increase in the relative risk of anastomotic leakage after colon cancer resection, but estimates were imprecise. Among rectal cancer patients, relative risk increased moderately for almost any subgroup of glucocorticoid use. For both cancers, differences in absolute risk among current and recent users versus never users were small, and the clinical impact of their use might therefore be limited.

This study extends previous research because it included considerably more subjects than previous studies and provided detailed data on different types of glucocorticoids and the timing of their use. In addition, we analyzed colon and rectal cancer patients separately. Previous studies that examined whether glucocorticoids predict anastomotic leakage after CRC resection had inconsistent results.[12-18] Based on 12 studies published between 1996 and 2012, a recent review provided combined rates for leakage: 6.8% (95% CI: 5.5-9.1%) in 1034 patients exposed to steroids

preoperatively versus 3.3% (95% CI: 2.9-3.6%) in 8410 unexposed patients.[37] Overall risk was higher in our cohort of colon and rectal cancer patients. Comparison of our findings to previous studies is difficult because of differences in definitions of exposure, study populations, indications for resection, and surgical procedures performed. Moreover, the lack of a standard definition of anastomotic leakage[38] is likely to explain some of the disparity.

Other major strengths of the present study include its population-based design within the setting of a tax-supported, uniformly organized health care system. Using electronic registries, we had accurate data on exposure and covariates.[25, 27, 39] The DCCG database provided a complete cohort of CRC patients during the study period, as well as detailed information about surgical treatment and anastomotic leakage.[22] Recording of postoperative complications in the DCCG registry has been validated against medical records and demonstrated almost 100% accuracy.[40] Nonetheless, because there are no clear standards for the recording of anastomotic leakage,[38] completeness and validity in the DCCG database may be imperfect. To assure complete capture of leakage cases, we also included those recorded in the DNPR, which increased the number of cases by 9%. Furthermore, in a sensitivity analysis we restricted to those that required reoperation to increase the validity of the outcome, which did not change the observed associations materially.

Although data in the NRMP are complete,[25] some limitations exist. First, the registry includes no detailed information regarding adherence, and misclassification of non-adherent patients as users is possible. However, copayment requirements and beneficial effects on serious symptoms increase the likelihood that filled prescriptions reflect actual use. Second, glucocorticoids dispensed during hospitalization and outpatient clinic visits are not logged in the NRMP. Nonetheless, stratified analyses based on discharge diagnoses did not differ materially from those of the main analysis. Third, we had no data about over-the-counter NSAIDs, which account for an estimated 14% of total use in Denmark.[41] These drugs may be associated with both glucocorticoid use and anastomotic leakage,[31] and our adjustment for this potential confounder may thus be imperfect.

Glucocorticoid users generally differ from non-users because of the diseases for which glucocorticoids are prescribed. This situation may lead to confounding by indication. Unfortunately, the NRMP provides no data regarding the indication for glucocorticoids; however,

we adjusted for comorbid conditions and treatments associated with their use. Unexpectedly, we observed that almost one-half of the glucocorticoid users had no record of comorbidity (CCI=0). Although some of these patients may have been treated solely by general practitioners (whose patients' files are not logged in the DNRP), recording of CCI conditions from hospitalizations and outpatient visits may be incomplete. Finally, we cannot exclude the possibility of some uncontrolled confounding by lifestyle factors. Data regarding smoking were incomplete (27% missing) and might suffer from underreporting. Although, we adjusted for smoking and associated diseases/COPD agents as proxies, residual confounding may explain the apparent association between inhaled glucocorticoids and anastomotic leakage in rectal cancer patients. Given their limited bioavailability, we would not expect a stronger association for inhaled glucocorticoids than for oral glucocorticoids.[42] Imputation of missing values, however, did not change our estimates.

In conclusion, we found that preadmission glucocorticoid use increased the risk of anastomotic leakage mainly after rectal cancer resection. However, differences in absolute risk were small, and glucocorticoids per se should probably not contraindicate a primary anastomosis.

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Tables (Paper III)

Table 1. Glucocorticoid exposure definitions

Never-users	Patients with no redemptions of any prescribed glucocorticoids (oral, inhaled, or intestinal-acting) before the surgery date
Users of oral or inhaled glucocorticoids[1]	Patients who filled 1 or more prescriptions for a particular glucocorticoid type but no prescriptions for the other two types of glucocorticoids before the surgery date
Current users	Patients who filled their most recent prescription within 90 days before the surgery date
Recent users	Patients who filled their most recent prescription within 91-365 days before the surgery date
Former users	Patients who filled their most recent prescription more than 365 days before the surgery date
Users of intestinal-acting glucocorticoids	Patients who filled 1 or more prescriptions for intestinal-acting glucocorticoids before the surgery date
Users of mixed glucocorticoids	Patients who filled prescriptions for more than one type of glucocorticoid before the surgery date

[1]Categories of glucocorticoid users were defined for both oral and inhaled glucocorticoids.

