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Preadmission glucocorticoid use and anastomotic leakage after colon and rectal cancer resection: a Danish cohort study

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Running title: Preadmission glucocorticoids and colorectal anastomoses

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ABSTRACT

Objective: To examine whether preadmission glucocorticoid use increases the risk of anastomotic leakage after colon and rectal cancer resections

Design: A population-based cohort study.

Setting: Denmark (2001-2011).

Participants: We identified all patients who had a primary anastomosis after a colorectal cancer resection by linking medical registries. Participants that filled their most recent glucocorticoid prescription ≤90, 91-365, and >365 days before their surgery date were categorized as current, recent, and former users, respectively.

Main outcome measures: We calculated 30-day absolute risk of anastomotic leakage and computed odds ratios (ORs) using logistic regression models adjusting for potential confounders.

Results: Of the 18,190 colon cancer patients included, anastomotic leakage occurred in 1184 (6.5%). Glucocorticoid use overall was not associated with an increased risk of leakage (6.4% versus 6.9% among never-users; OR 1.05; 95% confidence interval [CI]: 0.89, 1.23). Categories of oral, inhaled, or intestinal-acting glucocorticoids did not affect risk of leakage materially. Anastomotic leakage occurred in 695 (13.2%) of 5284 rectal cancer patients. Glucocorticoid use overall slightly increased risk of leakage (14.6% versus 12.8% among never-users; OR 1.36, 95% CI: 1.08, 1.72). Results did not differ significantly within glucocorticoid categories.

Conclusions: Preadmission glucocorticoids increased the risk of anastomotic leakage mainly after rectal cancer resection. However, absolute risk differences were small and the clinical impact of glucocorticoid use may therefore be limited.

Strengths and limitations of this study

- The study included all Danish patients with colon and rectal cancer who had a primary anastomosis after a colorectal cancer resection during the study period. The study had complete follow-up on all participants.
- Using electronic registries, we had accurate data on glucocorticoid prescriptions
- Because there were no clear standards for the recording of anastomotic leakage during the study period, completeness and validity in the registries may be imperfect.
- The completeness of the Danish National Registry of Patients may vary for different diseases, and we cannot exclude the possibility that confounding by indication influenced our results although we adjusted for comorbidity in multivariate models.

INTRODUCTION

Anastomotic leakage is a serious complication after colorectal cancer (CRC) resection that inevitably increases morbidity, mortality, and hospital resource utilisation.[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 per cent after colonic surgery compared with 11-12 per cent 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.

MATERIALS AND 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 database of the Danish Colorectal Cancer Group[21] (Figure 1). Beginning in 2001, this clinical database 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 per cent 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 Danish Colorectal Cancer Group using standardised forms that are completed by physicians.[21] We retrieved data regarding pre-operative American Society of Anesthesiologists' Physical Status Classification score,[23] cancer site, tumor extent, node involvement, and distant metastases allowing for staging (recorded as localised or non-localised 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 Danish National Registry of Medicinal Products 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 this registry to identify all prescriptions of oral, inhaled, and intestinal-acting glucocorticoids redeemed before the CRC surgery date (see *Supplementary File* 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.

Comorbidity and medication

The Danish National Registry of Patients has tracked all non-psychiatric hospitalisations since 1977 and outpatient visits since 1995, including essentially all specialist care in the country.[27] Recorded information includes 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 Danish National Registry of Patients and the Charlson Comorbidity Index, we summarised each patient's medical history from 1977 until the surgery date, excluding colon or rectal cancer diagnoses (see *Supplementary File* for ICD codes defining a modified CCI).[28] The Charlson Comorbidity Index 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 Charlson Comorbidity Index score: 0 (low comorbidity), 1–2 (moderate comorbidity), and 3+ (severe comorbidity). In addition, we obtained recorded diagnoses of inflammatory bowel disease, autoimmune disease, alcoholism, and obesity because these diagnoses are not included in the Charlson Comorbidity Index (see *Supplementary File* for ICD-codes).

Using the Danish National Registry of Medicinal Products, we also identified filled prescriptions of non-steroidal anti-inflammatory drugs, medications for chronic obstructive pulmonary disease other than glucocorticoids, and immuno-suppressants (see *Supplementary File* for ATC-codes).

Patients with anastomotic leakage after colon or rectal cancer resection

We identified patients with anastomotic leakage recorded in the Danish Colorectal Cancer Group database or in the Danish National Registry of Patients using the ICD codes associated with anastomotic leakage or surgery codes for reoperation of anastomotic leakage (see *Supplementary*

File for ICD-10 codes). Recording of anastomotic leakage in the database is typically based on clinically evident leakage which at the discretion of the surgeon is confirmed by contrast barium enema, computer tomography, or surgery.

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, Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification score (≤2, >2, unknown), history of inflammatory bowel disease, alcoholism/use of disulfiram (single variable), smoking status at the time of the surgery (current, former, never or unknown), and medications for chronic obstructive pulmonary disease as its proxy, as well as prescriptions for non-aspirin non-steroidal anti-inflammatory drugs 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 1 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,

Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification 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 restricted anastomotic leakage to patients who were re-operated upon to heighten the predictive value of our outcome. Leakages that were treated only by non-surgical drainage, e,g., ultrasonic, were not included in this analysis.

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 1). 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 Non-steroidal anti-inflammatory drugs and COPD agents were also more prevalent among these patients.

Table 1 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)	-	-

Table 1. continued				
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 (100.0)	967 (100.0)
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

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 2a). Absolute risk did not differ substantially among subgroups of users of oral, inhaled, intestinal-acting, or mixed glucocorticoids.

Compared with never-users, glucocorticoid use overall was not associated with an increased relative risk of anastomotic leakage (Table 2a). Although not statistically significant, risk was slightly increased among current (adjusted OR (aOR) = 1.24; 95% CI: 0.82, 1.88) and recent (aOR = 1.43; 95% CI: 0.87, 2.34) users of oral glucocorticoids. The relative risk estimate for use of intestinal-acting glucocorticoids was imprecise (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 (Figure 2a).

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). When we restricted analyses to anastomotic leakages that required surgical

Table 2a 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated

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

[b]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

intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown).

Rectal Cancer Patients

Of the 5284 rectal cancer patients resected, 458 (8.7%) 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 1). Similarly, severe comorbidity, high ASA score, and prescriptions of Non-steroidal anti-inflammatory drugs 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 (Table 2b). 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

Table 2b 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated

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

[b]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

(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 2b). 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 (Figure 2b).

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% CI for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cutoff (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).

DISCUSSION

In this nationwide population-based study, we found that current and recent users of oral glucocorticoids exhibited a non-significant modest increase in the relative risk of anastomotic leakage after colon cancer resection. 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 analysed 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.[32] 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[33] 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 organised health care system. Using electronic registries, we had accurate data on exposure and covariates.[25,27,34] The Danish Colorectal Cancer Group database provided a complete cohort of CRC patients during the study period, as well as detailed information about surgical treatment and anastomotic leakage.[22] However, we cannot entirely exclude some selection of study subjects if surgeons were more reluctant to create a primary anastomosis in glucocorticoid users than in never-users. Recording of postoperative complications in the Danish Colorectal Cancer Group database has been validated against medical records and demonstrated almost 100% accuracy.[35] Nonetheless, because there are no clear standards for the recording of anastomotic leakage,[33] completeness and validity in the database may be imperfect. To heighten capture of leakage cases, we also included those recorded in the Danish National Registry of Patients, 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 Danish National Registry of Medicinal Products are complete,[25] some limitations may exist. 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. Also, glucocorticoids dispensed during hospitalisation and outpatient clinic visits are not logged in the Danish National Registry of Medicinal Products. Nonetheless, stratified analyses based on discharge diagnoses did not differ materially from those of the main analysis. Misclassification of anastomotic leakage might also influence our results if glucocorticoid users had a temporary stoma together with their primary anastomosis more often than never-users. Because a diverting stoma may reduce the clinical symptoms of leakage, underreporting among glucocorticoid users could thus bias the estimates towards the null.

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 Danish National Registry of Medicinal Products 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 (Charlson Comorbidity Index score=0). Although some of these patients may have been treated solely by general practitioners whose patients' files are not logged in the Danish National Registry of Patients, recording of Charlson Comorbidity Index conditions from hospitalisations 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/medications for chronic obstructive pulmonary disease 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.[36]

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 the clinical impact of glucocorticoid use may therefore be limited.

CONTRIBUTORSHIP: HTS, RE and EBO designed the study. EBO and AHR were responsible for acquiring the data and conducting the analysis. EBO draftet the first version of the manuscript, but all authors (EBO, RE, AHR, LI, JAB, 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 submitted, including the authorship list.

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Data sharing: No additional data available

Ethical approval: The study was approved by the Danish Data Protection Agency (record number 2011-41-6151) and the National Board of Health. The study did not involve any contact with patients or any intervention, and it was not necessary to access permission from the Danish Ethical Committee.

FIGURE LEGENDS

Figure 1. Flowchart illustrating exclusions of colorectal cancer patients recorded in the Danish Colorectal Cancer Database, 2001-2011.

Figure 2a. Subgroup analysis associating glucocorticoids and anastomotic leakage following colon cancer surgery compared to never-use

Figure 2b. Subgroup analysis associating glucocorticoids and anastomotic leakage following rectal cancer surgery compared to never-use

REFERENCES

1. Kube R, Mroczkowski P, Granowski D, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. *Eur J Surg Oncol*. 2010;36(2):120-124.

2. Frye J, Bokey EL, Chapuis PH, Sinclair G, Dent OF. Anastomotic leakage after resection of colorectal cancer generates prodigious use of hospital resources. *Colorectal Dis*. 2009;11(9):917-920.

3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. 2011;253(5):890-899.

