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Perioperative Use of Nonsteroidal Anti-inflammatory Drugs Decreases the Risk of Recurrence of Cancer After Colorectal Resection: A Cohort Study Based on Prospective Data

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ABSTRACT

Background. Perioperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) is known to reduce inflammatory response in relation to surgery. Inflammation may promote recurrence of cancer, thus inhibition by use of NSAIDs could reduce recurrence after surgery.

Objective. The aim of this study was to examine the association between perioperative use of NSAIDs and cancer recurrence, as well as disease-free survival (DFS) and mortality after colorectal cancer surgery.

Methods. This was a cohort study based on data from a prospective clinical database, electronic medical records, and nationwide registers, and included patients from six major colorectal centers in Denmark. The primary outcome was cancer recurrence, while secondary outcomes included 5-year mortality and DFS.

Results. Overall, 2308 patients undergoing colorectal cancer surgery between 1 January 2006 and 31 December 2009 were included. A total of 909 patients received at least 2 days of treatment with NSAIDs, of whom 702 (77.2%) received ibuprofen and 204 (22.4%) received diclofenac. Cox regression analysis adjusting for NSAIDs resulted in decreased recurrence risk (adjusted hazard ratio [$HR_{adjusted}$] 0.84, 95% confidence interval [CI] 0.72–0.99; $p = 0.042$). Competing risk analysis confirmed the finding, with an $HR_{adjusted}$ of 0.76 (95% CI 0.60–0.97; $p = 0.026$). There was no significant effect on mortality or DFS. Sensitivity analysis of the effect of ibuprofen reported an $HR_{adjusted}$ of 0.83 (95% CI 0.70–1.00; $p = 0.047$). In restricted analyses of localized disease only (Union for International Cancer Control [UICC] I–II) and elective surgery only, no effect was found (localized: $HR_{adjusted}$ 0.81, 95% CI 0.62–1.06, $p = 0.12$; elective: $HR_{adjusted}$ 0.85, 95% CI 0.72–1.01, $p = 0.063$).

Conclusions. Perioperative use of NSAIDs was associated with a reduced risk of cancer recurrence after resection for colorectal cancer. No effect on 5-year mortality or DFS was found.

In curative-intent treatment of colorectal cancer, surgery remains the cornerstone. Surgery in itself induces an inflammatory response with the purpose of optimizing the healing process after surgical trauma.[1] This neural, inflammatory, angiogenetic response results in optimal wound healing.[2] At the same time, cancer cells thrive in this inflammatory environment, where local and systemic responses to tissue injury promote malignant growth.[3] Cancer cells that are not resected therefore have improved growth conditions, and postsurgical micrometastases have increased potential of leading to recurrence of cancer.[3] This has been demonstrated in several types of cancer, where surgery has been shown to increase the rate of recurrence.[4–6] Indeed, a prolonged inflammatory state leads to a greater risk of recurrence.[7,8] In addition, the magnitude of the surgical stress response could also influence the risk of recurrence.[3]

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Nonsteroidal anti-inflammatory drugs (NSAIDs), often used as part of a multimodal analgesic regimen after surgery, have been shown to decrease the tumor-associated inflammation in animal models and potentially prevent metastasis.[9–11] In humans, a decreased inflammatory response at surgery is found with perioperative use of NSAIDs. Furthermore, studies have shown a lower recurrence rate after surgery for breast cancer[12,13] and hepatocellular carcinoma.[14]

In an historic cohort of prospectively collected data from 2006 to 2009, postoperative use of diclofenac, a cyclooxygenase (COX)-2 selective NSAID, led to an increased risk of anastomotic leakage after primary colorectal resection for cancer.[15] This implies decreased local tissue healing after surgery, and thus decreased inflammatory response. The same effect was not found with respect to a nonselective NSAID such as ibuprofen. Paradoxically, anastomotic leakage itself has been shown to increase the risk of cancer recurrence due to inflammatory response to leakage.[16]

The aim of this study was to investigate whether the use of NSAIDs in the immediate postoperative period after elective colorectal resection influenced the risk of cancer recurrence.

METHODS

Study Cohort

This historic cohort study was reported according to the RECORD guidelines, an extension of the existing STROBE guidelines,[17] and was based on data from the Danish Colorectal Cancer Group's (DCCG) national prospective database. Patients from the six major colorectal cancer surgery centers in eastern Denmark were included. Patients underwent a curative-intent operation for colorectal cancer between 1 January 2006 and 31 December 2009 with either colonic or rectal resection, and received a primary anastomosis.