Table 2. Characteristics of patients who underwent resection for colon or rectal cancer, by use of any glucocorticoids, Denmark, 2001-2011.

Characteristics	Colon cancer		Rectal cancer	
	No glucocorticoid use N=14 041 N (%)	**Glucocorticoid use N=4149 N (%)**	**No glucocorticoid use N=4317 N (%)**	**Glucocorticoid use N=967 N (%)**
Sex				
Female	7122 (50.7)	2369 (57.1)	1737 (40.2)	463 (47.9)
Male	6919 (49.3)	1780 (42.9)	2580 (59.8)	504 (52.1)
Age, years				
<60	2399 (17.1)	482 (11.6)	1187 (27.5)	224 (23.3)
60-69	3841 (27.4)	949 (22.9)	1617 (37.5)	321 (33.2)
70-79	4688 (33.4)	1582 (38.1)	1152 (26.7)	326 (33.7)
80+	3113 (21.2)	1136 (27.4)	361 (8.4)	96 (9.9)
Year of resection				
2001-2004	4767 (34.0)	1074 (25.9)	1418 (32.9)	272 (28.1)
2005-2008	5327 (37.9)	1642 (39.6)	1651 (38.2)	372 (38.5)
2009-2011	3947 (28.1)	1433 (34.5)	1248 (28.9)	323 (33.4)
Stage				
Localized	7192 (51.2)	2261 (54.5)	2460 (57.0)	557 (57.6)
Non-localized	6510 (46.4)	1785 (43.0)	1775 (41.1)	390 (40.3)
Unknown	339 (2.4)	103 (2.5)	82 (1.9)	20 (2.1)
CCI score				
0	8557 (60.9)	1448 (34.9)	3131 (72.5)	490 (50.7)
1-2	4074 (29.0)	1812 (43.7)	970 (22.5)	355 (36.7)
3+	1410 (10.0)	889 (21.4)	216 (5.0)	122 (12.6)
ASA score				
≤2	10 616 (75.6)	2575 (62.1)	3827 (88.3)	766 (79.9)
>2	2812 (20.0)	1420 (34.2)	432 (10.0)	181 (18.7)
Unknown	613 (4.4)	154 (3.7)	77 (1.8)	23 (2.4)
IBD	91 (0.7)	108 (2.6)	25 (0.6)	6 (0.8)
Auto-immune disorders or immunosuppressive drug use	90 (0.6)	256 (6.2)	26 (0.6)	50 (5.2)
Obesity	405 (2.9)	208 (5.0)	77 (1.8)	29 (3.0)
Alcoholism	488 (3.5)	159 (3.8)	160 (3.7)	34 (3.5)
Tobacco use				
Current use	2088 (14.9)	563 (13.6)	819 (19.0)	182 (18.8)
Former use	4159 (29.6)	1429 (34.4)	1529 (35.4)	359 (37.1)
Never use	3569 (25.4)	898 (21.6)	1155 (26.8)	244 (25.2)
Unknown	4225 (30.1)	1259 (30.3)	814 (18.9)	182 (18.8)
NSAIDs	3337 (23.8)	1180 (28.4)	806 (18.7)	222 (23.0)
COPD medications	1,547 (11.0)	2404 (57.9)	403 (9.3)	550 (56.9)
Surgical urgency				
Planned	12 140 (86.5)	3617 (87.2)	4295 (99.5)	963 (99.6)
Acute	1894 (13.5)	532 (12.8)	22 (0.5)	4 (0.4)
Unknown	7 (0.1)	0 (0.0)	7 (0.1)	0 (0.0)
Surgical approach				
Laparoscopy	3446 (24.5)	1111 (26.8)	972 (22.5)	239 (24.7)
Laparotomy	10 595 (75.5)	3038 (73.2)	3345 (77.5)	728 (75.3)

Surgical Procedure				
Ileocecal resection	45 (0.3)	8 (0.2)	-	-
Right-sided hemicolectomy	6925 (49.3)	2239 (54.0)	-	-
Colon transversum resection	356 (2.5)	101 (2.4)	-	-
Left-sided hemicolectomy	1546 (11.0)	447 (10.8)	-	-
Sigmoid colon resection	4791 (34.1)	1238 (29.8)	-	-
Other resections	15 (0.1)	8 (0.2)	-	-
Colectomy and IRA	363 (2.6)	108 (2.6)	-	-
Rectal resection	-	-	4317	967
Perioperative blood transfusion				
Yes	3312 (23.6)	1120 (27.0)	830 (19.2)	189 (19.5)
No	10 611 (75.6)	2999 (72.3)	3465 (80.3)	774 (80.0)
Missing/Unknown	118 (0.8)	30 (0.7)	22 (0.5)	4 (0.4)

Abbreviations: CRC, colorectal cancer; CCI, Charlson Comorbidity Index, ASA, American Society of Anesthesiologists Physical Status Classification; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease; IRA, ileorectal anastomosis

Table 3a. Risk Differences and odds ratios (ORs), associating use of glucocorticoids and anastomotic leakage following colon cancer resection, Denmark, 2001-2011.