4. Jacobs JWG, Bijlsma JWJ. Glucocorticoid Therapy. In: Firestein GS, Budd RC, Harris ED, McInnes IB, Sergent JS, eds. *Kelly's Textbook of Rheumatology.* 8th ed. 11830 Westline Industrial Drive, St. Louis, MO 63136-3318: W.B. Saunders Company; 2008:863.

5. Anstead GM. Steroids, retinoids, and wound healing. *Adv Wound Care*. 1998;11(6):277-285.

6. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther*. 2002;96(1):23-43.

7. Baca B, Ozben V, Boler DE, et al. Effect of corticosteroid dose and duration of administration on colonic anastomosis. *Inflamm Bowel Dis*. 2010;16(12):2162-2167.

8. Furst MB, Stromberg BV, Blatchford GJ, Christensen MA, Thorson AG. Colonic anastomoses: bursting strength after corticosteroid treatment. *Dis Colon Rectum*. 1994;37(1):12-15.

9. Phillips JD, Kim CS, Fonkalsrud EW, Zeng H, Dindar H. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. *Am J Surg*. 1992;163(1):71-77.

10. Mastboom WJ, Hendriks T, de Man BM, de Boer HH. Influence of methylprednisolone on the healing of intestinal anastomoses in rats. *Br J Surg*. 1991;78(1):54-56.

11. Eubanks TR, Greenberg JJ, Dobrin PB, Harford FJ, Gamelli RL. The effects of different corticosteroids on the healing colon anastomosis and cecum in a rat model. *Am Surg*. 1997;63(3):266-269.

12. Suding P, Jensen E, Abramson MA, Itani K, Wilson SE. Definitive risk factors for anastomotic leaks in elective open colorectal resection. *Arch Surg*. 2008;143(9):907-11; discussion 911-2.

13. Slieker JC, Komen N, Mannaerts GH, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. *Arch Surg*. 2012;147(5):447-452.

14. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. *J Am Coll Surg*. 2006;202(3):439-444.

15. Ziegler MA, Catto JA, Riggs TW, Gates ER, Grodsky MB, Wasvary HJ. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. *Arch Surg*. 2012;147(7):600-605.

16. Lake JP, Firoozmand E, Kang JC, et al. Effect of high-dose steroids on anastomotic complications after proctocolectomy with ileal pouch-anal anastomosis. *J Gastrointest Surg*. 2004;8(5):547-551.

17. Tresallet C, Royer B, Godiris-Petit G, Menegaux F. Effect of systemic corticosteroids on elective left-sided colorectal resection with colorectal anastomosis. *Am J Surg*. 2008;195(4):447-451.

18. Richards CH, Campbell V, Ho C, Hayes J, Elliott T, Thompson-Fawcett M. Smoking is a major risk factor for anastomotic leak in patients undergoing low anterior resection. *Colorectal Dis*. 2012;14(5):628-633.

19. Krarup PM, Jorgensen LN, Andreasen AH, Harling H, Danish Colorectal Cancer Group. A nationwide study on anastomotic leakage after colonic cancer surgery. *Colorectal Dis*. 2012;14(10):e661-7.

20. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287(5462):2398-2399.

21. Hjerrild Iversen L. *Aspects of survival from colorectal cancer in Denmark: doctoral thesis.* [Aarhus]: Faculty of Health Sciences, Aarhus University; 2011:Ca. 220 sider, ill.

22. Danish Colorecal Cancer Group. *Nationwide database of colorectal cancer: annual report 2010.* Copenhagen: DCCG; 2011:103 p.

23. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J Anaesth*. 2011;55(2):111-115.

24. Ostenfeld EB, Froslev T, Friis S, Gandrup P, Madsen MR, Sogaard M. Completeness of colon and rectal cancer staging in the Danish Cancer Registry, 2004-2009. *Clin Epidemiol*. 2012;4 Suppl 2:33-38.

25. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41.

26. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. *JAMA Intern Med*. 2013:1-10.

27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30-33.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

29. Fleiss JL, Levin BA, Paik MC. *Statistical methods for rates and proportions.* 3. ed. ed. Hoboken, N.J.: J. Wiley; 2003:xxvii, 760 s., ill.

30. Davis B, Rivadeneira DE. Complications of colorectal anastomoses: leaks, strictures, and bleeding. *Surg Clin North Am*. 2013;93(1):61-87.

31. Klein M, Gogenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ*. 2012;345:e6166.

32. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: A literature survey. *Colorectal Dis*. 2013.

33. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339-351.

34. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

35. Nickelsen TN, Harling H, Kronborg O, Bulow S, Jorgensen T. The completeness and quality of the Danish Colorectal Cancer clinical database on colorectal cancer. *Ugeskr Laeger*. 2004;166(36):3092-3095.

36. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43(3):519-527.