The DCCG database includes, among others, information on demographic factors, such as comorbidities and perioperative and postoperative treatment. Overall, 98.6% of patients with a diagnosis of colorectal cancer are included as part of the database population.[18] Information including age at diagnosis, American Society of Anesthesiologists (ASA) score (1–5), Charlson Comorbidity Index (CCI),[19] WHO performance score (1–5), alcohol consumption (categorized as the number of weekly drinks of alcohol [1 drink = 12 g ethanol]: 0 drinks, 1–14 drinks, 15–21 drinks, > 21 drinks), tobacco use (current smoker, former smoker, or never smoker), blood transfusion in the perioperative period, body mass index (BMI; < 20 kg/m^2, 20–24.9 kg/m^2, 25–29.9 kg/m^2, > 30 kg/m^2), tumor classification (TNM and Union for International Cancer Control [UICC]), operative procedure(s), type of surgery (emergency or elective surgery), and date of surgery was obtained from the DCCG database. A unique personal identification number (CPR number) is assigned to all Danish citizens and information on mortality is documented in the Danish Civil Registration System. The database is complete and virtually no registered individuals are lost to follow-up.[20] The CPR number is used as an inter-source linkage throughout all registries. Hospital contacts are registered in the Danish National Patient Register (NPR),[21] where data regarding hospital admissions, such as date of admission and discharge, diagnoses, and procedures, as well as outpatient visits, are registered.

Regarding biological specimens, standard data are coded using the Danish version of the Systemized Nomenclature of Medicine (SNOMED) codes by all Danish pathology departments. The Danish Pathology Register (DPR)[22] use SNOMED codes, and pathologically diagnosed recurrences are documented in the Register.

Assessment of Nonsteroidal Anti-inflammatory Drug Use

Electronic medical records have been used in Danish hospitals since 2003. All treatments administered at a hospital are prospectively documented. Medical staff administer treatment and simultaneously complete electronic registration, rendering data collection thorough and close to complete. Postoperative NSAID consumption, including type, regimen, date of prescription and dose, was registered for each patient by three independent reviewers. Postoperative consumption of NSAIDs was defined as a minimum of 2 days of treatment with a clinically relevant dose of an NSAID through the first 7 days after surgery, while relevant daily dose was defined as at least 50 mg for diclofenac and at least 800 mg for ibuprofen.[23] The presence or absence of NSAID treatment in the perioperative period was confirmed to be based primarily on perioperative standard analgesic treatment, and not based on indication.[23]

Study Design

Patients from the historical cohort were included in the study and grouped/stratified according to the presence or absence of NSAID treatment as defined above. The primary outcome was recurrence of cancer within 5 years after surgery, while overall survival (OS) and disease-free survival (DFS) were secondary outcomes.

Recurrence during follow-up was estimated using a validated algorithm described in detail elsewhere.[24] This algorithm is based on:

- NPR-registered metastasis codes 180 days after the first colorectal cancer surgery, and, at the same time, no new primary cancer diagnosis from the date of colorectal cancer surgery to the date of the metastasis code.
- Cytostatic therapy, registered in the NPR, at least 180 days after primary colorectal cancer surgery and at least 60 days after the last NPR-registered cytostatic therapy code, without a new occurrence of primary tumor from the date of colorectal cancer surgery to the date of the cytostatic therapy code.
- DPR-registered SNOMED combinations indicating recurrence documented at least 180 days after the primary colorectal cancer surgery, with no new primary cancer diagnosis.
- Specific codes for local colorectal cancer recurrence in the NPR (used since the beginning of 2012), any time after primary colorectal surgery: DC189X and DC209X.

Exclusion criteria were death within 180 days after surgery, or metastases at surgery or within 180 days after surgery, since investigation of recurrence is irrelevant in such cases.[24] Furthermore, other cancer diagnoses (except nonmelanoma skin cancer) before the registered date of colorectal cancer diagnosis were also considered exclusion criteria as the NPR-registered metastasis codes do not specify the origin of metastasis.

Statistical Methods

Cox regression models were used to estimate all-cause survival, recurrence-free survival (RFS), and DFS. Patients underwent censoring if a new primary tumor occurred or if death from any cause occurred within 180 days of surgery.

RFS was defined as the time from 180 days after surgery to cancer recurrence. Death was not defined as an event for this outcome. OS was defined as the time from 180 days after surgery to death from any cause within 5 years of surgery. Finally, DFS, combined the two abovementioned definitions with the occurrence of a new primary cancer as it was defined as the first of three possible events within 5 years after surgery: (1) recurrence of cancer; (2) death by any cause; and (3) development of a new primary cancer.

