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Association of Statin Use and Oncological Outcomes After Neoadjuvant Radiotherapy in Patients With Rectal Cancer

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Abstract. *Aim: The aim of the study was to examine if statin exposure during neoadjuvant chemoradiotherapy improves oncological outcomes in patients with rectal cancer. Patients and Methods: The study cohort consisted of patients who were undergoing neoadjuvant chemoradiotherapy and resection for rectal cancer. The statin users were matched 1:1 with non-users using propensity score-based matching. The primary outcome of the study was disease-free survival; secondary outcomes were recurrence-free survival and all-cause mortality. Results: A total of 704 patients were included in the study. Disease-free survival was not different between the two groups [hazard ratio (HR)=0.98, 95% confidence intervaI (CI)=0.77-1.25, p=0.88]. Both recurrence-free survival (HR=1.02, 95% CI=0.74-1.39, p=0.92) and all-cause mortality (HR=0.92, 95% CI=0.68-1.23, p=0.56) were similar for the two groups. Conclusion: The study does not support that statin use is associated with response to neoadjuvant chemoradiotherapy in terms of disease-free survival, recurrence-free survival or all-cause mortality.*

In Denmark, more than 5,000 patients annually are diagnosed with colorectal cancer (CRC) (1) and the only curative treatment is surgical removal of the tumor. However, a considerable number of patients with potentially curable CRC subsequently develop metastatic disease (2). Dissemination is, therefore, suspected to be an early event that may happen pre- or intra-operatively (3).

In recent years, statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, have received a lot of attention because, in addition to their lipid-lowering properties (4), they are believed to have anti-inflammatory effects. Even in the perioperative period, statins, compared with placebo, were found to attenuate the inflammatory stress response (5, 6).

Currently, neoadjuvant radiotherapy followed by total mesorectal excision is considered the standard treatment for locally advanced rectal cancer. Neoadjuvant chemo-radiotherapy improves resectability, allows better likelihood of sphincter preservation and leads to reduced risk of local recurrence and improved survival (7-9). The subgroup of patients with pathological complete response (pCR) has the most favorable long-term oncological survival. Preliminary studies have shown that statins may sensitize rectal cancer to chemoradiotherapy, but clinical evidence investigating whether such findings translate to improved pCR and risk of recurrence or disease-free survival is still limited (10-12).

The aim of this study was to examine if statin exposure during neoadjuvant chemoradiotherapy improves oncological outcomes in patients with rectal cancer.

Patients and Methods

Patients receiving neoadjuvant chemoradiotherapy and subsequently undergoing curatively intended resection for rectal cancer in Denmark between January 1, 2003 and July 1, 2015 were included in the study. The patients were identified through the National Clinical Registry of the Danish Colorectal Cancer Group (DCCG) (1).

Since 2001 detailed information regarding comorbidity and demographic factors, as well as peri-and postoperative treatment have been registered in the DCCG registry (1). Outpatient visits and admissions to hospitals are registered in the Danish National Patient Register (NPR) (13). From the NPR, information regarding procedure codes, diagnoses, date of admission and discharge was obtained. A unique personal identification number (CPR number) is assigned to all Danish residents and information on immigration, emigration, and mortality among all patients is recorded in the Danish Civil Registration System (14). It is possible to link the registers used due to the unique CPR number. Standard data on biological specimens including pathologically diagnosed recurrences

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are documented in the Danish Pathology Register using the Danish version of the Systemized Nomenclature of Medicine (SNOMED) codes (15). The Danish Cancer Registry (16) contains data on all incident cancer cases in the Danish population since 1943. In order to identify and exclude patients with a history of cancer, the cohort members were linked to the Danish Cancer Registry. The Danish National Prescription Registry (17) collects information on all prescriptions redeemed at community pharmacies in Denmark, including their WHO defined daily doses and date of dispensing.

Information regarding equivalized disposable income and highest attained educational level were obtained from Statistics Denmark. Equivalized disposable income is the household disposable income divided by the number of members of the household converted into equalized adults. The income was adjusted according to the consumer price index (2015 prices).

Outcome definitions. Cancer recurrence is not recorded in DCCG, therefore, a validated algorithm (18) was used to estimate recurrence during follow-up. The algorithm uses data from the NPR, the Danish Cancer Registry and Danish Pathology Register. One criterion in the algorithm is an arbitrary 180-day limit, meaning that patients who died or were diagnosed with metastases within 180 days of surgery were excluded from the study. The reason for this 180-day limit is that metastases recorded in this timeframe must have been present at the time of surgery and it is not meaningful to examine recurrence in these patients. In brief, the algorithm is based on meeting at least one of four criteria: i) ICD-10 metastasis codes (DC76-DC80) without diagnosis of a new primary tumor 180 days or more after the day of surgery. ii) Cytostatic therapy codes 180 or more days after the day of surgery and 60 or more days after the last cytostatic therapy code and without a new primary tumor between colorectal cancer surgery and date of cytostatic therapy code. iii) Pathologically recorded recurrence using SNOMED combinations. iv) Specific ICD-10 code for local colorectal cancer recurrence (C18.9X and C20.9X). These codes were introduced to the NPR in 2012.