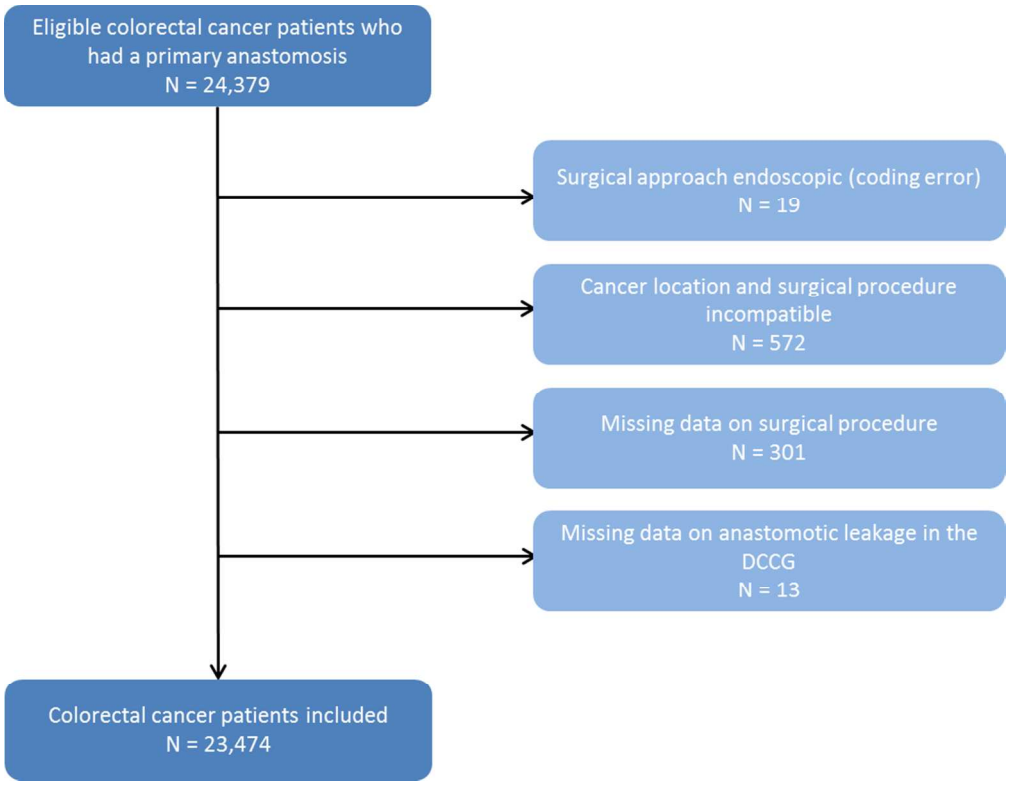

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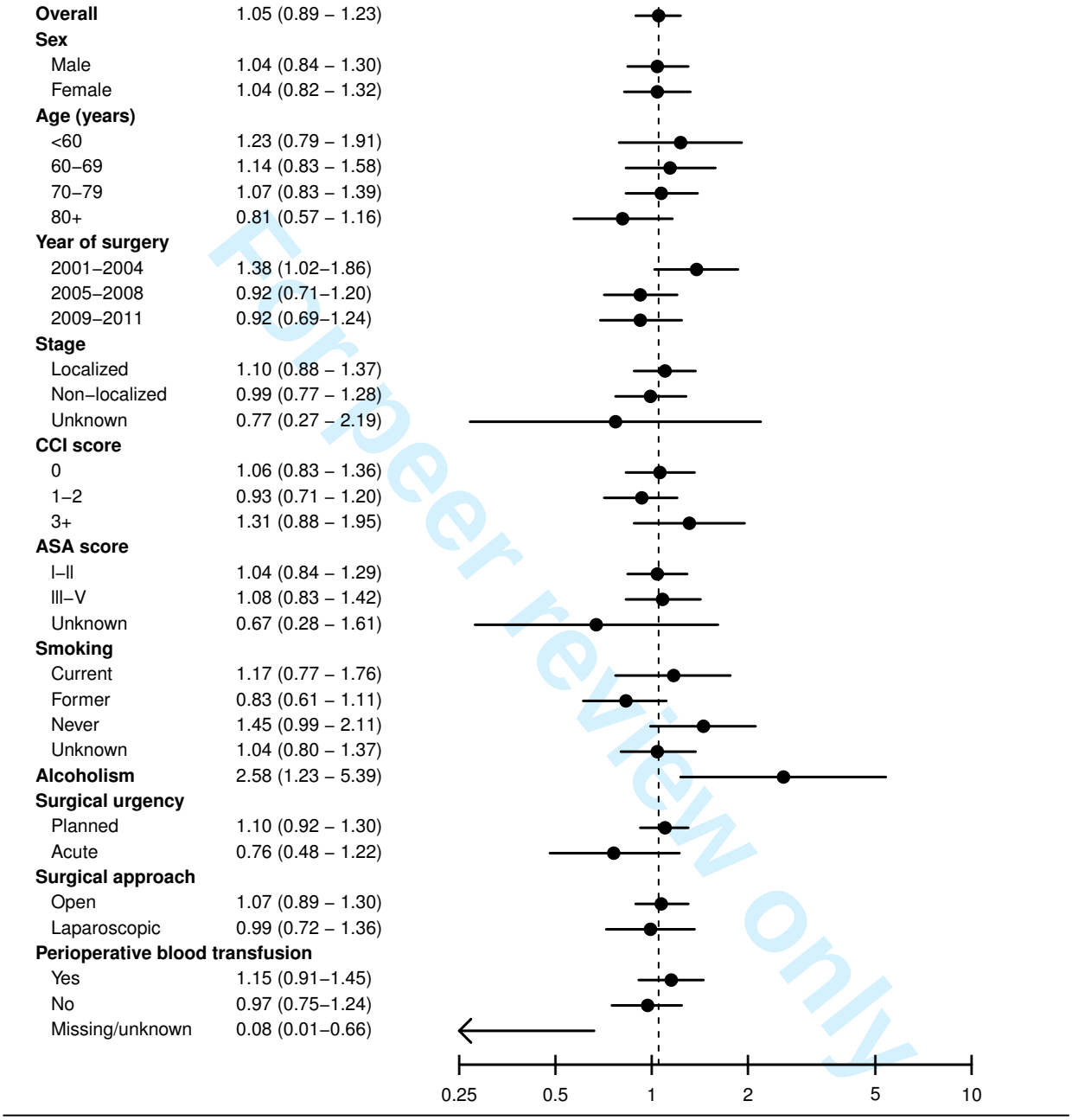
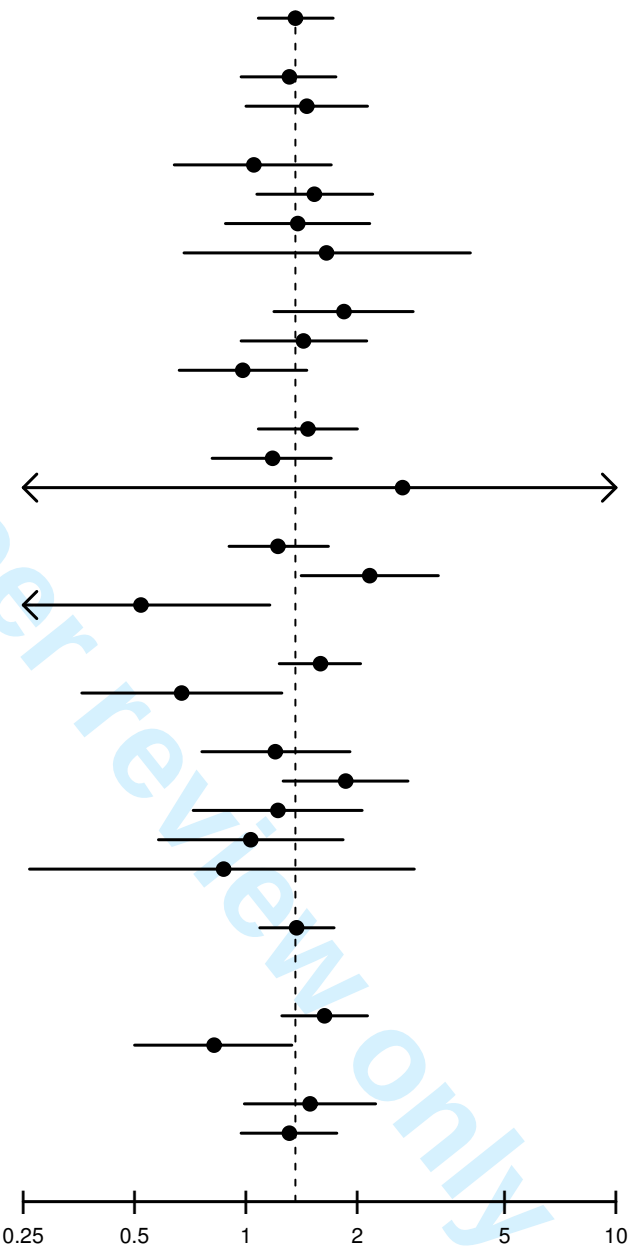
Figure 2a. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following colon cancer surgery compared to never–use, Denmark 2001–2011**



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; IRA, ileorectal anastomosis. ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorder medications, and non–steroidal anti–inflammatory drugs.

Figure 2b. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following rectum cancer surgery compared to never–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	–



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorde medications, and non–steroidal anti–inflammatory drugs.

SUPPORTING INFORMATION

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

Table S1. 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.

Table S2. 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

Table S3. 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.

Table S4. 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

Table S5. ICD-codes defining Anastomotic leakage

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

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	

		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, 12
		(b) Give reasons for non-participation at each stage	Figure
		(c) Consider use of a flow diagram	Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the	18

	present study and, if applicable, for the original study on which the present article is based

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Preadmission glucocorticoid use and anastomotic leakage after colon and rectal cancer resection: a Danish cohort study

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Keywords:	EPIDEMIOLOGY, Colorectal surgery < SURGERY, Gastrointestinal tumours < GASTROENTEROLOGY

Title: Preadmission glucocorticoid use and anastomotic leakage after colon and rectal cancer resection: a Danish cohort study

Running title: Preadmission glucocorticoids and colorectal anastomoses

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Keywords: Colorectal cancer resection; glucocorticoids; cohort study; epidemiology

Word counts: Text 3087

ABSTRACT

Objective: To examine whether preadmission glucocorticoid use increases the risk of anastomotic leakage after colon and rectal cancer resections

Design: A population-based cohort study.

Setting: Denmark (2001-2011).

Participants: We identified all patients who had a primary anastomosis after a colorectal cancer resection by linking medical registries. Participants that filled their most recent glucocorticoid prescription ≤90, 91-365, and >365 days before their surgery date were categorized as current, recent, and former users, respectively.

Main outcome measures: We calculated 30-day absolute risk of anastomotic leakage and computed odds ratios (ORs) using logistic regression models with adjustment for potential confounders.

Results: Of the 18,190 colon cancer patients included, anastomotic leakage occurred in 1184 (6.5%). Glucocorticoid use overall was not associated with an increased risk of leakage (6.4% versus 6.9% among never-users; OR 1.05; 95% confidence interval [CI]: 0.89, 1.23). Categories of oral, inhaled, or intestinal-acting glucocorticoids did not affect risk of leakage materially. Anastomotic leakage occurred in 695 (13.2%) of 5284 rectal cancer patients. Glucocorticoid use overall slightly increased risk of leakage (14.6% versus 12.8% among never-users; OR 1.36, 95% CI: 1.08, 1.72). Results did not differ significantly within glucocorticoid categories.

Conclusions: Preadmission glucocorticoids modestly increased the risk of anastomotic leakage mainly after rectal cancer resection. However, absolute risk differences were small and the clinical impact of glucocorticoid use may therefore be limited.

Strengths and limitations of this study

- The study included all Danish patients with colon and rectal cancer who had a primary anastomosis after a colorectal cancer resection during the study period. The study had complete follow-up on all participants.
- Using electronic registries, we had accurate data on glucocorticoid prescriptions
- Because there were no clear standards for the recording of anastomotic leakage during the study period, completeness and validity in the registries may be imperfect.
- The completeness of the Danish National Registry of Patients may vary for different diseases, and we cannot exclude the possibility that confounding by indication influenced our results although we adjusted for comorbidity in multivariate models.

INTRODUCTION

Anastomotic leakage is a serious complication after colorectal cancer (CRC) resection that inevitably increases morbidity, mortality, and hospital resource utilisation.[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 predispose to leakage,[12-15] although others have not.[16-18] Unfortunately, existing 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 per cent after colonic surgery compared with 11-12 per cent 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.

MATERIALS AND 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 database of the Danish Colorectal Cancer Group[21] (Figure 1). Beginning in 2001, this clinical database has registered all patients diagnosed or treated in surgical departments in Denmark with an incident colon or rectal adenocarcinoma, the latter defined as those located 15 cm or less from the anus.[21] Completeness of cancer registration (i.e. the proportion of those registered in the database out of those registered in Danish National Registry of Patients) in the database was 98-100 per cent 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 Danish Colorectal Cancer Group using standardised forms that are completed by the treating physicians.[21] We retrieved data regarding pre-operative American Society of Anesthesiologists' Physical Status Classification

score,[23] cancer site, tumor extent, node involvement, and distant metastases allowing for staging (recorded as localised or non-localised 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 collected by the Danish Colorectal Cancer Group until 2009 and by the treating physicians hereafter.

Use of glucocorticoids

The Danish National Registry of Medicinal Products 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 this registry to identify all prescriptions of oral, inhaled, and intestinal-acting glucocorticoids redeemed before the CRC surgery date (see *Supplementary File* 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.

Comorbidity and medication

The Danish National Registry of Patients has tracked all non-psychiatric hospitalisations since 1977 and outpatient visits since 1995, including essentially all specialist care in the country.[27] Recorded information includes 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 Danish National Registry of Patients and the Charlson Comorbidity Index, we summarised each patient's medical history from 1977 until the surgery date, excluding colon or rectal cancer diagnoses (see *Supplementary File* for ICD codes defining a modified CCI).[28] The Charlson Comorbidity Index 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 Charlson Comorbidity Index score: 0 (low comorbidity), 1–2 (moderate comorbidity), and 3+ (severe comorbidity). In addition, we obtained recorded diagnoses of inflammatory bowel disease, autoimmune disease, alcoholism, and obesity because these diagnoses are not included in the Charlson Comorbidity Index (see *Supplementary File* for ICD-codes).

Using the Danish National Registry of Medicinal Products, we also identified filled prescriptions of non-steroidal anti-inflammatory drugs, medications for chronic obstructive pulmonary disease other than glucocorticoids, and immuno-suppressants (see *Supplementary File* for ATC-codes).

