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

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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 patients who had undergone a primary anastomosis after a colorectal cancer resection by linking medical registries. Participants who filled their most recent glucocorticoid prescription ≤90, 91–365 and >365 days before their surgery date were categorised as current, recent and former users, respectively.

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

Results: Of the 18 190 patients with colon cancer, anastomotic leakage occurred in 1184 (6.5%). Glucocorticoid use overall was not associated with an increased risk of leakage (6.4% vs 6.9% among never-users; OR 1.05; 95% CI 0.89 to 1.23). Categories of oral, inhaled or intestinal-acting glucocorticoids did not greatly affect risk of leakage. Anastomotic leakage occurred in 695 (13.2%) of 5284 patients with rectal cancer. Glucocorticoid use overall slightly increased risk of leakage (14.6% vs 12.8% among never-users; OR 1.36, 95% CI 1.08 to 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, and 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 immunosuppressive 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 by the consideration of colon and rectal surgery together rather than separately.[12–14 17] It is important to

distinguish between colon and rectal procedures, because the anatomy and surgical techniques differ, leading to substantial differences in leakage rates: 3–4% after colonic surgery compared with 11–12% after rectal surgery.[19]

On the basis of 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 patients with colon and rectal cancer.

MATERIALS AND METHODS

Setting

We conducted a cohort study in the setting of the entire Danish population, comprising approximately 6.5 million individuals cumulatively over the study period. The Danish National Health Care provides free access to tax-supported health services for all residents and refunds a part of patient costs for most prescribed drugs. Health service utilisation is registered to individual patients by use of the personal identification number assigned to each Danish citizen at birth and to residents on immigration. The use of this system facilitates unambiguous individual-level linkage of nationwide registries.[20]

Patients with colon and rectal cancer

We identified all 23 474 residents of Denmark who had a colonic or rectal cancer resection and primary anastomosis between 1 May 2001 and 31 December 2011, and who were reported in 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, the latter defined as those located 15 cm or less from the anus, diagnosed or treated in surgical departments in Denmark.[21] Completeness of cancer registration (ie, the proportion of those registered in the database out of those registered in Danish National Registry of Patients) in the database was 98–100% during 2001–2010.[22] Data regarding patient, tumour 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 preoperative American Society of Anesthesiologists' Physical Status Classification (ASA) score,[23] cancer site, tumour 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), 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 thereafter by the treating physicians.

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

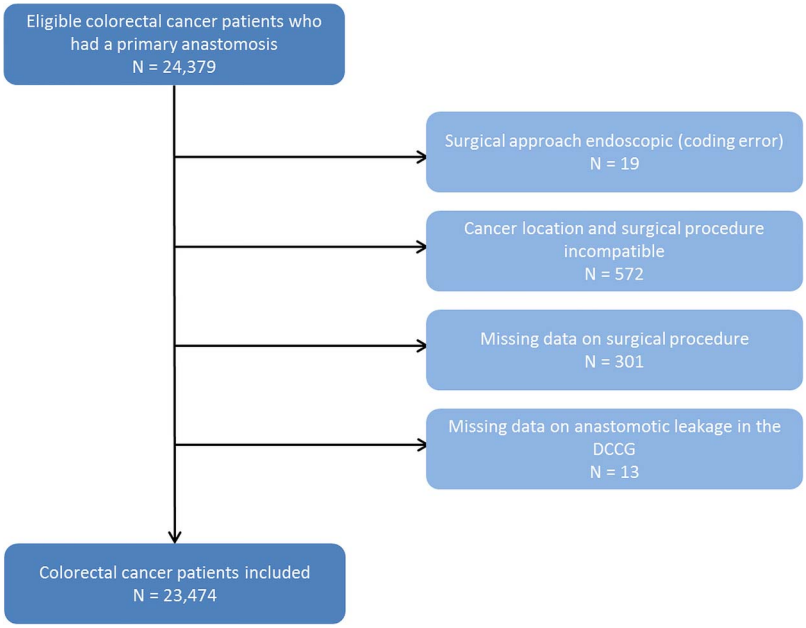

Figure 1 Flow chart illustrating exclusions of patients with colorectal cancer recorded in the Danish Colorectal Cancer Database (DCCD), 2001–2011.