Primary analyses were adjusted for age and sex, whereas the multivariate models were adjusted for age at diagnosis, sex, BMI, preoperative oncological treatment, CCI, perioperative blood transfusions, surgical priority, anatomical cancer localization (colon or rectum), UICC stage, and anastomotic leakage. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A p value < 0.05 was considered statistically significant. Competing risk analyses were performed using the Fine and Grey method[25] in regard to RFS.

Sensitivity Analyses

Three separate sensitivity analyses were conducted. In one, a sensitivity analysis regarding the type of NSAID was conducted, adjusting in the same manner as the primary analysis. In the subsequent two analyses, the primary analysis was repeated using restrictions: (1) to create an homogenous group, patients undergoing acute surgery were excluded; and (2) to identify those with localized disease, only patients with UICC stage I or II disease were included.

SAS® Proprietary Software 9.4 (SAS Institute Inc., Cary, NC USA) was used for statistical analysis. This study was approved by the Scientific Council of the DCCG, and by the Danish Data Protection Agency (REG-081-2018) prior to initiation.

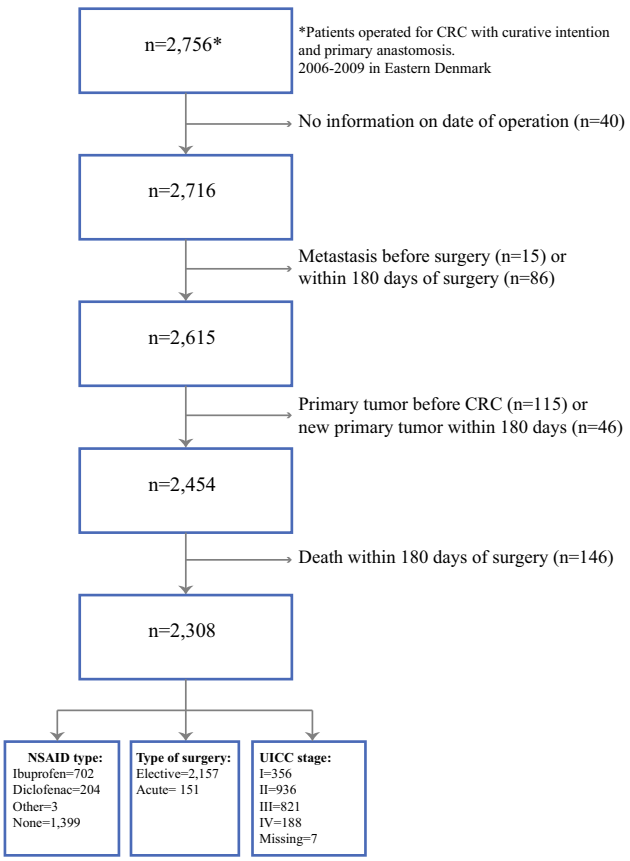

FIG. 1 Selection of patients included in the study. *CRC* colorectal cancer, *UICC* Union for International Cancer Control, *NSAID* nonsteroidal anti-inflammatory drug

TABLE 1 Demography of the study population, stratified by NSAID use (yes/no)

	NSAID		All	*p* value
	No	Yes		
Acute surgery	84 (6)	67 (7)	151 (7)	0.19
ASA classification				
1	322 (23)	254 (28)	576 (25)	0.018
2	840 (60)	534 (59)	1374 (60)	
3	211 (15)	113 (12)	324 (14)	
4	9 (0.6)	3 (0.3)	12 (0.5)	
Missing	17 (1)	5 (1)	22 (1)	
NSAID type				
Other	–	3 (0.3)	1402 (61)	–
Ibuprofen	–	702 (77)	702 (30)	
Diclofenac	–	204 (22)	204 (9)	
Male	698 (50)	491 (54)	1189 (52)	0.053
Tobacco use				
Active	256 (18)	123 (14)	379 (16)	< 0.0001
Former	521 (37)	278 (31)	799 (35)	
Never	446 (32)	296 (33)	742 (32)	
Missing	176 (13)	212 (23)	388 (17)	
Alcohol				
0	353 (25)	175 (19)	528 (23)	< 0.0001
1–14	619 (44)	369 (41)	988 (43)	
15–21	91 (7)	62 (7)	153 (7)	
> 21	153 (11)	87 (10)	240 (10)	
Missing	183 (13)	216 (24)	399 (17)	
Tumor site				
Colon	1031 (74)	720 (79)	1751 (76)	0.003
Rectum	368 (26)	189 (21)	557 (24)	
T stage				
1	75 (5)	62 (7)	137 (6)	0.074
2	186 (13)	99 (11)	285 (12)	
3	906 (65)	562 (62)	1468 (64)	
4	220 (16)	177 (19)	397 (17)	
Missing	12 (1)	9 (1)	21 (1)	
Perioperative transfusion				
Yes	243 (17)	202 (22)	445 (19)	0.013
Missing	3 (0.2)	1 (0.1)	4 (0.2)	
Anastomotic leakage	63 (5)	73 (8)	136 (6)	< 0.001
CCI score				
0	956 (68)	652 (72)	1608 (70)	0.22
1–2	359 (26)	209 (23)	568 (25)	
> 2	84 (6)	48 (5)	132 (6)	
Age, years				
≤ 60	282 (20)	221 (24)	503 (22)	0.11
> 60–70	471 (34)	298 (33)	769 (33)	
> 70–80	457 (33)	270 (30)	727 (32)	
> 80	189 (14)	120 (13)	309 (13)	