Patients with anastomotic leakage after colon or rectal cancer resection

We identified patients with anastomotic leakage recorded in the Danish Colorectal Cancer Group database or in the Danish National Registry of Patients using the ICD codes associated with anastomotic leakage or surgery codes for reoperation of anastomotic leakage (see *Supplementary File* for ICD-10 codes). Recording of anastomotic leakage in the database is typically based on clinically evident leakage which at the discretion of the surgeon is confirmed by contrast barium enema, computer tomography, or surgery.

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, Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification score (≤2, >2, unknown), history of inflammatory bowel disease, alcoholism/use of disulfiram (single variable), smoking status at the time of the surgery (current, former, never or unknown), and medications for chronic obstructive pulmonary disease as its proxy, as well as prescriptions for non-aspirin non-steroidal anti-inflammatory drugs 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 1 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, Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification 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, because there are no clear standards for the recording of anastomotic leakage, we restricted anastomotic leakage to patients who were re-operated upon to heighten the predictive value of our outcome. Leakages that were treated only by non-surgical drainage, e,g., ultrasonic, were not included in this analysis.

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 1). 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 Non-steroidal anti-inflammatory drugs and COPD agents were also more prevalent among these patients.

Table 1 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)

Table 1. continued				
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 (100.0)	967 (100.0)
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

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 2a). Absolute risk did not differ substantially among subgroups of users of oral, inhaled, intestinal-acting, or mixed glucocorticoids.

Compared with never-users, glucocorticoid use overall was not associated with an increased relative risk of anastomotic leakage (Table 2a). Although not statistically significant, risk was slightly increased among current (adjusted OR (aOR) = 1.24; 95% CI: 0.82, 1.88) and recent (aOR = 1.43; 95% CI: 0.87, 2.34) users of oral glucocorticoids. The relative risk estimate for use of intestinal-acting glucocorticoids was imprecise (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 (Figure 2a).

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). When we restricted analyses to anastomotic leakages that required surgical

Table 2a 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated
[a]Calculated by subtracting the estimate for never-use from those for glucocorticoid users
[b]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

intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown).

Rectal Cancer Patients

Of the 5284 rectal cancer patients resected, 458 (8.7%) 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 1). Similarly, severe comorbidity, high ASA score, and prescriptions of Non-steroidal anti-inflammatory drugs 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 (Table 2b). 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

Table 2b 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated
[a]Calculated by subtracting the estimate for never-use from those for glucocorticoid users
[b]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

(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 2b). 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 (Figure 2b).

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% CI for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cutoff (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).

DISCUSSION

In this nationwide population-based study, we found that current and recent users of oral glucocorticoids exhibited a non-significant modest increase in the relative risk of anastomotic leakage after colon cancer resection. 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 investigations and provided detailed data on different types of glucocorticoids and the

timing of their use. In addition, we analysed 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.[32] 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[33] 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 organised health care system. Using electronic registries, we had accurate data on exposure and covariates.[25,27,34] The Danish Colorectal Cancer Group database provided a complete cohort of CRC patients during the study period, as well as detailed information about surgical treatment and anastomotic leakage.[22] However, as in all observational studies of leakage, we cannot entirely exclude the possibility of selection bias. If surgeons are more reluctant to create a primary anastomosis in glucocorticoid users than in never-users, patients who receive that procedure might be a selected group, presumably at lower risk of leakage. Recording of postoperative complications in the Danish Colorectal Cancer Group database has been validated against medical records and demonstrated almost 100% accuracy.[35] Nonetheless, because there are no clear standards for the recording of anastomotic leakage,[33] completeness and validity in the database may be imperfect. To heighten capture of leakage cases, we also included those only recorded in the Danish National Registry of Patients, 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 Danish National Registry of Medicinal Products are complete,[25] some limitations may exist. 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. Also, glucocorticoids dispensed during hospitalisation and outpatient clinic visits are not logged in the Danish National Registry of Medicinal Products. Nonetheless, stratified analyses based on discharge diagnoses did not differ materially from those of the main analysis. Finally, due to a limited number of individuals in each glucocorticoid category, we were unable to subcategorize according to dosages of glucocorticoids. Likewise, the paucity of patients using intestinal-acting glucocorticoids did not allow for exploring subcategories according to the timing of use.

Misclassification of anastomotic leakage might also influence our results if glucocorticoid users had a temporary stoma together with their primary anastomosis more often than never-users. Because a diverting stoma may reduce the clinical symptoms of leakage, underreporting among glucocorticoid users could thus bias the estimates towards the null.

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 Danish National Registry of Medicinal Products 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 (Charlson Comorbidity Index score=0). Although some of these patients may have been treated solely by general practitioners whose patients' files are not logged in the Danish National Registry of Patients, recording of Charlson Comorbidity Index conditions from hospitalisations and outpatient visits may be incomplete. Also, we cannot exclude the possibility of some uncontrolled confounding by preoperative radio-chemotherapy which was not recorded in the Danish Colorectal Cancer Database before 2009. However, standard neo-adjuvant treatment for rectal cancer with long-course radiotherapy and concomitant chemotherapy including 5-flourouracil[36] is low-emetogen and does not commonly imply the requirement of anti-emetics such as glucocorticoids. Therefore, preoperative oncologic treatment seems unlikely to explain our findings for rectal cancer. Although rarely indicated, preoperative chemotherapy for cancer in the colon may involve glucocorticoids. However, assuming that chemotherapy may increase risk of anastomotic leakage after colorectal cancer resection, lack of adjustment for this potential confounding factor would not explain our null results for colon cancer. Finally, data regarding smoking were incomplete (27% missing) and might suffer from underreporting. Although, we adjusted for smoking and associated diseases/medications for chronic obstructive pulmonary disease 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.[37] 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 the clinical impact of glucocorticoid use may therefore be limited.

CONTRIBUTORSHIP: HTS, RE and EBO designed the study. EBO and AHR were responsible for acquiring the data and conducting the analysis. EBO draftet the first version of the manuscript, but all authors (EBO, RE, AHR, LI, JAB, 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 submitted, including the authorship list.

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Data sharing: No additional data available

Ethical approval: The study was approved by the Danish Data Protection Agency (record number 2011-41-6151) and the National Board of Health. The study did not involve any contact with patients or any intervention, and it was not necessary to access permission from the Danish Ethical Committee.

FIGURE LEGENDS

Figure 1. Flowchart illustrating exclusions of colorectal cancer patients recorded in the Danish Colorectal Cancer Database, 2001-2011.

Figure 2a. Subgroup analysis associating glucocorticoids and anastomotic leakage following colon cancer surgery compared to never-use

Figure 2b. Subgroup analysis associating glucocorticoids and anastomotic leakage following rectal cancer surgery compared to never-use

REFERENCES

1. Kube R, Mroczkowski P, Granowski D, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. *Eur J Surg Oncol*. 2010;36(2):120-124.

2. Frye J, Bokey EL, Chapuis PH, Sinclair G, Dent OF. Anastomotic leakage after resection of colorectal cancer generates prodigious use of hospital resources. *Colorectal Dis*. 2009;11(9):917-920.

3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. 2011;253(5):890-899.

4. Jacobs JWG, Bijlsma JWJ. Glucocorticoid Therapy. In: Firestein GS, Budd RC, Harris ED, McInnes IB, Sergent JS, eds. *Kelly's Textbook of Rheumatology.* 8th ed. 11830 Westline Industrial Drive, St. Louis, MO 63136-3318: W.B. Saunders Company; 2008:863.

5. Anstead GM. Steroids, retinoids, and wound healing. *Adv Wound Care*. 1998;11(6):277-285.

6. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther*. 2002;96(1):23-43.

7. Baca B, Ozben V, Boler DE, et al. Effect of corticosteroid dose and duration of administration on colonic anastomosis. *Inflamm Bowel Dis*. 2010;16(12):2162-2167.

8. Furst MB, Stromberg BV, Blatchford GJ, Christensen MA, Thorson AG. Colonic anastomoses: bursting strength after corticosteroid treatment. *Dis Colon Rectum*. 1994;37(1):12-15.

9. Phillips JD, Kim CS, Fonkalsrud EW, Zeng H, Dindar H. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. *Am J Surg*. 1992;163(1):71-77.

10. Mastboom WJ, Hendriks T, de Man BM, de Boer HH. Influence of methylprednisolone on the healing of intestinal anastomoses in rats. *Br J Surg*. 1991;78(1):54-56.

11. Eubanks TR, Greenberg JJ, Dobrin PB, Harford FJ, Gamelli RL. The effects of different corticosteroids on the healing colon anastomosis and cecum in a rat model. *Am Surg*. 1997;63(3):266-269.

12. Suding P, Jensen E, Abramson MA, Itani K, Wilson SE. Definitive risk factors for anastomotic leaks in elective open colorectal resection. *Arch Surg*. 2008;143(9):907-11; discussion 911-2.

13. Slieker JC, Komen N, Mannaerts GH, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. *Arch Surg*. 2012;147(5):447-452.

14. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. *J Am Coll Surg*. 2006;202(3):439-444.

15. Ziegler MA, Catto JA, Riggs TW, Gates ER, Grodsky MB, Wasvary HJ. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. *Arch Surg*. 2012;147(7):600-605.

16. Lake JP, Firoozmand E, Kang JC, et al. Effect of high-dose steroids on anastomotic complications after proctocolectomy with ileal pouch-anal anastomosis. *J Gastrointest Surg*. 2004;8(5):547-551.

17. Tresallet C, Royer B, Godiris-Petit G, Menegaux F. Effect of systemic corticosteroids on elective left-sided colorectal resection with colorectal anastomosis. *Am J Surg*. 2008;195(4):447-451.

18. Richards CH, Campbell V, Ho C, Hayes J, Elliott T, Thompson-Fawcett M. Smoking is a major risk factor for anastomotic leak in patients undergoing low anterior resection. *Colorectal Dis*. 2012;14(5):628-633.