CRC surgery date (see online supplementary 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. On the basis of methods used previously,[26] we categorised 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 (ie, treatment with glucocorticoids from at least two of the previous three groups). We further categorised 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 that 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 (CCI), we summarised each patient's medical history from 1977 until the surgery date, excluding colon or rectal cancer diagnosis (see online supplementary table S2 for ICD codes defining a modified CCI).[28] The CCI assigns between 1 and 6 points to a range of diseases, which are then summed to obtain an aggregate score. We grouped patients according to their CCI score: 0 (low comorbidity), 1–2 (moderate comorbidity) and 3+ (severe comorbidity). In addition, we obtained recorded diagnoses of inflammatory bowel disease, autoimmune disease, alcoholism and obesity, because these diagnoses are not included in the CCI (see online supplementary 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 (COPD) other than glucocorticoids, and immunosuppressants (see online supplementary 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 online supplementary 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, CT or surgery.

Statistical analysis

We analysed patients with colon and rectal cancer separately. We tabulated the frequencies of glucocorticoid use with regard to the characteristics of the patient, the tumour and the surgery, including p values, by using Pearson's χ^2 test. According to our predefined glucocorticoid exposure groups, we estimated absolute risk of anastomotic leakage within 30 days postoperatively and 95% CIs using Jeffreys' method.[29] Corresponding risk differences were calculated subtracting the estimate for never-use from those for glucocorticoid users. We computed 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. On the basis of their associations with both anastomotic leakage risk and glucocorticoid use, we included the following covariates in the model as potential confounders: sex, age, CCI score, ASA score (≤2, >2, unknown), history of inflammatory bowel disease, alcoholism/use of disulfiram (single variable) and smoking status at the time of the surgery (current, former, never or unknown), with medications for COPD 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 (eg, for smoking) were categorised separately and included in the analysis (see tables 1 and 2 for a description of categories within each covariate). To examine variations in postoperative anastomotic leakage, ORs were calculated within subgroups of sex, age, year of surgery, cancer site, cancer stage, CCI score, ASA score and smoking status, as well as surgical urgency and approach, type of procedure and perioperative blood transfusion.

In sensitivity analyses, we first changed the time window for filled glucocorticoid prescriptions to 60 and 120 days before the surgery dates. Second, because there are no clear standards for the recording of anastomotic leakage, we restricted anastomotic leakage to patients who were re-operated on, to heighten the predictive value of our outcome. Leakages that were treated only by non-surgical drainage, for example, ultrasonic, were not included in this analysis.

Statistical analyses were performed using Stata V.12.0 (StataCorp LP, College Station, Texas, USA) and SAS V.9.2 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Patients with colon cancer

We identified 18 190 patients with colon cancer who had a primary anastomosis after tumour resection during

Table 1 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 (%)	Colon cancer: 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
Localised	7192 (51.2)	2261 (54.5)	
Non-localised	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
Autoimmune 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
COPD medications	1547 (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 approach			0.004
Laparoscopy	3446 (24.5)	1111 (26.8)	
Laparotomy	10 595 (75.5)	3038 (73.2)	
Surgical procedure			0.000
Ileocaecal resection	45 (0.3)	8 (0.2)	
Right-sided hemicolectomy	6925 (49.3)	2239 (54.0)	
Transverse colon 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)	

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

Table 2 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
Localised	2460 (57.0)	557 (57.6)	
Non-localised	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
Autoimmune 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)	
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)	

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

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 vs 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.