Furthermore, patients with other primary cancer types before a colorectal cancer diagnosis, except non-melanoma skin cancer, were excluded as NPR-registered metastasis codes cannot distinguish between which primary cancer the metastasis was due to.

Drug exposure and statistical methods. Patients who were under active treatment with statins at the beginning of chemoradiotherapy were categorized as users. Moreover, in the year preceding the first date of neoadjuvant treatment, users had to have redeemed a prescription for statins (ATC-code C10A and C10BA02) as well as within 180 days after surgery.

Patients only receiving statins prior to diagnosis were excluded and patients classified as non-users were censored if a statin prescription was redeemed after the time of neoadjuvant chemoradiotherapy.

The statin users were matched 1:1 with non-users using propensity score-based matching. The propensity score was based on sex, age at diagnosis, Charlson comorbidity index, smoking, alcohol consumption, body mass index, T-stage, lymph node status, year of surgery, highest attained educational level and equivalized disposable income. The matching was performed by nearest-neighbor matching, without replacement, and a caliper of width of 0.2 of the standard deviation of the logit was allowed.

To examine for a dose–response association, statin use was categorized into three levels: ≤0.60, 0.61-1.10 and ≥1.11 defined daily dose/day.

Table I. *Patient characteristics*.

	Statin users (n=352)	Non-users (n=352)
Age		
≤60 Years	62 (17.6)	66 (18.8)
61-70 Years	157 (44.6)	151 (42.9)
71-80 Years	124 (35.2)	129 (36.7)
>80 Years	9 (2.6)	6 (1.7)
Gender, n (%)		
Male	225 (63.9)	212 (60.2)
Female	127 (36.1)	140 (39.8)
Charlson comorbidity index, n (%)		
0	223 (63.4)	226 (64.2)
1-2	103 (29.3)	99 (28.1)
3+	26 (7.4)	27 (7.7)
BMI, n (%)		
≤24.9	109 (31.0)	113 (32.1)
25-29.9	145 (41.2)	132 (37.5)
≥30	49 (13.9)	55 (15.6)
Missing data	49 (13.9)	52 (14.8)
Smoking, n (%)		
Current smoker	74 (21.0)	71 (20.2)
Former smoker	132 (37.5)	134 (38.1)
Never-smoker	87 (24.7)	87 (24.7)
Missing data	59 (16.8)	60 (17.1)
Alcohol, drinks/week		
0	55 (15.6)	49 (13.9)
1-14	192 (54.6)	197 (56.0)
15-21	28 (8.0)	34 (9.7)
>21	18 (5.1)	14 (4.0)
Missing data	59 (16.8)	58 (16.5)
T-Stage, n (%)		
1	57 (16.2)	58 (16.5)
2	99 (28.1)	92 (26.1)
3	166 (47.2)	167 (47.4)
4	16 (4.6)	22 (6.3)
Missing data	14 (4.0)	13 (3.7)
Regional lymph node metastasis, n (%)		
N0	255 (72.4)	265 (75.3)
N1	59 (16.8)	55 (15.6)
N2	27 (7.7)	24 (6.8)
Nx	11 (3.1)	8 (2.3)
Education, n (%)		
Primary	150 (42.6)	144 (40.9)
Vocational/upper secondary	143 (40.6)	146 (41.5)
Short-/medium-term higher	45 (12.8)	45 (12.8)
Master/Ph.D. program	10 (2.8)	12 (3.4)
Missing	4 (1.1)	5 (1.4)
Equivalized disposable income, n (%)		
<175,000 DKK	123 (34.9)	118 (33.5)
175,000-250,000 DKK	114 (32.4)	115 (32.7)
>250,000 DKK	108 (30.7)	114 (32.4)
Missing data	7 (2.0)	5 (1.4)
Year of surgery, n (%)		
2004-2005	87 (24.7)	94 (26.7)
2006-2009	151 (42.9)	138 (39.2)
2010-2012	114 (32.4)	120 (34.1)

BMI: Body mass index; DDK: Danish kroners.