Glucocorticoid use	Study population N=18 190 n (%)	Leakage N=1184 n (%)	Leakage risk % (95% CI)	Risk difference % (95% CI)[2]	Unadjusted OR (95% CI)	Adjusted[1] OR (95% CI)
No use	14 041 (77.2)	897 (75.8)	6.4 (6.0-6.8)	Referent	Referent	Referent
Any use	4149 (22.8)	287 (24.2)	6.9 (6.0-6.8)	0.5 (-0.3-1.4)	1.09 (0.95-1.25)	1.05 (0.89-1.23)
Oral use						
Current use	345 (1.9)	26 (2.2)	7.5 (5.1-10.7)	1.1 (-1.7-4.0)	1.19 (0.80-1.79)	1.24 (0.82-1.88)
Recent use	207 (1.1)	18 (1.5)	8.7 (5.4-13.1)	2.3 (-1.6-6.2)	1.40 (0.86-2.27)	1.43 (0.87-2.34)
Former use	948 (5.2)	53 (4.5)	5.6 (4.3-7.2)	-0.8 (-2.3-0.7)	0.87 (0.65-1.15)	0.90 (0.67-1.20)
Inhaled use						
Current use	434 (2.4)	32 (2.7)	7.4 (5.2-10.1)	1.0 (-1.5-3.5)	1.17 (0.81-1.68)	1.04 (0.70-1.53)
Recent use	252 (1.4)	16 (1.4)	6.3 (3.8-9.9)	-0.0 (-3.1-3.0)	0.99 (0.60-1.66)	0.96 (0.57-1.62)
Former use	742 (4.1)	51 (4.3)	6.9 (5.2-8.9)	0.5 (-1.4-2.3)	1.08 (0.81-1.45)	1.06 (0.78-1.44)
Intestinal-acting use	54 (0.3)	5 (0.4)	9.3 (3.6-19.1)	2.9 (-4.9-10.6)	1.50 (0.59-3.76)	1.47 (0.56-3.84)
Mixed use	1167 (6.4)	86 (7.3)	7.4 (6.0-9.0)	1.0 (-0.6-2.5)	1.17 (0.93-1.47)	1.02 (0.78-1.35)

[1]Adjusted for sex, age, Charlson Comorbidity Index score, American Society of Anesthesiologists Physical Status Classification (ASA) score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorder medications, and non-steroidal anti-inflammatory drugs

[2]Calculated by subtracting the estimate for never-use from those for glucocorticoid users

Table 3b. Risk differences and odds ratios (ORs), associating use of glucocorticoids and anastomotic leakage following rectal cancer resection, Denmark, 2001-2011.

Glucocorticoid use	Study population N=5284 n (%)	Leakage N=695 n (%)	Leakage risk % (95% CI)	Risk difference % (95% CI)[2]	Unadjusted OR (95% CI)	Adjusted[1] OR (95% CI)
No use	4,317 (81.7)	554 (79.7)	12.8 (11.9-13.9)	Referent	Referent	Referent
Any use	967 (18.3)	141 (20.3)	14.6 (12.5-16.9)	1.7 (-0.7-4.2)	1.16 (0.95-1.42)	1.36 (1.08-1.72)
Oral use						
Current use	63 (1.2)	10 (1.4)	15.9 (8.5-26.3)	3.0 (-6.0-12.1)	1.28 (0.65-2.53)	1.28 (0.64-2.56)
Recent use	46 (0.9)	6 (0.9)	13.0 (5.6-24.9)	0.2 (-9.6-10.0)	1.02 (0.43-2.41)	1.22 (0.51-2.92)
Former use	258 (4.9)	42 (6.0)	16.3 (12.2-21.1)	3.4 (-1.2-8.1)	1.32 (0.94-1.86)	1.42 (1.00-2.01)
Inhaled use						
Current use	113 (2.1)	20 (2.9)	17.7 (11.5-25.5)	4.9 (-2.2-12.0)	1.46 (0.89-2.39)	1.91 (1.11-3.30)
Recent use	45 (0.9)	5 (0.7)	11.1 (4.4-22.7)	-1.7 (-11.0-7.5)	0.85 (0.33-2.16)	1.04 (0.40-2.71)
Former use	190 (3.6)	28 (4.0)	14.7 (10.2-20.3)	1.9 (-3.2-7.0)	1.17 (0.78-1.77)	1.39 (0.89-2.17)
Intestinal-acting use	12 (0.2)	2 (0.3)	16.7 (3.6-43.6)	3.8 (-17.3-24.9)	1.36 (0.30-6.22)	1.27 (0.27-5.95)
Mixed use	240 (4.5)	28 (4.0)	11.7 (8.1-16.2)	-1.2 (-5.3-3.0)	0.90 (0.60-1.34)	1.15 (0.72-1.84)