TABLE 1 continued

	NSAID		All	*p* value
	No	Yes		
BMI				
≤ 20	363 (26)	278 (31)	641 (28)	0.017
> 20–25	463 (33)	312 (34)	775 (34)	
> 25–30	405 (29)	216 (24)	621 (27)	
> 30	168 (12)	103 (11)	271 (12)	
Surgical type				
Open	875 (63)	635 (70)	1510 (65)	< 0.001
Laparoscopic	524 (37)	274 (30)	798 (35)	
UICC stage				
1	217 (16)	139 (15)	356 (15)	< 0.001
2	582 (42)	354 (39)	936 (41)	
3	510 (37)	311 (34)	821 (36)	
4	86 (6)	102 (11)	188 (8)	
Missing	4 (0.3)	3 (0.3)	7 (0.3)	
Recurrence	390 (28)	240 (26)	630 (27)	0.44
Disease-free survival	693 (50)	463 (51)	1156 (50)	0.51
Overall survival	360 (26)	250 (28)	610 (26)	0.35

Data are expressed as number of patients (%)

The total number of patients in each category does not necessarily add up to 2308 due to missing data

ASA American Society of Anesthesiologists, *NSAID* nonsteroidal anti-inflammatory drug, *CCI* Charlson Comorbidity Index, *BMI* body mass index, *UICC* Union for International Cancer Control

RESULTS

Overall Identification of Population

A total of 2756 patients fulfilled the inclusion criteria and were eligible for inclusion in this study. Of these, 448 patients had missing data regarding the date of operation ($n = 40$) or were excluded due to other reasons (Fig. 1). Thus, 2308 patients were included in the study, of whom 909 received at least 2 days of treatment with any type of NSAID. Of the treated patients, 702 (77.2%) received ibuprofen and 204 (22.4%) received diclofenac; 3 (0.4%) patients received a different type of NSAID. No patients received two or more types of NSAIDs.

Table 1 presents demographic variables and patient characteristics. The mean age of the entire population was 68.5 years (standard deviation ± 10.8), and sex was equally distributed (1189 [52%] men). Overall, 630 (27%) patients were diagnosed with recurrence of cancer, and 610 (26%) patients died within 5 years after surgery. A total of 1751 (76%) patients had colonic tumors, whereas the remaining had rectal tumors. Among patients who did not receive NSAIDs, 63 (5%) experienced an anastomotic leak, along with 73 (8%) of the treated patients ($p < 0.001$).

Table 2 presents demographic variables and patient characteristics regarding the type of NSAID use.

Recurrence-Free Survival

Recurrence of cancer occurred in 390 (28%) controls, compared with 240 (26%) NSAID-treated patients ($p = 0.44$). In the primary analysis, no association with RFS was found (HR 0.94, 95% CI 0.80–1.01; $p = 0.41$); however, in the adjusted analysis, an association was found where treatment with NSAIDs resulted in a decreased risk of recurrence (adjusted HR [$HR_{adjusted}$] 0.84, 95% CI 0.72–0.99; $p = 0.042$) (Table 3). This association was confirmed in the competing risk model, with an $HR_{adjusted}$ of 0.76 (95% CI 0.60–0.97; $p = 0.026$).