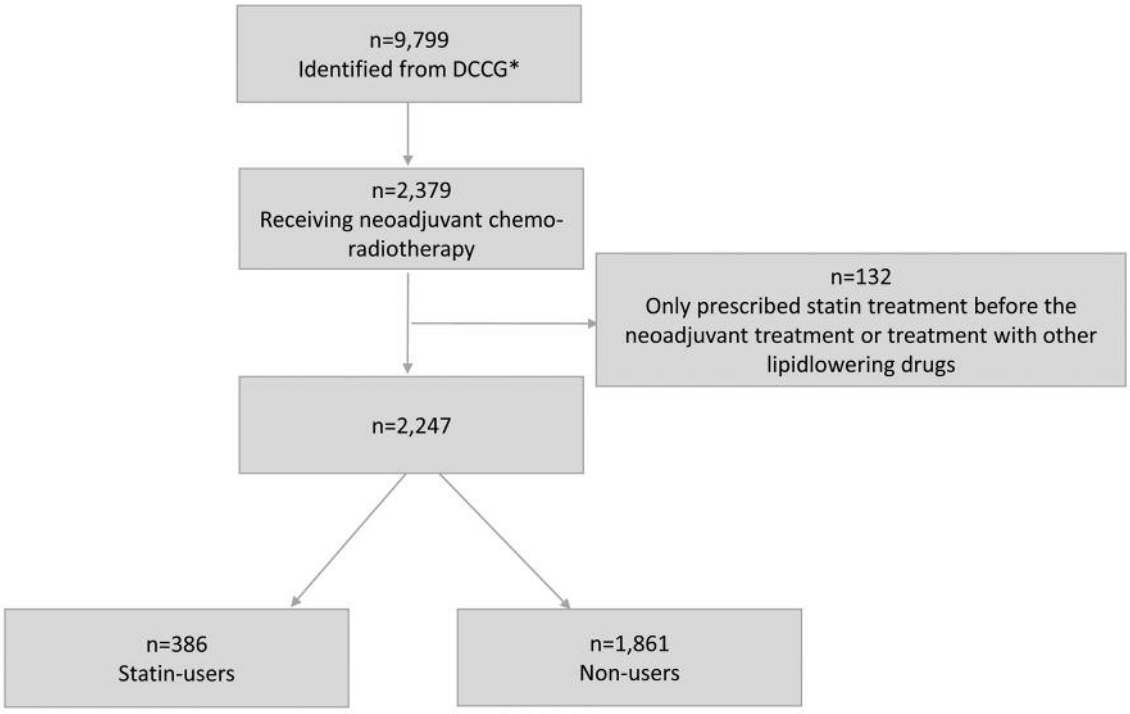

Figure 1. *STROBE flow diagram. *Patients undergoing surgery for colorectal cancer with curative intent in the period from January 1, 2003-July 1, 2015. DCCG: National Clinical Registry of the Danish Colorectal Cancer Group.*

The study population was followed-up from 180 days after surgery until the end of observation (December 31, 2015), occurrence of a new primary tumor, relapse of colorectal cancer, or death (from any cause), whichever occurred first.

Disease-free survival (DFS) was the primary outcome, recurrence-free survival (RFS) and all-cause mortality were the secondary outcomes. All outcomes were estimated using Cox regression models. DFS describes the time from 180 days after surgery to diagnosis of new primary tumor, recurrence, or death regardless of cause, whereas RFS was the time from 180 days after surgery to diagnosis of recurrence. All-cause mortality was the time from 180 days after surgery to the time of death regardless of cause. When a new primary tumor occurred or when death from any cause occurred patients were censored. Results were presented as hazard ratios (HR) with 95% confidence intervals (95%CI), and *p*-values below 0.05 were considered statistically significant. The study was approved by the Danish Data Protection Agency (J.no. 2008-58-0020-Reg-052-2017) and the recommendations of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (19) were used. SAS® Proprietary Software 9.4 (SAS Institute Inc., Cary, NC USA) was used to conduct the statistical analysis.

Results

Between January 1, 2003 and July 1, 2015, 9,799 patients were diagnosed with rectal cancer and underwent surgery with curative intend. In the year preceding surgery, 2,379 received neoadjuvant chemoradiotherapy. A total of 386 patients were classified as statin users and 1,861 as non-users (Figure 1). It was possible to match 352 statin users to non-users (Table I).

During follow-up, 180 patients (25.6%) died [93 (26.4%) in the statin-treated group and 87 (24.7%) among the non-users] and 157 (22.3%) were diagnosed with recurrence [82 (23.3%) in the statin treated group and 75 (21.3%) among the non-users].

Neither DFS nor RFS were statistically significant different between the two groups and all-cause mortality was also similar (Table II).

No statistically significant association between daily dose of statins and DFS, RFS or all-cause mortality were found. However, for all three outcomes, there was a trend towards improved DFS, RFS and all-cause mortality with increasing daily dose of statins (Table III).

Discussion

The study showed no association between statin use and DFS, RFS and all-cause mortality in patients undergoing neoadjuvant treatment for rectal cancer. The dose–response analysis showed a trend towards improved DFS, RFS and all-cause mortality with increasing daily dose of statins, yet the association did not reach statistical significance.