19. Krarup PM, Jorgensen LN, Andreasen AH, Harling H, Danish Colorectal Cancer Group. A nationwide study on anastomotic leakage after colonic cancer surgery. *Colorectal Dis*. 2012;14(10):e661-7.

20. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287(5462):2398-2399.

21. Iversen LH. *Aspects of survival from colorectal cancer in Denmark: doctoral thesis.* [Aarhus]: Faculty of Health Sciences, Aarhus University; 2011.

22. Danish Colorecal Cancer Group. *Nationwide database of colorectal cancer: annual report 2010.* Copenhagen: DCCG; 2011:103 p.

23. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J Anaesth*. 2011;55(2):111-115.

24. Ostenfeld EB, Froslev T, Friis S, Gandrup P, Madsen MR, Sogaard M. Completeness of colon and rectal cancer staging in the Danish Cancer Registry, 2004-2009. *Clin Epidemiol*. 2012;4 Suppl 2:33-38.

25. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41.

26. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. *JAMA Intern Med*. 2013:1-10.

27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30-33.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

29. Fleiss JL, Levin BA, Paik MC. *Statistical methods for rates and proportions.* 3. ed. ed. Hoboken, N.J.: J. Wiley; 2003:xxvii, 760 s., ill.

30. Davis B, Rivadeneira DE. Complications of colorectal anastomoses: leaks, strictures, and bleeding. *Surg Clin North Am*. 2013;93(1):61-87.

31. Klein M, Gogenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ*. 2012;345:e6166.

32. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: A literature survey. *Colorectal Dis*. 2013.

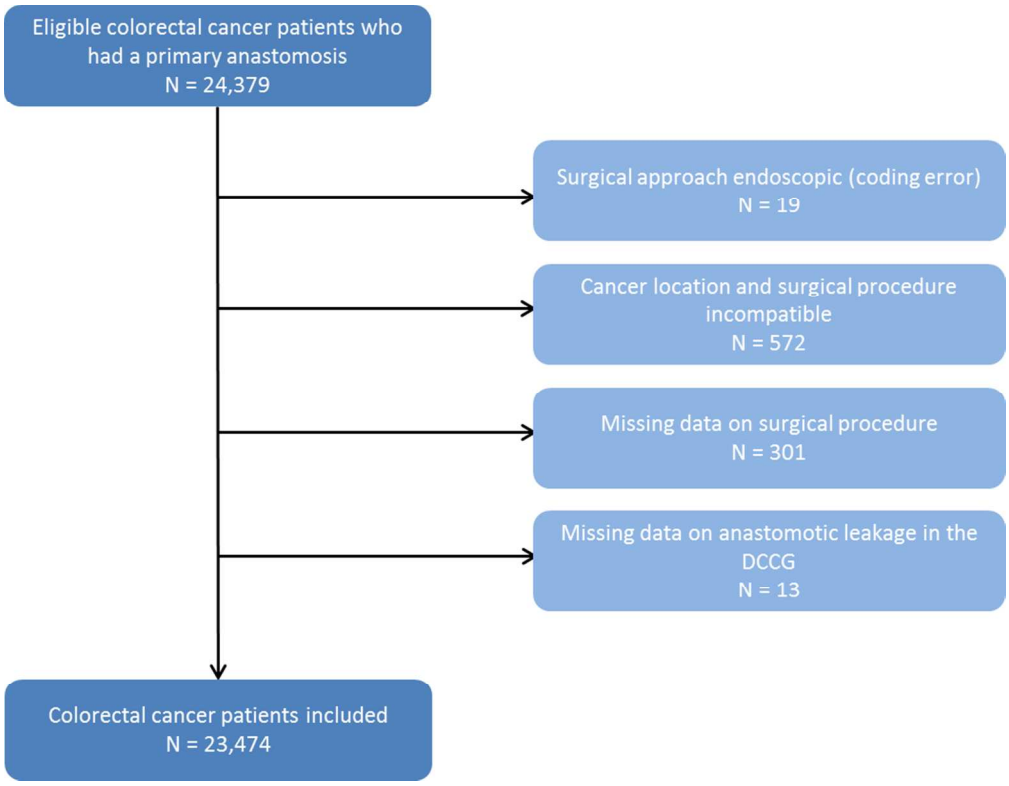
33. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339-351.

34. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

35. Nickelsen TN, Harling H, Kronborg O, Bulow S, Jorgensen T. The completeness and quality of the Danish Colorectal Cancer clinical database on colorectal cancer. *Ugeskr Laeger*. 2004;166(36):3092-3095.

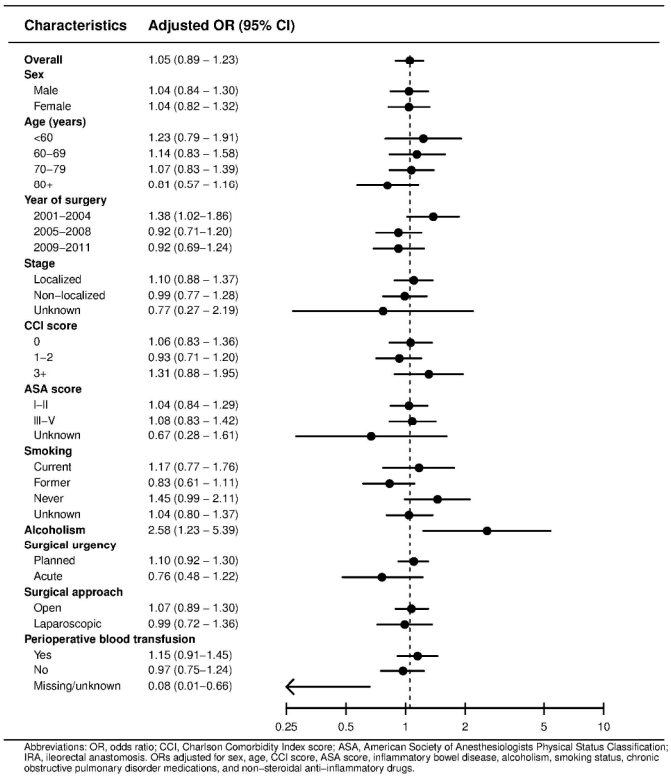
36. Danish Colorectal Cancer Group. *DCCG's nationale retningslinier.* Available at http://dccg.dk/retningslinjer/indeks.html. Accessed 5/14/2015

37. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43(3):519-527.



278x215mm (96 x 96 DPI)

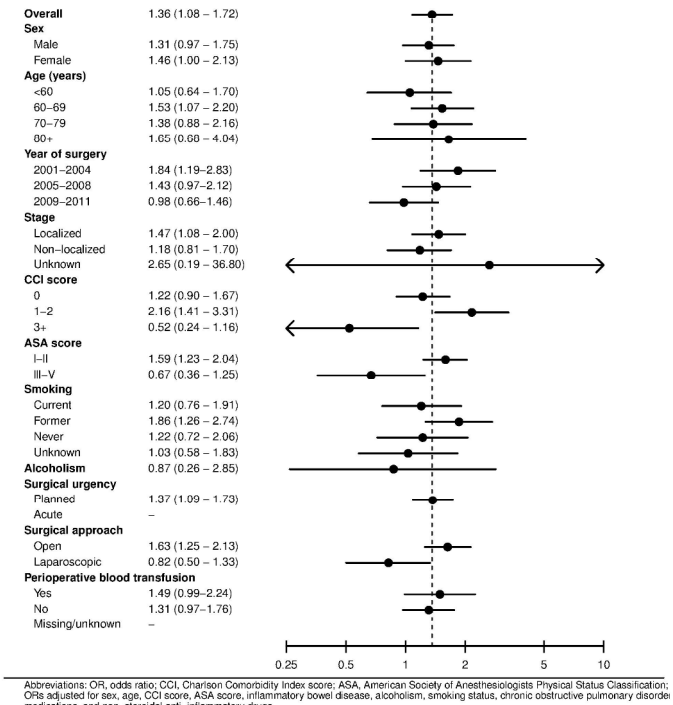
Figure 2a. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following colon cancer surgery compared to never–use, Denmark 2001–2011**



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; IRA, ileorectal anastomosis. ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorder medications, and non–steroidal anti–inflammatory drugs.

209x297mm (300 x 300 DPI)

Figure 2b. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following rectum cancer surgery compared to never–use, Denmark 2001–2011**



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorde medications, and non–steroidal anti–inflammatory drugs.

209x297mm (300 x 300 DPI)

SUPPORTING INFORMATION

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

Table S1. 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.

Table S2. 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

Table S3. 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.

Table S4. 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

Table S5. ICD-codes defining Anastomotic leakage

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

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	

		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, 12
		(b) Give reasons for non-participation at each stage	Figure
		(c) Consider use of a flow diagram	Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the	18

	present study and, if applicable, for the original study on which the present article is based

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Preadmission glucocorticoid use and anastomotic leakage after colon and rectal cancer resection: a Danish cohort study

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Title: Preadmission glucocorticoid use and anastomotic leakage after colon and rectal cancer resection: a Danish cohort study

Running title: Preadmission glucocorticoids and colorectal anastomoses

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Keywords: Colorectal cancer resection; glucocorticoids; cohort study; epidemiology

Word counts: Text 3111

ABSTRACT

Objective: To examine whether preadmission glucocorticoid use increases the risk of anastomotic leakage after colon and rectal cancer resections

Design: A population-based cohort study.

Setting: Denmark (2001-2011).

Participants: We identified all patients who had a primary anastomosis after a colorectal cancer resection by linking medical registries. Participants that filled their most recent glucocorticoid prescription ≤90, 91-365, and >365 days before their surgery date were categorized as current, recent, and former users, respectively.