Disease-Free Survival and Overall Survival

In the primary analysis, use of an NSAID was not associated with benefits in either DFS (HR 1.04, 95% CI 0.93–1.17; $p = 0.49$) or 5-year mortality (HR 1.10, 95% CI 0.94–1.30; $p = 0.24$). In the subsequent multivariate analyses, no association between NSAID use and DFS ($HR_{adjusted}$ 0.97, 95% CI 0.86–1.10; $p = 0.65$) or 5-year mortality was found ($HR_{adjusted}$ 0.96, 95% CI 0.81–1.13,

TABLE 2 Demography of the study population, stratified by type of NSAID[a]

	NSAID type			All	*p* value
	None	Ibuprofen	Diclofenac		
Acute surgery	85 (6)	51 (7)	15 (7)		
ASA classification					
1	323 (23)	212 (30)	41 (20)	576 (25)	0.004
2	842 (60)	396 (56)	136 (67)	1374 (60)	
3	211 (15)	86 (12)	27 (13)	324 (14)	
4	9 (1)	3 (0.4)	0 (0)	12 (1)	
Missing	17 (1)	5 (1)	0 (0)	22 (1)	
Male	699 (50)	374 (53)	116 (57)	1189 (52)	0.093
Tobacco					
Active	256 (18)	91 (13)	32 (16)	379 (16)	< 0.0001
Former	521 (37)	244 (35)	34 (17)	799 (35)	
Never	448 (32)	188 (27)	106 (52)	742 (32)	
Missing	177 (13)	179 (26)	32 (16)	388 (17)	
Alcohol					
0	354 (25)	116 (17)	58 (28)	528 (23)	< 0.0001
1–14	620 (44)	282 (40)	86 (42)	988 (43)	
15–21	91 (6)	48 (7)	14 (7)	153 (7)	
> 21	153 (11)	73 (10)	14 (7)	240 (10)	
Missing	184 (13)	183 (26)	32 (16)	399 (17)	
Tumor site					
Colon	1034 (74)	555 (79)	162 (79)	1751 (76)	0.013
Rectum	368 (26)	147 (21)	42 (21)	557 (24)	
T-stage					
1	76 (5)	52 (7)	9 (4)	137 (6)	0.002
2	186 (13)	77 (11)	22 (11)	285 (12)	
3	907 (65)	420 (69)	141 (69)	1468 (64)	
4	221 (16)	149 (21)	27 (13)	397 (17)	
5	10 (1)	3 (0.4)	5 (2)	18 (1)	
Missing	2 (0.1)	1 (0.1)	0 (0)	3 (0.1)	
Perioperative transfusion	243 (17)	178 (25)	24 (12)	445 (19)	< 0.0001
Anastomotic leakage	63 (4)	44 (6)	29 (14)	136 (6)	< 0.0001
CCI-score					
CCI score					
0	959 (68)	496 (71)	153 (75)	1608 (70)	0.29
1–2	359 (26)	165 (24)	44 (22)	568 (25)	
> 2	84 (6)	41 (6)	7 (3)	132 (6)	
Age, years					
≤ 60	284 (20)	162 (23)	57 (28)	503 (22)	0.23
> 60–70	471 (34)	238 (34)	60 (29)	769 (33)	
> 70–80	457 (33)	209 (30)	61 (30)	727 (32)	
> 80	190 (14)	93 (13)	26 (13)	309 (13)	
BMI					
≤ 20	365 (26)	234 (33)	42 (21)	641 (28)	< 0.0001
> 20–25	463 (33)	247 (35)	65 (32)	775 (34)	
> 25–30	405 (29)	159 (23)	57 (28)	621 (27)	
> 30	169 (12)	62 (9)	40 (20)	271 (12)	

TABLE 2 continued

	NSAID type			All	*p* value
	None	Ibuprofen	Diclofenac		
Surgical type					
Open	877 (63)	485 (69)	148 (73)	1510 (65)	< 0.001
Laparoscopic	525 (37)	217 (31)	56 (27)	798 (35)	
UICC stage					
1	218 (16)	113 (16)	25 (12)	356 (15)	0.002
2	582 (42)	271 (39)	83 (41)	936 (41)	
3	512 (37)	239 (34)	70 (34)	821 (36)	
4	86 (6)	78 (11)	24 (12)	188 (8)	
Missing	4 (0.3)	1 (0.1)	2 (1)	7 (0.3)	
Recurrence	392 (28)	182 (26)	56 (27)	630 (27)	0.61
Disease-free survival	695 (50)	363 (52)	98 (48)	1156 (50)	0.54
Overall survival	361 (26)	191 (27)	58 (28)	610 (26)	0.61

Data are expressed as number of patients (%)

The total number of patients in each category does not necessarily add up to 2308 due to missing data

ASA American Society of Anesthesiologists, *NSAID* nonsteroidal anti-inflammatory drug, *CCI* Charlson Comorbidity Index, *BMI* body mass index, *UICC* Union for International Cancer Control

[a]Three patients who received a different NSAID were excluded

$p = 0.60$) (Table 3). The open approach was a risk factor for overall mortality ($HR_{adjusted}$ 1.27, 95% CI 1.06–1.52; $p = 0.009$).