[1]Adjusted for sex, age, Charlson Comorbidity Index score, American Society of Anesthesiologists Physical Status Classification (ASA) score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorder medications, and non-steroidal anti-inflammatory drugs

[2]Calculated by subtracting the estimate for never-use from those for glucocorticoid users

Supplemental Digital Content (Paper lll)

Supplemental Digital Content 1:

Anatomical Therapeutic Classification (ATC) codes and International Classification of Disease (ICD) codes version 8 and 10 used in the present study

Table 1. ATC codes defining glucocorticoids

Glucocorticoids	ATC-codes
Systemic glucocorticoids[a]	
Betamethasone	H02AB01
Dexamethasone	H02AB02
Methylprednisone	H02AB04
Prednisolone	H02AB06
Prednisone	H02AB07
Triamcinolone	H02AB08
Hydrocortisone	H02AB09
Cortisone	H02AB10
Inhaled glucocorticoids	
Beclomethason	R03BA01
Budesonide	R03BA02
Flunisolid	R03BA03
Fluticasone	R03BA05
Mometason	R03BA07
Salmeterole	R03AK06
Formoterole	R03AK07
Intestinal-acting glucocorticoids[b]	
Prednisolone	A07EA01
Hydrocortisone	A07EA02
Prednisone	A07EA03
Betamethason	A07EA04
Tixocortol	A07EA05
Budesonide	A07EA06
Beclometason	A07EA07

[a]Hereof injections identified by the variable "dosform".

[b]Medications with local effects in the intestines, e.g., foam or tablets that release active substances in the intestines.

Supplemental Digital Content 2:

Table 2. ICD codes defining a modified Charlson Comorbidity Index

Disease	ICD-8	ICD-10	Score
Myocardial infarction	410	I21;I22;I23	1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
Cerebrovascular disease	430-438	I60-I69; G45; G46	1
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1	1
Connective tissue disease	712; 716; 734; 446; 135.99	J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Ulcer disease	530.91; 530.98; 531-534	M05; M06; M08; M09;M30;M31;	1
Mild liver disease	571; 573.01; 573.04	M32; M33; M34; M35; M36; D86	1
Diabetes type 1/type 2	249.00; 249.06; 249.07; 249.09	K22.1; K25-K28	1
Any tumor	140-194 (excluding 153-154)	C00-C75 (excluding C18-C20)	2
Hemiplegia	250.00; 250.06; 250.07; 250.09	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	2
Moderate to severe renal disease	344	E10.0, E10.1; E10.9	2
Diabetes with end organ damage type 1/type 2	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	E11.0; E11.1; E11.9	2
Moderate/severe liver disease		G81; G82	3
Metastatic solid tumor	195-198; 199	C76-C80	6
AIDS	249.01-249.05; 249.08	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	6

Supplemental Digital Content 3:

Table 3. ICD-codes defining comorbidity

Diseases	ICD-8 codes	ICD-10 codes
Inflammatory bowel disease	563.01, 563.19, 563.99, 569.04	K50, K51 (excl 51.4), M07.4, M07.5
Alcoholism	291, 303 (excl 303.90), 571.09, 571.10, 577.10, 979, 980	F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, K70, R78.0, T51, Z72.1.

Supplemental Digital Content 4:

Table 4. ATC-codes defining medication use

Medication	**ACT code**
NSAIDs	M01A, N02BA01, N02BA51, B01AC06 N02BA01
COPD medication	R03 exept R03AK06, R03AK07, and R03BA
Disulfiram	ATC N07BB01

Supplemental Digital Content 5:

Table 5. ICD-codes defining Anastomotic leakage

Anastomotic leakage	**ICD-10 code**
Anastomotic leakage diagnosis	DT81.3A
Anastomotic leakage reoperation	KJWF00

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. *2002*.

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9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. *2003*.

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14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

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18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

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20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. *2007*.

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41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. *2009*.

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51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. *2010*.

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54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

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