Main outcome measures: We calculated 30-day absolute risk of anastomotic leakage and computed odds ratios (ORs) using logistic regression models with adjustment for potential confounders.

Results: Of the 18,190 colon cancer patients included, anastomotic leakage occurred in 1184 (6.5%). Glucocorticoid use overall was not associated with an increased risk of leakage (6.4% versus 6.9% among never-users; OR 1.05; 95% confidence interval [CI]: 0.89, 1.23). Categories of oral, inhaled, or intestinal-acting glucocorticoids did not affect risk of leakage materially. Anastomotic leakage occurred in 695 (13.2%) of 5284 rectal cancer patients. Glucocorticoid use overall slightly increased risk of leakage (14.6% versus 12.8% among never-users; OR 1.36, 95% CI: 1.08, 1.72). Results did not differ significantly within glucocorticoid categories.

Conclusions: Preadmission glucocorticoids modestly increased the risk of anastomotic leakage mainly after rectal cancer resection. However, absolute risk differences were small and the clinical impact of glucocorticoid use may therefore be limited.

Strengths and limitations of this study

- The study included all Danish patients with colon and rectal cancer who had a primary anastomosis after a colorectal cancer resection during the study period. The study had complete follow-up on all participants.
- Using electronic registries, we had accurate data on glucocorticoid prescriptions
- Because there were no clear standards for the recording of anastomotic leakage during the study period, completeness and validity in the registries may be imperfect.
- The completeness of the Danish National Registry of Patients may vary for different diseases, and we cannot exclude the possibility that confounding by indication influenced our results although we adjusted for comorbidity in multivariate models.

INTRODUCTION

Anastomotic leakage is a serious complication after colorectal cancer (CRC) resection that inevitably increases morbidity, mortality, and hospital resource utilisation.[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 predispose to leakage,[12-15] although others have not.[16-18] Unfortunately, existing 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 per cent after colonic surgery compared with 11-12 per cent 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.

MATERIALS AND 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 database of the Danish Colorectal Cancer Group[21] (Figure 1). Beginning in 2001, this clinical database has registered all patients diagnosed or treated in surgical departments in Denmark with an incident colon or rectal adenocarcinoma, the latter defined as those located 15 cm or less from the anus.[21] Completeness of cancer registration (i.e. the proportion of those registered in the database out of those registered in Danish National Registry of Patients) in the database was 98-100 per cent 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 Danish Colorectal Cancer Group using standardised forms that are completed by the treating physicians.[21] We retrieved data regarding pre-operative American Society of Anesthesiologists' Physical Status Classification

score,[23] cancer site, tumor extent, node involvement, and distant metastases allowing for staging (recorded as localised or non-localised 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 collected by the Danish Colorectal Cancer Group until 2009 and by the treating physicians thereafter.

Use of glucocorticoids

The Danish National Registry of Medicinal Products 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 this registry to identify all prescriptions of oral, inhaled, and intestinal-acting glucocorticoids redeemed before the CRC surgery date (see *Supplementary File* Table S1 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.

Comorbidity and medication

The Danish National Registry of Patients has tracked all non-psychiatric hospitalisations since 1977 and outpatient visits since 1995, including essentially all specialist care in the country.[27] Recorded information includes 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 Danish National Registry of Patients and the Charlson Comorbidity Index, we summarised each patient's medical history from 1977 until the surgery date, excluding colon or rectal cancer diagnoses (see *Supplementary File* Table S2 for ICD codes defining a modified CCI).[28] The Charlson Comorbidity Index 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 Charlson Comorbidity Index score: 0 (low comorbidity), 1–2 (moderate comorbidity), and 3+ (severe comorbidity). In addition, we obtained recorded diagnoses of inflammatory bowel disease, autoimmune disease, alcoholism, and obesity because these diagnoses are not included in the Charlson Comorbidity Index (see *Supplementary File* Table S3 for ICD-codes).

Using the Danish National Registry of Medicinal Products, we also identified filled prescriptions of non-steroidal anti-inflammatory drugs, medications for chronic obstructive pulmonary disease other than glucocorticoids, and immuno-suppressants (see *Supplementary File* Table S4 for ATC-codes).

Patients with anastomotic leakage after colon or rectal cancer resection

We identified patients with anastomotic leakage recorded in the Danish Colorectal Cancer Group database or in the Danish National Registry of Patients using the ICD codes associated with anastomotic leakage or surgery codes for surgical repair of anastomotic leakage (see *Supplementary File* Table S5 for ICD-10 codes). Recording of anastomotic leakage in the database is typically based on clinically evident leakage which at the discretion of the surgeon is confirmed by contrast barium enema, computer tomography, or surgery.

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 including p-values by using Pearson's chi-squared test. 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, Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification score (≤2, >2, unknown), history of inflammatory bowel disease, alcoholism/use of disulfiram (single variable), smoking status at the time of the surgery (current, former, never or unknown), and medications for chronic obstructive pulmonary disease as its

proxy, as well as prescriptions for non-aspirin non-steroidal anti-inflammatory drugs 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 1.a and Table 1.b 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, Charlson Comorbidity Index score, American Society of Anesthesiologists' Physical Status Classification 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, because there are no clear standards for the recording of anastomotic leakage, we restricted anastomotic leakage to patients who were re-operated upon to heighten the predictive value of our outcome. Leakages that were treated only by non-surgical drainage, e,g., ultrasonic, were not included in this analysis.

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 1.a). 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 Non-steroidal anti-inflammatory drugs and COPD agents were also more prevalent among these patients.

Table 1.a Characteristics of patients who underwent resection for colon cancer, by use of any glucocorticoids, Denmark, 2001-2011.

Characteristics	Colon cancer		
	No glucocorticoid use N=14,041 n (%)	Glucocorticoid use N=4149 n (%)	p-value
Sex			0.000
Female	7122 (50.7)	2369 (57.1)	
Male	6919 (49.3)	1780 (42.9)	
Age, years			0.000
<60	2399 (17.1)	482 (11.6)	
60-69	3841 (27.4)	949 (22.9)	
70-79	4688 (33.4)	1582 (38.1)	
80+	3113 (21.2)	1136 (27.4)	
Year of resection			0.000
2001-2004	4767 (34.0)	1074 (25.9)	
2005-2008	5327 (37.9)	1642 (39.6)	
2009-2011	3947 (28.1)	1433 (34.5)	
Stage			0.001
Localized	7192 (51.2)	2261 (54.5)	
Non-localized	6510 (46.4)	1785 (43.0)	
Unknown	339 (2.4)	103 (2.5)	
CCI score			0.001
0	8557 (60.9)	1448 (34.9)	
1-2	4074 (29.0)	1812 (43.7)	
3+	1410 (10.0)	889 (21.4)	
ASA score			0.000
≤2	10,616 (75.6)	2575 (62.1)	
>2	2812 (20.0)	1420 (34.2)	
Unknown	613 (4.4)	154 (3.7)	
IBD	91 (0.7)	108 (2.6)	0.000
Auto-immune disorders or immunosuppressive drug use	90 (0.6)	256 (6.2)	0.000
Obesity	405 (2.9)	208 (5.0)	0.000
Alcoholism	488 (3.5)	159 (3.8)	0.276
Tobacco use			0.000
Current use	2088 (14.9)	563 (13.6)	
Former use	4159 (29.6)	1429 (34.4)	
Never use	3569 (25.4)	898 (21.6)	
Unknown	4225 (30.1)	1259 (30.3)	
NSAIDs	3337 (23.8)	1180 (28.4)	0.000

Table 1.a continued			
COPD medications	1,547 (11.0)	2404 (57.9)	0.000
Surgical urgency			0.190
Planned	12,140 (86.5)	3617 (87.2)	
Acute	1894 (13.5)	532 (12.8)	
Unknown	7 (0.1)	0 (0.0)	
Surgical aproach0.004	3446 (24.5)	1111 (26.8)	
Laparoscopy			
Laparotomy	10 595 (75.5)	3038 (73.2)	
Surgical Procedure			0.000
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	-	-	
Perioperative blood transfusion			0.000
Yes	3312 (23.6)	1120 (27.0)	
No	10 611 (75.6)	2999 (72.3)	
Missing/Unknown	118 (0.8)	30 (0.7)	

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

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 2a). Absolute risk did not differ substantially among subgroups of users of oral, inhaled, intestinal-acting, or mixed glucocorticoids.

Compared with never-users, glucocorticoid use overall was not associated with an increased relative risk of anastomotic leakage (Table 2a). Although not statistically significant, risk was slightly increased among current (adjusted OR (aOR) = 1.24; 95% CI: 0.82, 1.88) and recent (aOR = 1.43; 95% CI: 0.87, 2.34) users of oral glucocorticoids. The relative risk estimate for use of intestinal-acting glucocorticoids was imprecise (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 (Figure 2a).

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). When we restricted analyses to anastomotic leakages that required surgical

Table 2a 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated
[a]Calculated by subtracting the estimate for never-use from those for glucocorticoid users
[b]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

intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown).

Rectal Cancer Patients

Of the 5284 rectal cancer patients resected, 458 (8.7%) 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 1.b). Similarly, severe

comorbidity, high ASA score, and prescriptions of Non-steroidal anti-inflammatory drugs and COPD agents were more prevalent among patients using glucocorticoids.

Table 1.b Characteristics of patients who underwent resection for rectal cancer, by use of any glucocorticoids, Denmark, 2001-2011.