Anastomotic leakage occurred in 1184 patients with colon cancer (6.5%). Glucocorticoid users contributed 287 cases (24.2%), yielding an overall absolute risk of leakage of 6.9% vs 6.4% among never-users (table 3). 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 3). Although not statistically significant, risk was slightly increased among current (adjusted OR (aOR)=1.24; 95% CI 0.82 to 1.88) and recent (aOR=1.43; 95% CI 0.87 to 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 to 3.84). We observed no association for inhaled glucocorticoids. With the exception of alcoholism (aOR=2.58; 95% CI 1.23 to 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 cut-off (data not shown). When we restricted analyses to anastomotic leakages that required surgical intervention, we observed 98 (8%) fewer outcomes. However, absolute and relative risk estimates were essentially unchanged (data not shown).

Rectal cancer patients

Of the 5284 patients with rectal cancer resected, 458 (8.7%) used glucocorticoids within 1 year before surgery. Among patients with rectal cancer, glucocorticoid users were more likely than never-users to be female and elderly (median age 68 years vs 66 years) (table 2). 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 patients with rectal cancer (13.2%). Overall, the absolute risk of leakage was 14.6% among glucocorticoid users versus 12.8% among never-users (table 4). Absolute risks among current, recent and former users of oral glucocorticoids were 15.9%, 13.0% and 16.3%, respectively. Current users of inhaled glucocorticoids had the highest absolute risk (17.7%); recent users of inhaled glucocorticoids and those using mixed glucocorticoids had the lowest risks (11.1% and 11.7%, respectively). Anastomotic leakage occurred among 16.7% of users of intestinal-acting glucocorticoids.

Table 3 Absolute and relative risk (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 to 6.8)	Referent	Referent	Referent
Any use	4149 (22.8)	287 (24.2)	6.9 (6.0 to 6.8)	0.5 (−0.3 to 1.4)	1.09 (0.95 to 1.25)	1.05 (0.89 to 1.23)
Oral use						
Current use	345 (1.9)	26 (2.2)	7.5 (5.1 to 10.7)	1.1 (−1.7 to 4.0)	1.19 (0.80 to 1.79)	1.24 (0.82 to 1.88)
Recent use	207 (1.1)	18 (1.5)	8.7 (5.4 to 13.1)	2.3 (−1.6 to 6.2)	1.40 (0.86 to 2.27)	1.43 (0.87 to 2.34)
Former use	948 (5.2)	53 (4.5)	5.6 (4.3 to 7.2)	−0.8 (−2.3 to 0.7)	0.87 (0.65 to 1.15)	0.90 (0.67 to 1.20)
Inhaled use						
Current use	434 (2.4)	32 (2.7)	7.4 (5.2 to 10.1)	1.0 (−1.5 to 3.5)	1.17 (0.81 to 1.68)	1.04 (0.70 to 1.53)
Recent use	252 (1.4)	16 (1.4)	6.3 (3.8 to 9.9)	−0.0 (−3.1 to 3.0)	0.99 (0.60 to 1.66)	0.96 (0.57 to 1.62)
Former use	742 (4.1)	51 (4.3)	6.9 (5.2 to 8.9)	0.5 (−1.4 to 2.3)	1.08 (0.81 to 1.45)	1.06 (0.78 to 1.44)
Intestinal acting use	54 (0.3)	5 (0.4)	9.3 (3.6 to 19.1)	2.9 (−4.9 to 10.6)	1.50 (0.59 to 3.76)	1.47 (0.56 to 3.84)
Mixed use	1167 (6.4)	86 (7.3)	7.4 (6.0 to 9.0)	1.0 (−0.6 to 2.5)	1.17 (0.93 to 1.47)	1.02 (0.78 to 1.35)

Values in parentheses are 95% CIs unless otherwise indicated.
*Calculated by subtracting the estimate for never-use from that for glucocorticoid users.
†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.