Sensitivity Analyses

All sensitivity analyses found similar tendencies regarding the association between NSAID use and RFS, as well as 5-year OS and DFS. Analysis regarding the type of NSAID, as seen in Table 4, presented an association between the use of ibuprofen and RFS ($HR_{adjusted}$ 0.83, 95% CI 0.67–1.00; $p = 0.047$).

The sensitivity analyses with restrictions are presented in Table 5. For the population consisting of elective surgical patients only, an $HR_{adjusted}$ of 0.85 (95% CI 0.72–1.01; $p = 0.063$) was found with respect to DFS. For the population with limited disease only, i.e. patients presenting with UICC stage I and II disease, no significant association was found with respect to RFS ($HR_{adjusted}$ 0.81, 95% CI 0.62–1.06; $p = 0.12$).

DISCUSSION

In this study, based on prospective data from nationwide clinical databases and electronic medical records including information on postoperative treatment, we used multivariate analyses to demonstrate a decreased risk of cancer recurrence with NSAID treatment after surgical resection for colorectal cancer. A competing risk analysis confirmed this finding. No effect was found on DFS or OS. Likewise, patients receiving postoperative ibuprofen had a significant reduction in risk of recurrence. In sensitivity analyses of UICC stage I–II, elective surgery, and treatment with diclofenac, similar tendencies were found as NSAIDs reduced the risk of recurrence but failed to reach statistical significance, perhaps due to the limited sample size in these subgroups. This is the first study to provide novel evidence that treatment with NSAIDs in immediate relation to surgery for colorectal cancer may influence the risk of recurrence.

NSAIDs are known to inhibit tumor-associated inflammation and reduce angiogenesis and lymphangiogenesis, thereby inhibiting the recurrence of cancer, as well as having several chemopreventive effects.[3] This is in part explained by inhibition of COX-2, which has been shown to be a promising antineoplastic target.[11,26] The COX-2 inflammatory pathway relies on prostaglandins, which are known as tumor-promoting agents.[27] The COX-2 pathway has been shown to be overexpressed in > 80% of colorectal cancers,[28] and overexpression affects the effect of aspirin treatment, which also inhibits COX-2.[29,30] Furthermore, alternative targets have been suggested as an explanation for the anticancer activities of NSAIDs, such as inhibition of the cancer-specific surface protein tNOX[31] and increased expression of human leukocyte antigen (HLA) class I and HLA-DR antigen of cancer cells.[32,33] In our study, we observed a pooled effect of NSAIDs, as well as ibuprofen alone. Diclofenac[34] is known to primarily inhibit

TABLE 3 Multivariate analysis

	p value	HR	95% CI	
Recurrence-free survival				
NSAID				
No		1		
Yes	0.0419	0.84	0.72	0.99
Preoperative oncological treatment				
No		1		
Yes	0.0739	1.45	0.97	2.18
UICC stage				
I		1		
II	0.0840	1.30	0.97	1.75
III	< 0.0001	2.35	1.76	3.12
IV	< 0.0001	6.53	4.70	9.05
Missing	0.87	0.85	0.12	6.18
Sex				
Female		1		
Male	0.41	1.07	0.91	1.26
Tumor site				
Rectum		1		
Colon	0.37	1.01	0.90	1.34
CCI				
0		1		
1–2	0.76	1.03	0.85	1.25
> 2	0.32	0.82	0.55	1.21
Surgical type				
Laparoscopic		1		
Open	0.47	1.07	0.90	1.26
Anastomotic leakage				
No		1		
Yes	0.19	1.24	0.90	1.70
Age, years				
≤ 60		1		
> 60–70	0.0832	0.84	0.68	1.02
> 70–80	0.0013	0.70	0.57	0.87
> 80	0.0005	0.57	0.41	0.78
BMI				
> 20–25		1		
≤ 20	0.69	1.04	0.85	1.28
> 25–30	0.69	0.96	0.78	1.18
> 30	0.25	0.85	0.65	1.12
Perioperative transfusion				
No		1		
Yes	0.43	0.92	0.75	1.13
Disease-free survival				
NSAID				
No		1		
Yes	0.65	0.97	0.86	1.01
Preoperative oncological treatment				
No		1		
Yes	0.0407	1.40	1.01	1.91
UICC stage				
I		1		
II	0.29	1.11	0.91	1.35
III	< 0.0001	1.62	1.34	1.96
IV	< 0.0001	3.92	3.10	4.96
Missing	0.41	1.53	0.56	4.15
Sex				
Female		1		
Male	0.11	1.10	0.98	1.24
Tumor site				
Rectum		1		
Colon	0.20	1.11	0.95	1.29
CCI				
0		1		
1–2	< 0.0001	1.31	1.14	1.50
>2	0.0001	1.56	1.24	1.96
Surgical type				
Laparoscopic		1		
Open	0.0861	1.12	0.98	1.27
Anastomotic leakage				
No		1		
Yes	0.13	1.21	0.95	1.53
Age, years				
≤60		1		
>60–70	0.67	1.04	0.88	1.23
>70–80	0.91	1.01	0.85	1.20
>80	0.0329	1.25	1.02	1.54
BMI				
>20–25		1		
≤20	0.33	1.08	0.93	1.25
>25–30	0.96	1.00	0.86	1.17
>30	0.0432	0.81	0.66	0.99
Perioperative transfusion				
No		1		
Yes	0.10	0.89	0.77	1.03
Overall survival				
NSAID				
No		1		
Yes	0.60	0.96	0.81	1.13
Preoperative oncological treatment				
No		1		
Yes	0.0566	1.60	0.99	2.58
UICC stage				
I		1		
II	0.0044	1.66	1.17	2.35
III	< 0.0001	3.23	2.30	4.53
IV	< 0.0001	8.30	5.73	12.02