Characteristics	Rectal cancer		
	No glucocorticoid use N=4317 n (%)	Glucocorticoid use N=967 n (%)	p-value
Sex			0.000
Female	1737 (40.2)	463 (47.9)	
Male	2580 (59.8)	504 (52.1)	
Age, years			0.000
<60	1187 (27.5)	224 (23.3)	
60-69	1617 (37.5)	321 (33.2)	
70-79	1152 (26.7)	326 (33.7)	
80+	361 (8.4)	96 (9.9)	
Year of resection			0.004
2001-2004	1418 (32.9)	272 (28.1)	
2005-2008	1651 (38.2)	372 (38.5)	
2009-2011	1248 (28.9)	323 (33.4)	
Stage			0.866
Localized	2460 (57.0)	557 (57.6)	
Non-localized	1775 (41.1)	390 (40.3)	
Unknown	82 (1.9)	20 (2.1)	
CCI score			0.000
0	3131 (72.5)	490 (50.7)	
1-2	970 (22.5)	355 (36.7)	
3+	216 (5.0)	122 (12.6)	
ASA score			0.000
≤2	3827 (88.3)	766 (79.9)	
>2	432 (10.0)	181 (18.7)	
Unknown	77 (1.8)	23 (2.4)	
IBD	25 (0.6)	6 (0.8)	0.879
Auto-immune disorders or immunosuppressive drug use	26 (0.6)	50 (5.2)	0.000
Obesity	77 (1.8)	29 (3.0)	0.015
Alcoholism	160 (3.7)	34 (3.5)	0.776
Tobacco use			0.718
Current use	819 (19.0)	182 (18.8)	
Former use	1529 (35.4)	359 (37.1)	
Never use	1155 (26.8)	244 (25.2)	
Unknown	814 (18.9)	182 (18.8)	
NSAIDs	806 (18.7)	222 (23.0)	0.002
COPD medications	403 (9.3)	550 (56.9)	0.000
Surgical urgency			0.700
Planned	4295 (99.5)	963 (99.6)	
Acute	22 (0.5)	4 (0.4)	
Unknown	7 (0.1)	0 (0.0)	
Surgical approach			0.141
Laparoscopy	972 (22.5)	239 (24.7)	

Table 1.b continued			
Laparotomy	3345 (77.5)	728 (75.3)	
Surgical Procedure			
Rectal resection	4317 (100.0)	967 (100.0)	
Perioperative blood transfusion			0.907
Yes	830 (19.2)	189 (19.5)	
No	3465 (80.3)	774 (80.0)	
Missing/Unknown	22 (0.5)	4 (0.4)	

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 (Table 2b). 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

Table 2b 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)

Values in parentheses are 95 per cent confidence intervals unless otherwise indicated
[a]Calculated by subtracting the estimate for never-use from those for glucocorticoid users
[b]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

(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 2b). 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 (Figure 2b).

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% CI for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cutoff (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).

DISCUSSION

In this nationwide population-based study, we found that current and recent users of oral glucocorticoids exhibited a non-significant modest increase in the relative risk of anastomotic leakage after colon cancer resection. Among rectal cancer patients, relative risk increased moderately for almost any type 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 is therefore limited.

This study extends previous research because it included considerably more subjects than previous investigations and provided detailed data on different types of glucocorticoids and the timing of their use. In addition, we analysed 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.[32] 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[33] 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 organised health care system. Using electronic registries, we had accurate data on exposure and covariates.[25,27,34] The Danish Colorectal Cancer Group database provided a complete cohort of CRC patients during the study period, as well as detailed information about surgical treatment and anastomotic leakage.[22] However, as in all observational studies of leakage, we cannot entirely exclude the possibility of selection bias. If surgeons are more reluctant to create a primary anastomosis in glucocorticoid users than in never-users, patients who receive that procedure might be a selected group, presumably at lower risk of leakage. Recording of postoperative complications in the Danish Colorectal Cancer Group

database has been validated against medical records and demonstrated almost 100% accuracy.[35] Nonetheless, because there are no clear standards for the recording of anastomotic leakage,[33] completeness and validity in the database may be imperfect. To heighten capture of leakage cases, we also included those only recorded in the Danish National Registry of Patients, 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 Danish National Registry of Medicinal Products are complete,[25] some limitations may exist. 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. Also, glucocorticoids dispensed during hospitalisation and outpatient clinic visits are not logged in the Danish National Registry of Medicinal Products. Nonetheless, stratified analyses based on discharge diagnoses did not differ materially from those of the main analysis. Finally, due to a limited number of individuals in each glucocorticoid category, we were unable to subcategorize according to dosages of glucocorticoids. Likewise, the paucity of patients using intestinal-acting glucocorticoids did not allow for exploring subcategories according to the timing of use.

Misclassification of anastomotic leakage might also influence our results if glucocorticoid users had a temporary stoma together with their primary anastomosis more often than never-users. Because a diverting stoma may reduce the clinical symptoms of leakage, underreporting among glucocorticoid users could thus bias the estimates towards the null.

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 Danish National Registry of Medicinal Products 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 (Charlson Comorbidity Index score=0). Although some of these patients may have been treated solely by general practitioners whose patients' files are not logged in the Danish National Registry of Patients. As a result, recording of Charlson Comorbidity Index conditions from hospitalisations and outpatient visits may be incomplete. Also, we cannot exclude the possibility of some uncontrolled confounding by preoperative radio-chemotherapy which was not recorded in the Danish Colorectal Cancer Database before 2009. However, standard neo-adjuvant treatment for rectal cancer with long-course radiotherapy and concomitant chemotherapy including 5-flourouracil[36] is low-emetogen and does not commonly imply the requirement of anti-emetics such as glucocorticoids. Therefore, preoperative oncologic treatment seems unlikely to explain our findings for rectal cancer. Although rarely indicated, preoperative chemotherapy for cancer in the colon may involve glucocorticoids. However, assuming that chemotherapy may increase risk of anastomotic leakage after colorectal cancer resection, lack of adjustment for this potential confounding factor would not explain our null results for colon cancer. Finally, data regarding smoking were incomplete (27% missing) and might suffer from underreporting. Although we adjusted for smoking and associated diseases/medications for chronic obstructive pulmonary disease 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.[37] 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 the clinical impact of glucocorticoid use may therefore be limited.

CONTRIBUTORSHIP: HTS, RE and EBO designed the study. EBO and AHR were responsible for acquiring the data and conducting the analysis. EBO draftet the first version of the manuscript, but all authors (EBO, RE, AHR, LI, JAB, 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 submitted, including the authorship list.

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Data sharing: No additional data available

Ethical approval: The study was approved by the Danish Data Protection Agency (record number 2011-41-6151) and the National Board of Health. The study did not involve any contact with patients or any intervention, and it was not necessary to access permission from the Danish Ethical Committee.

FIGURE LEGENDS

Figure 1. Flowchart illustrating exclusions of colorectal cancer patients recorded in the Danish Colorectal Cancer Database, 2001-2011.

Figure 2a. Subgroup analysis associating glucocorticoids and anastomotic leakage following colon cancer surgery compared to never-use

Figure 2b. Subgroup analysis associating glucocorticoids and anastomotic leakage following rectal cancer surgery compared to never-use

REFERENCES

1. Kube R, Mroczkowski P, Granowski D, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. *Eur J Surg Oncol*. 2010;36(2):120-124.

2. Frye J, Bokey EL, Chapuis PH, Sinclair G, Dent OF. Anastomotic leakage after resection of colorectal cancer generates prodigious use of hospital resources. *Colorectal Dis*. 2009;11(9):917-920.

3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. 2011;253(5):890-899.

4. Jacobs JWG, Bijlsma JWJ. Glucocorticoid Therapy. In: Firestein GS, Budd RC, Harris ED, McInnes IB, Sergent JS, eds. *Kelly's Textbook of Rheumatology.* 8th ed. 11830 Westline Industrial Drive, St. Louis, MO 63136-3318: W.B. Saunders Company; 2008:863.

5. Anstead GM. Steroids, retinoids, and wound healing. *Adv Wound Care*. 1998;11(6):277-285.

6. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. *Pharmacol Ther*. 2002;96(1):23-43.

7. Baca B, Ozben V, Boler DE, et al. Effect of corticosteroid dose and duration of administration on colonic anastomosis. *Inflamm Bowel Dis*. 2010;16(12):2162-2167.

8. Furst MB, Stromberg BV, Blatchford GJ, Christensen MA, Thorson AG. Colonic anastomoses: bursting strength after corticosteroid treatment. *Dis Colon Rectum*. 1994;37(1):12-15.

9. Phillips JD, Kim CS, Fonkalsrud EW, Zeng H, Dindar H. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. *Am J Surg*. 1992;163(1):71-77.

10. Mastboom WJ, Hendriks T, de Man BM, de Boer HH. Influence of methylprednisolone on the healing of intestinal anastomoses in rats. *Br J Surg*. 1991;78(1):54-56.

11. Eubanks TR, Greenberg JJ, Dobrin PB, Harford FJ, Gamelli RL. The effects of different corticosteroids on the healing colon anastomosis and cecum in a rat model. *Am Surg*. 1997;63(3):266-269.

12. Suding P, Jensen E, Abramson MA, Itani K, Wilson SE. Definitive risk factors for anastomotic leaks in elective open colorectal resection. *Arch Surg*. 2008;143(9):907-11; discussion 911-2.

13. Slieker JC, Komen N, Mannaerts GH, et al. Long-term and perioperative corticosteroids in anastomotic leakage: a prospective study of 259 left-sided colorectal anastomoses. *Arch Surg*. 2012;147(5):447-452.

14. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. *J Am Coll Surg*. 2006;202(3):439-444.

15. Ziegler MA, Catto JA, Riggs TW, Gates ER, Grodsky MB, Wasvary HJ. Risk factors for anastomotic leak and mortality in diabetic patients undergoing colectomy: analysis from a statewide surgical quality collaborative. *Arch Surg*. 2012;147(7):600-605.

16. Lake JP, Firoozmand E, Kang JC, et al. Effect of high-dose steroids on anastomotic complications after proctocolectomy with ileal pouch-anal anastomosis. *J Gastrointest Surg*. 2004;8(5):547-551.