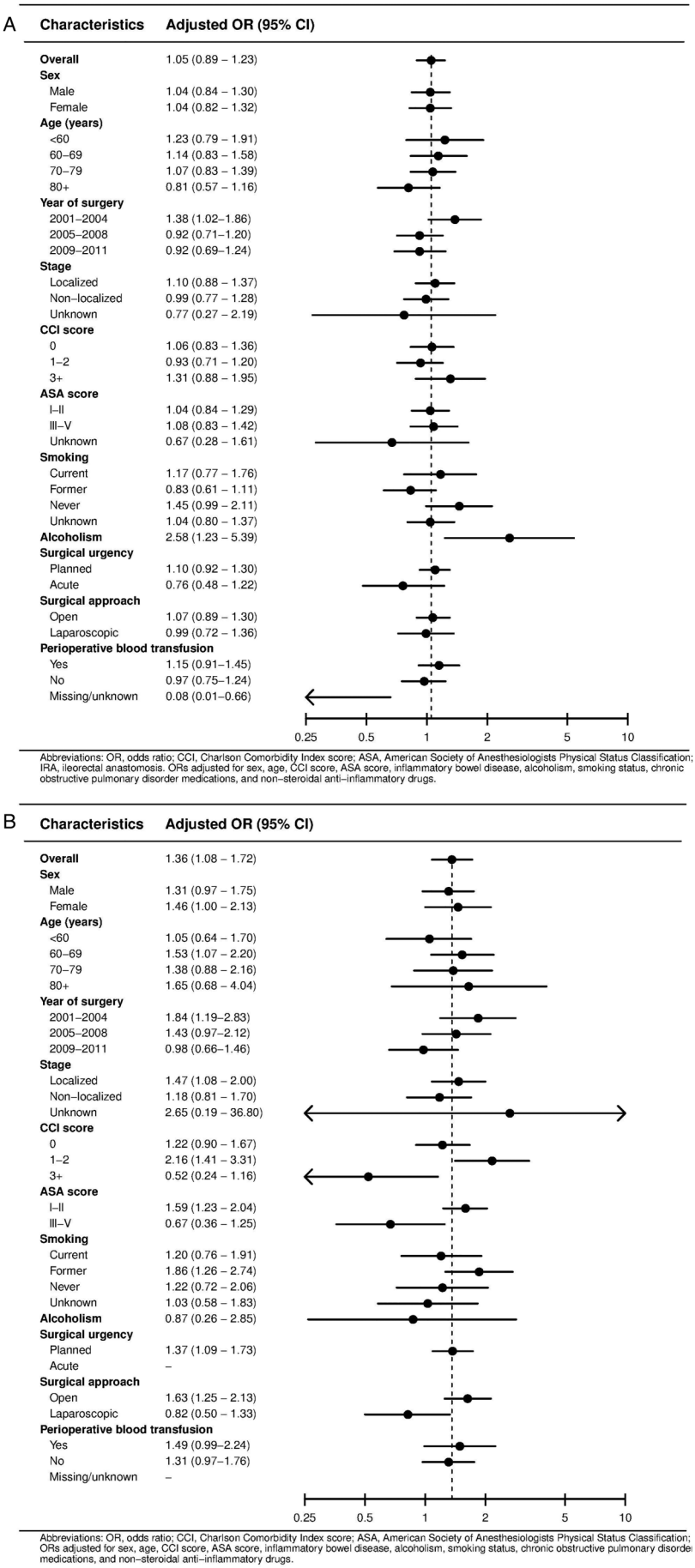

Figure 2 (A) Subgroup analysis associating glucocorticoids and anastomotic leakage following colon cancer surgery compared to never-use. (B) Subgroup analysis associating glucocorticoids and anastomotic leakage following rectal cancer surgery compared to never-use.