TABLE 3 continued

	p value	HR	95% CI	
Missing	0.39	1.86	0.45	7.80
Sex				
Female		1		
Male	0.62	1.04	0.88	1.23
Tumor site				
Rectum		1		
Colon	0.0278	1.30	1.03	1.64
CCI				
0		1		
1–2	< 0.0001	1.46	1.22	1.75
> 2	< 0.0001	2.18	1.65	2.87
Surgical type				
Laparoscopic		1		
Open	0.0093	1.27	1.06	1.52
Anastomotic leakage				
No		1		
Yes	0.12	1.29	0.94	1.77
Age, years				
≤ 60		1		
> 60–70	0.90	1.02	0.79	1.31
> 70–80	0.0037	1.44	1.13	1.85
> 80	< 0.0001	2.40	1.82	3.16
BMI				
> 20–25		1		
≤ 20	0.11	1.18	0.96	1.44
> 25–30	0.82	0.98	0.79	1.21
> 30	0.43	0.89	0.66	1.19
Perioperative transfusion				
No		1		
Yes	0.0050	0.76	0.63	0.92

HR hazard ratio, *CI* confidence interval, *NSAID* nonsteroidal anti-inflammatory drug, *UICC* Union for International Cancer Control, *CCI* Charlson Comorbidity Index, *BMI* body mass index

TABLE 4 Sensitivity analyses

	p value	HR	95% CI	
Recurrence-free survival				
Ibuprofen	0.0473	0.83	0.70	1.00
Diclofenac	0.22	0.84	0.63	1.12
Disease-free survival				
Ibuprofen	0.88	0.99	0.87	1.13
Diclofenac	0.32	0.90	0.72	1.11
5-year mortality				
Ibuprofen	0.52	0.94	0.79	1.13
Diclofenac	0.99	1.00	0.75	1.33

HR (95% CI) associated with the use of specific NSAIDs compared with no NSAID use; multivariate analysis adjusted for the same variables as reported in Tables 3, type of NSAID

HR hazard ratio, *CI* confidence interval, *NSAID* nonsteroidal anti-inflammatory drug

TABLE 5 Sensitivity analyses, with restrictions on population

	p value	HR	95% CI	
Recurrence-free survival				
Elective surgery only	0.0630	0.85	0.72	1.01
UICC stage I and II	0.12	0.81	0.62	1.06
Disease-free survival				
Elective surgery only	0.74	0.98	0.86	1.11
UICC stage I and II	0.68	1.04	0.87	1.23
5-year mortality				
Elective surgery only	0.89	0.99	0.83	1.18
UICC stage I and II	0.62	0.93	0.71	1.23

HR (95% CI) associated with the use of NSAIDs in a specified population, including only patients undergoing elective surgery or with localized disease, i.e. UICC stage I and II. Multivariate analysis adjusted for the same variables as reported in Tables 3

HR hazard ratio, *CI* confidence interval, *NSAID* nonsteroidal anti-inflammatory drug, *UICC* Union for International Cancer Control score

the inducible COX-2, whereas nonselective NSAIDs such as ibuprofen also inhibit the constitutively expressed COX-1.[35] An effect of ibuprofen alone is not commonly described or examined in the literature, but several factors beyond COX inhibition could play a role.[36]

NSAIDs are often used in postoperative analgesic regimens. The period immediately after surgery is known to be particularly valuable in improving long-term cancer outcomes.[3] In our study, an effect is observed with the use of NSAIDs for a minimum of 2 days within the first 7 postoperative days. In our population, an increased rate of postoperative anastomotic leakage was previously found when treated with diclofenac, but not ibuprofen.[23] This adds to the point that NSAIDs play a role at the surgical lesion during postsurgical inflammation, influencing the risk of leakage.[37] Paradoxically, anastomosis leakage is known to increase the risk of recurrence,[38] but this seemed to be counteracted by the anti-inflammatory benefits of NSAIDs. Given that the association of anastomotic leakage with ibuprofen is either non-existent or weak, and that in our sensitivity analysis we could demonstrate an association with lower recurrence, ibuprofen might be the drug to investigate in more detail with respect to an effect on recurrence.

