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.

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.14,16-18 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. 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.

**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 (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. 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. 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. We retrieved data regarding preoperative American Society of Anesthesiologists’ Physical Status Classification (ASA) score, 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) 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. 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...
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 $\chi^2$ 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. 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 ($\leq 2$, $>2$, 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. 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 18190 patients with colon cancer who had a primary anastomosis after tumour resection during

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

| Characteristics                          | Colon cancer |     | Glucocorticoid use, N=4149 |     | p Value |
|------------------------------------------|--------------|-----|---------------------------|-----|---------|
|                                          | No glucocorticoid use, N=14 041 |     |                           |     |         |
|                                          | n (%)        |     | n (%)                     |     |         |
| Sex                                      |              |     |                           |     |         |
| Female                                   | 7122 (50.7)  |     | 2369 (57.1)               |     | 0.000   |
| Male                                     | 6919 (49.3)  |     | 1780 (42.9)               |     |         |
| Age, years                               |              |     |                           |     |         |
| <60                                       | 2399 (17.1)  |     | 482 (11.6)                |     | 0.000   |
| 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                        |              |     |                           |     |         |
| 2001–2004                                 | 4767 (34.0)  |     | 1074 (25.9)               |     | 0.000   |
| 2005–2008                                 | 5327 (37.9)  |     | 1642 (39.6)               |     |         |
| 2009–2011                                 | 3947 (28.1)  |     | 1433 (34.5)               |     |         |
| Stage                                     |              |     |                           |     |         |
| Localised                                 | 7192 (51.2)  |     | 2261 (54.5)               |     | 0.001   |
| Non-localised                             | 6510 (46.4)  |     | 1785 (43.0)               |     |         |
| Unknown                                   | 339 (2.4)    |     | 103 (2.5)                 |     |         |
| CCI score                                 |              |     |                           |     |         |
| 0                                         | 8557 (60.9)  |     | 1448 (34.9)               |     | 0.001   |
| 1–2                                       | 4074 (29.0)  |     | 1812 (43.7)               |     |         |
| 3+                                        | 1410 (10.0)  |     | 889 (21.4)                |     |         |
| ASA score                                 |              |     |                           |     |         |
| ≤2                                        | 10 616 (75.6)|     | 2575 (62.1)               |     | 0.000   |
| >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                               |              |     |                           |     |         |
| Current use                               | 2088 (14.9)  |     | 563 (13.6)                |     | 0.000   |
| Former use                                | 4159 (29.6)  |     | 1429 (34.4)               |     |         |
| Never use                                 | 3569 (25.4)  |     | 896 (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 hemicolecotomy                | 6925 (49.3)  |     | 2239 (54.0)               |     |         |
| Transverse colon resection                | 356 (2.5)    |     | 101 (2.4)                 |     |         |
| Left-sided hemicolecotomy                 | 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.
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 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. We observed no association for inhaled glucocorticoids. With the exception of intestinal-acting glucocorticoids, which was imprecise (aOR=1.47, 95% CI 0.56 to 3.84). We observed no association between use of intestinal-acting glucocorticoids and anastomotic leakage after colon cancer resection, Denmark, 2001–2011.

| Glucocorticoid use          | Leakage, n=1184 | Leakage, n=1184 |
|----------------------------|-----------------|-----------------|
| No use                     | 897 (75.8)      | 897 (75.8)      |
| Any use                    | 287 (24.2)      | 287 (24.2)      |

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 (15.2%). 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.
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.

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A Characteristics Adjusted OR (95% CI)