Table 4 Absolute and relative risk (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 to 13.9)	Referent	Referent	Referent
Any use	967 (18.3)	141 (20.3)	14.6 (12.5 to 16.9)	1.7 (−0.7 to 4.2)	1.16 (0.95 to 1.42)	1.36 (1.08 to 1.72)
Oral use						
Current use	63 (1.2)	10 (1.4)	15.9 (8.5 to 26.3)	3.0 (−6.0 to 12.1)	1.28 (0.65 to 2.53)	1.28 (0.64 to 2.56)
Recent use	46 (0.9)	6 (0.9)	13.0 (5.6 to 24.9)	0.2 (−9.6 to 10.0)	1.02 (0.43 to 2.41)	1.22 (0.51 to 2.92)
Former use	258 (4.9)	42 (6.0)	16.3 (12.2 to 21.1)	3.4 (−1.2 to 8.1)	1.32 (0.94 to 1.86)	1.42 (1.00 to 2.01)
Inhaled use						
Current use	113 (2.1)	20 (2.9)	17.7 (11.5 to 25.5)	4.9 (−2.2 to 12.0)	1.46 (0.89 to 2.39)	1.91 (1.11 to 3.30)
Recent use	45 (0.9)	5 (0.7)	11.1 (4.4 to 22.7)	−1.7 (−11.0 to 7.5)	0.85 (0.33 to 2.16)	1.04 (0.40 to 2.71)
Former use	190 (3.6)	28 (4.0)	14.7 (10.2 to 20.3)	1.9 (−3.2 to 7.0)	1.17 (0.78 to 1.77)	1.39 (0.89 to 2.17)
Intestinal-acting use	12 (0.2)	2 (0.3)	16.7 (3.6 to 43.6)	3.8 (−17.3 to 24.9)	1.36 (0.30 to 6.22)	1.27 (0.27 to 5.95)
Mixed use	240 (4.5)	28 (4.0)	11.7 (8.1 to 16.2)	−1.2 (−5.3 to 3.0)	0.90 (0.60 to 1.34)	1.15 (0.72 to 1.84)

Values in parentheses are 95% CIs unless otherwise indicated.
*Calculated by subtracting the estimate for never-use from those for glucocorticoid users.
†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.

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 to 1.72) (table 4). Relative risks were modestly increased in all subgroups of oral glucocorticoid users (current use: aOR=1.28; 95% CI 0.64 to 2.56; recent use: aOR=1.22; 95% CI 0.51 to 2.92; and former use: aOR=1.42; 95% CI 1.00 to 2.01). Among users of inhaled glucocorticoids, current users had the highest risk: aOR=1.91; 95% CI 1.11 to 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 to 3.46) and somewhat lower for recent users (aOR=0.97; 95% CI 0.44 to 2.17). However, the 95% CIs for these estimates overlapped with those of the main analysis. Remaining estimates were virtually unchanged using either cut-off (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 patients with rectal cancer, relative risk increased moderately for almost any type 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 is therefore limited.

This study extends previous research because it includes considerably more participants than previous investigations and provides detailed data on different types of glucocorticoids and the timing of their use. In addition, we analysed patients with colon and rectal cancer separately. Previous studies that examined whether glucocorticoids predict anastomotic leakage after CRC resection had inconsistent results.[12–18] On the basis of 12 studies published between 1996 and 2012, a recent review provided combined rates for leakage: 6.8% (95% CI 5.5% to 9.1%) in 1034 patients exposed to steroids preoperatively versus 3.3% (95% CI 2.9% to 3.6%) in 8410 unexposed patients.[32] Overall risk was higher in our cohort of patients with colon and rectal cancer. 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 healthcare 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 patients with CRC 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, increasing the number of cases by 9%. Furthermore, a sensitivity analysis we restricted to those who required reoperation, to increase the validity of the outcome, did not greatly change the observed associations.

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, co-payment 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 subcategorise 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 (CCI score=0). However, 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 CCI conditions from hospitalisations and outpatient visits may be incomplete. Also, we cannot exclude the possibility of some uncontrolled confounding by preoperative radiochemotherapy that 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] has low emetogenicity and does not commonly imply the requirement of anti-emetics such as glucocorticoids. Therefore, preoperative oncological 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 CRC 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 under-reporting. Although we adjusted for smoking and associated diseases/medications for COPD as proxies, residual confounding may explain the apparent association between inhaled glucocorticoids and anastomotic leakage in patients with rectal cancer. 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.

Contributors HTS, RE and EBO designed the study. EBO and AHR were responsible for acquiring the data and conducting the analysis. EBO drafted the first version of the manuscript, and all the authors contributed to the interpretation of the findings and critical revision of the draft. All the authors approved the final version of the manuscript submitted, including the authorship list.

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