The use of NSAIDs in relation to colorectal cancer has been investigated in several studies. A 2011 study investigated colorectal cancer-specific survival and patient-

reported use of NSAIDs prior to a diagnosis of cancer, and found improved survival in patients reporting use of NSAIDs.[39] Another study investigated the effect of aspirin preoperatively and found a higher rate of downstaging when receiving neoadjuvant therapy in users of aspirin.[40]

Several investigators have reported an association between postoperative treatment with NSAIDs and outcome. A nationwide cohort study including 15,544 patients found a reduced risk of early recurrence within 2 years after resection for hepatocellular carcinoma. The use of NSAIDs was assessed by the pharmacy register and included both COX-2 selective and nonselective NSAIDs, and aspirin, until 4 months after surgery. No evaluation of type, dose, or timing of NSAIDs was made.[14]

A 2018 study prospectively investigated the influence of ketorolac, a COX-2 selective NSAID, in relation to primary surgery for breast cancer. The authors demonstrated that a single intraoperative dose of ketorolac was associated with a reduced risk of recurrence. But this was not seen in patients receiving intraoperative diclofenac.[13] Finally, in a study investigating cancer recurrence after mastectomy, a retrospective analysis of 327 cases favored ketorolac over other analgesics with respect to recurrence of cancer.[12]

The primary strength of this study relies on the study design, as well as the accuracy and validity of the data. The DCCG database is consecutively controlled, and validation showed that 98.6% of all patients diagnosed with colorectal cancer are registered.[18,41] Furthermore, our results regarding cancer recurrence rely on a previously validated algorithm used to identify recurrence in both colonic and rectal cancer.[24,42] The assessment of NSAID use was not based on analgesic regimens, but instead performed as individual patient-by-patient registrations by separate observers, including only doses registered as taken. In our multivariate analysis, a purposeful selection of variables was made, based on the potential clinical influence on the primary outcome, taking the validity of each variable into account.

The findings of this study should be interpreted with caution as a causal association between NSAIDs and the risk of recurrence of colorectal cancer cannot be deduced on the basis of an observational study. Potential unmeasured confounders may cause a difference in outcomes; for instance, our data lack the granularity to investigate specific segments of colonic and rectal resections as the tissue trauma varies, resulting in variation in the surgical stress response.

In our study, no data regarding NSAID use beyond postoperative day 7 are included, and patients treated with only 1 day of NSAID use were interpreted as non-users; however, both these limitations would only lead to an underestimation of our findings. Furthermore, our study was constrained to a limited sample size, leading to an increased risk of type II errors of primary and secondary analyses. Our results failed to show an effect on mortality and DFS, which in part could be explained by these limitations. Furthermore, in recent years, the treatment of recurrence of cancer has improved, and it is possible that the effect of NSAIDs is too small to break through on the two secondary outcomes within the time frame of our study.

In our sensitivity analyses, the additional reduction in study population impacts the power of the analyses, and results in insignificant results, while similar tendencies are still observed with respect to NSAID use and recurrence of cancer. Comparable results are observed with respect to both our restrictions, as well as both specific NSAIDs in the sensitivity analyses. Future studies should increase the size of the study population to repeat the sensitivity analyses, as well as investigate whether an effect on mortality or DFS can also be demonstrated. A future prospective study should also investigate biomarkers related to inflammation in order to add translational evidence to the epidemiological evidence provided in this article.

CONCLUSION

This study showed that postoperative use of NSAIDs was associated with a reduced risk of recurrence after resection for colorectal cancer. Our results justify the requirement for further studies on the potential of NSAIDs in the colorectal cancer treatment routine.

AUTHOR CONTRIBUTIONS Anders Schack participated in study design, data collection, data analysis, data interpretation, and drafting and critical revision of the manuscript. Tina Fransgaard participated in study design, data collection, data analysis, data interpretation, and critical revision of the manuscript. Mads Klein participated in data collection, data interpretation, and critical revision of the manuscript. Ismail Gögenur participated in study design, data interpretation, and critical revision of the manuscript.

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