| Overall | 1.05 (0.89 – 1.23) |
|---------|-------------------|
| Sex     |                   |
| Male    | 1.04 (0.84 – 1.30) |
| Female  | 1.04 (0.82 – 1.32) |
| Age (years) |               |
| <60     | 1.23 (0.78 – 1.91) |
| 60–69   | 1.14 (0.83 – 1.58) |
| 70–79   | 1.07 (0.83 – 1.39) |
| 80+     | 0.91 (0.53 – 1.56) |
| Year of surgery |     |
| 2001–2004 | 1.38 (1.02 – 1.96) |
| 2005–2008 | 0.02 (0.71 – 1.20) |
| 2009–2011 | 0.02 (0.69 – 1.24) |
| Stage   |                   |
| Localized | 1.10 (0.88 – 1.37) |
| Non-localized | 0.99 (0.77 – 1.28) |
| Unknown  | 0.77 (0.27 – 2.19) |
| CCI score |                 |
| 0       | 1.06 (0.83 – 1.36) |
| 1–2     | 0.93 (0.71 – 1.20) |
| 3+      | 1.31 (0.88 – 1.95) |
| ASA score |             |
| I–II    | 1.04 (0.84 – 1.29) |
| III–IV  | 1.08 (0.83 – 1.42) |
| Unknown | 0.67 (0.28 – 1.61) |
| Smoking |                   |
| Current | 1.17 (0.77 – 1.76) |
| Former  | 0.83 (0.61 – 1.11) |
| Never   | 1.45 (0.99 – 2.11) |
| Unknown | 1.04 (0.80 – 1.37) |
| Alcoholism |             |
| Yes     | 2.58 (1.23 – 5.39) |
| No      |                   |
| Surgical urgency |         |
| Planned | 1.10 (0.92 – 1.30) |
| Acute   | 0.76 (0.48 – 1.22) |
| Surgical approach |         |
| Open    | 1.07 (0.89 – 1.30) |
| Laparoscopic | 0.99 (0.72 – 1.36) |
| Perioperative blood transfusion | |
| Yes     | 1.15 (0.91 – 1.45) |
| No      | 0.97 (0.75 – 1.24) |
| Missing/unknown | 0.08 (0.01–0.90) |

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 disorder medications, and non-steroidal anti-inflammatory drugs.

B 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 | 0.99 (0.66–1.48) |
| Stage   |                   |
| Localized | 1.47 (1.05 – 2.00) |
| Non-localized | 1.18 (0.81 – 1.70) |
| Unknown  | 2.65 (0.19 – 36.90) |
| 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–IV  | 0.67 (0.36 – 1.25) |
| Smoking |                   |
| Current | 1.20 (0.76 – 1.91) |
| Former  | 1.86 (1.26 – 2.74) |
| Never   | 1.02 (0.72 – 1.46) |
| Unknown | 1.03 (0.58 – 1.83) |
| Alcoholism |             |
| Yes     | 0.87 (0.26 – 2.85) |
| No      |                   |
| Surgical urgency |         |
| Planned | 1.37 (1.09 – 1.73) |
| Acute   |                   |
| Surgical approach |         |
| Open    | 1.63 (1.25 – 2.13) |
| Laparoscopic | 0.92 (0.50 – 1.73) |
| Perioperative blood transfusion | |
| Yes     | 1.49 (0.99–2.24) |
| No      | 1.31 (0.87 – 1.96) |

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 disorder medications, and non-steroidal anti-inflammatory drugs.
### 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 | Leakage, N=695 | 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.

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, the relative risk increased moderately for almost any type of glucocorticoid use. In addition, we observed 215 (31%) fewer outcomes. However, this study extends previous research because it includes considerably more participants than previous investigations and provides the detailed data on different types of glucocorticoids and the timing of their use. In this study, we extended previous analyses by analysing the association between glucocorticoids and postoperative anastomotic leakage (figure 2B).

### DISCUSSION

Compared with non-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=1.11; 95% CI 0.77 to 1.64; recent use: aOR=1.21; 95% CI 0.80 to 1.84; former use: aOR=1.30; 95% CI 0.86 to 2.02). Relative risks associated with the use of inhaled glucocorticoids increased modestly from current use (aOR=1.27; 95% CI 0.82 to 1.97) to recent use (aOR=1.46; 95% CI 0.97 to 2.19) to former use (aOR=1.92; 95% CI 1.20 to 3.04). The current use of intestinal-acting glucocorticoids was associated with an increased risk of anastomotic leakage (aOR=2.06; 95% CI 1.08 to 3.92). The current use of mixed glucocorticoids showed no strong association (aOR=0.83; 95% CI 0.50 to 1.41).

For both cancers, relative risks were modestly increased in all subgroups of oral glucocorticoid users (current use: aOR=1.11; 95% CI 0.77 to 1.64; recent use: aOR=1.21; 95% CI 0.80 to 1.84; former use: aOR=1.30; 95% CI 0.86 to 2.02). Relative risks associated with the use of inhaled glucocorticoids increased modestly from current use (aOR=1.27; 95% CI 0.82 to 1.97) to recent use (aOR=1.46; 95% CI 0.97 to 2.19) to former use (aOR=1.92; 95% CI 1.20 to 3.04). The current use of intestinal-acting glucocorticoids was associated with an increased risk of anastomotic leakage (aOR=2.06; 95% CI 1.08 to 3.92). The current use of mixed glucocorticoids showed no strong association (aOR=0.83; 95% CI 0.50 to 1.41).
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{35} Nonetheless, because there are no clear standards for the recording of anastomotic leakage,\textsuperscript{35} 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,\textsuperscript{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\textsuperscript{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.\textsuperscript{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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