17. Tresallet C, Royer B, Godiris-Petit G, Menegaux F. Effect of systemic corticosteroids on elective left-sided colorectal resection with colorectal anastomosis. *Am J Surg*. 2008;195(4):447-451.

18. Richards CH, Campbell V, Ho C, Hayes J, Elliott T, Thompson-Fawcett M. Smoking is a major risk factor for anastomotic leak in patients undergoing low anterior resection. *Colorectal Dis*. 2012;14(5):628-633.

19. Krarup PM, Jorgensen LN, Andreasen AH, Harling H, Danish Colorectal Cancer Group. A nationwide study on anastomotic leakage after colonic cancer surgery. *Colorectal Dis*. 2012;14(10):e661-7.

20. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287(5462):2398-2399.

21. Iversen LH. *Aspects of survival from colorectal cancer in Denmark: doctoral thesis.* [Aarhus]: Faculty of Health Sciences, Aarhus University; 2011.

22. Danish Colorecal Cancer Group. *Nationwide database of colorectal cancer: annual report 2010.* Copenhagen: DCCG; 2011:103 p.

23. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J Anaesth*. 2011;55(2):111-115.

24. Ostenfeld EB, Froslev T, Friis S, Gandrup P, Madsen MR, Sogaard M. Completeness of colon and rectal cancer staging in the Danish Cancer Registry, 2004-2009. *Clin Epidemiol*. 2012;4 Suppl 2:33-38.

25. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41.

26. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of Glucocorticoids and Risk of Venous Thromboembolism: A Nationwide Population-Based Case-Control Study. *JAMA Intern Med*. 2013:1-10.

27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30-33.

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

29. Fleiss JL, Levin BA, Paik MC. *Statistical methods for rates and proportions.* 3. ed. ed. Hoboken, N.J.: J. Wiley; 2003:xxvii, 760 s., ill.

30. Davis B, Rivadeneira DE. Complications of colorectal anastomoses: leaks, strictures, and bleeding. *Surg Clin North Am*. 2013;93(1):61-87.

31. Klein M, Gogenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ*. 2012;345:e6166.

32. Eriksen TF, Lassen CB, Gogenur I. Treatment with corticosteroids and the risk of anastomotic leakage following lower gastrointestinal surgery: A literature survey. *Colorectal Dis*. 2013.

33. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339-351.

34. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.

35. Nickelsen TN, Harling H, Kronborg O, Bulow S, Jorgensen T. The completeness and quality of the Danish Colorectal Cancer clinical database on colorectal cancer. *Ugeskr Laeger*. 2004;166(36):3092-3095.

36. Danish Colorectal Cancer Group. *DCCG's nationale retningslinier.* Available at http://dccg.dk/retningslinjer/indeks.html. Accessed 5/14/2015

37. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43(3):519-527.

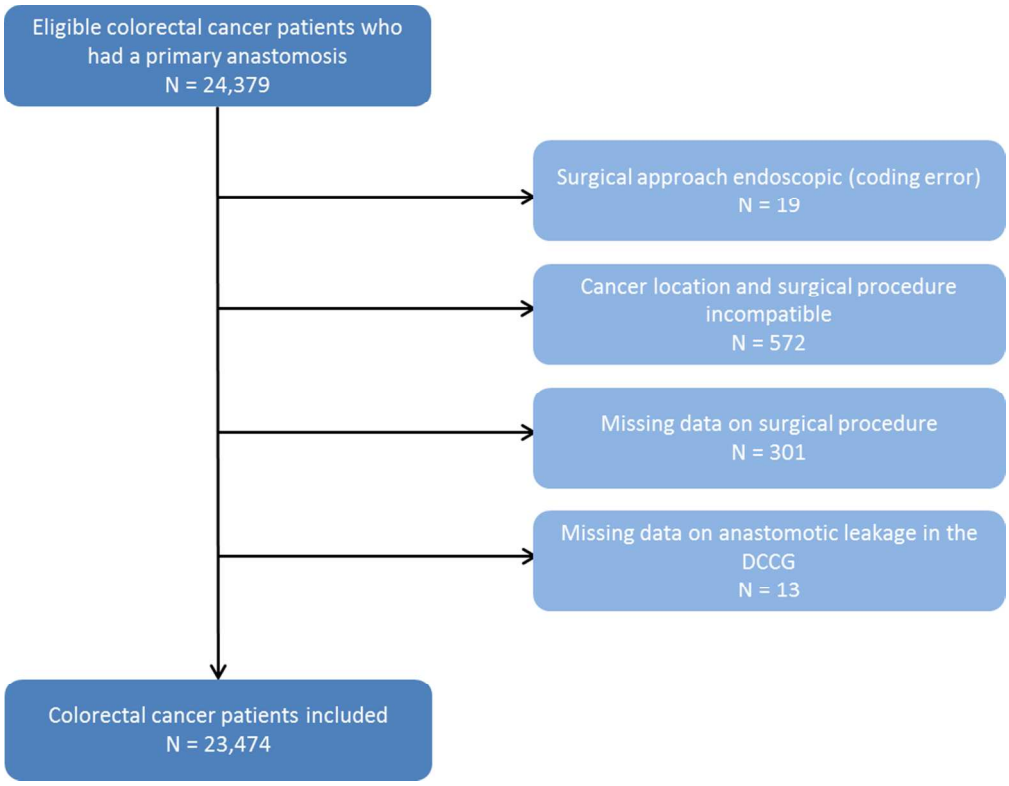

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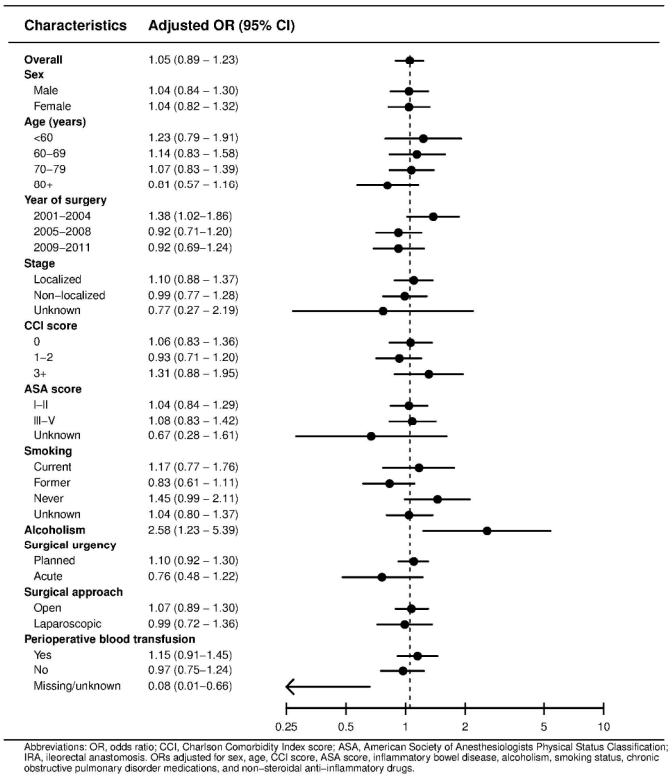
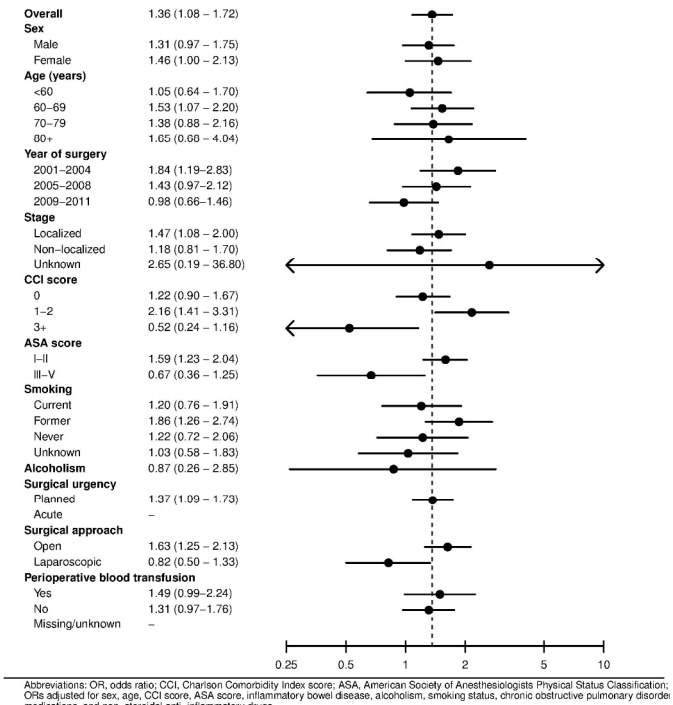
Figure 2a. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following colon cancer surgery compared to never–use, Denmark 2001–2011**



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; IRA, ileorectal anastomosis. ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorder medications, and non–steroidal anti–inflammatory drugs.

209x297mm (300 x 300 DPI)

Figure 2b. **Subgroup analysis associating use of any glucocorticoids and anastomotic leakage following rectum cancer surgery compared to never–use, Denmark 2001–2011**



Abbreviations: OR, odds ratio; CCI, Charlson Comorbidity Index score; ASA, American Society of Anesthesiologists Physical Status Classification; ORs adjusted for sex, age, CCI score, ASA score, inflammatory bowel disease, alcoholism, smoking status, chronic obstructive pulmonary disorde medications, and non–steroidal anti–inflammatory drugs.

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SUPPORTING INFORMATION

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

Table S1. 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.

Table S2. 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

Table S3. 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.

Table S4. 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

Table S5. ICD-codes defining Anastomotic leakage

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

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	

		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9, 12
		(b) Give reasons for non-participation at each stage	Figure
		(c) Consider use of a flow diagram	Figure
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12, 14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the	18

	present study and, if applicable, for the original study on which the present article is based