Table II. *Disease-free survival, recurrence-free survival and all-cause mortality. Statin users were matched with non-users 1:1 by propensity score. The propensity score was based on sex, age at diagnosis, Charlson comorbidity index, smoking, alcohol consumption, body mass index, T-stage, lymph node status, year of surgery, highest attained educational level and equivalized disposable income.*

Outcome	n (%)	HR	95% CI	*p*-Value
Disease-free survival				
Non-users	129 (36.7)	1		
Statin users	141 (40.1)	0.98	0.77-1.25	0.88
Recurrence-free survival				
Non-users	75 (21.3)	1		
Statin users	82 (23.3)	1.02	0.74-1.39	0.92
All cause mortality				
Non-users	87 (24.7)	1		
Statin users	93 (26.4)	0.92	0.68-1.23	0.56

CI: Confidence intervaI; HR: hazard ratio.

Table III. *Statin dose–response association between statin use and disease-free, recurrence-free survival and all-cause mortality. Statin users were matched with non-users 1:1 by propensity score. The propensity score was based on sex, age at diagnosis Charlson comorbidity index, smoking, alcohol consumption, body mass index, T-stage, lymph node status, year of surgery highest attained educational level and equivalized disposable income.*

Outcome	HR	95% CI	*p*-Value
Disease-free survival			
Statin user			
≤0.60 DDD/day	1.18	0.85-1.63	0.33
0.60-1.10 DDD/day	1.03	0.75-1.42	0.84
≥1.11 DDD/day	0.75	0.52-1.09	0.13
Non-user	1		
Recurrence-free survival			
Statin user			
≤0.60 DDD/day	1.41	0.94-2.12	0.10
0.60-1.10 DDD/day	1.01	0.66-1.54	0.96
≥1.11 DDD/day	0.69	0.42-1.14	0.15
Non-user	1		
All-cause Mortality			
Statin user			
≤0.60 DDD/day	1.05	0.70-1.56	0.82
0.60-1.10 DDD/day	0.95	0.64-1.40	0.80
≥1.11 DDD/day	0.74	0.47-1.17	0.20
Non-user	1		

CI: Confidence intervaI; DDD: defined daily dose.

Statins have demonstrated several antineoplastic effects such as inhibiting cell proliferation, increasing apoptosis and promote differentiation (4, 20, 21). The main mechanism of action of statins, however, is the reduction of cholesterol level by inhibiting HMG-CoA reductase, the rate limiting step in the mevalonate synthesis pathway (22). The downstream products of this pathway (such as cholesterol, dolichol, geranyl pyrophosphate and farnesyl pyrophosphate) are all implicated in several processes of carcinogenesis (4, 20, 21).

The hypothesis regarding statin use and an improved response to chemoradiotherapy relates to their direct effects on tumors described above or to effects on normal tissue. The effects on the normal tissue include reducing inflammation and inhibiting radiotherapy-induced toxicities (12). *In vitro* studies have demonstrated that statins have the ability to improve the response to neoadjuvant treatment by sensitizing rectal cancer cells to chemoradiotherapy but clinical information has been limited (23). Only few retrospective studies with patients taking statin during chemoradiotherapy for rectal cancer have been conducted (10, 11, 24, 25). The primary endpoint of these studies was pathological complete response (pCR), and all the studies found higher rates in statin users compared with non-users. The studies, however, were limited by small sample sizes and did not investigate the effect on RFS or DFS. pCR or tumor regression grade were not available for our study. However, even though statin use should improve tumor regression grade and pCR, the impact seems not to be pronounced enough to affect long-term oncological outcomes.

This registry-based observational study has certain limitations. Unmeasured confounding can be present, however, propensity score matching was used in this study and the propensity score was based on clinically relevant factors, including comorbidity, body mass index and year of surgery, thereby taking differences in treatments strategies into account. Compliance with cancer treatment and screening colonoscopies (20, 26), as well as socioeconomic status (27), have been associated with statin use. Socioeconomic status was included in the propensity score in terms of equivalized disposable income and highest attained educational level. Yet residual confounding by health-seeking behavior cannot be completely excluded (28).

The primary indication for statin treatment is ischemic heart disease, which is also associated with survival outcomes, and therefore confounding by indication may occur. In order to limit the risk of confounding by indication, the statin users were matched with non-users using propensity score including Charlson comorbidity score, however, residual confounding by indication cannot be completely ruled out.

In conclusion, our study does not support that statin use is associated with response to neoadjuvant chemoradiotherapy in terms of DFS, RFS or all-cause mortality.

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Conflicts of Interest

There are no conflicts of interest in regard to this study.

Authors' Contributions

All Authors were responsible for the study concepts and design, data acquisition, analysis, interpretation and statistical analysis were carried out by TF, JH and LCT. TF were responsible for drafting the manuscript and all Authors were involved in the editing process. All Authors approved the final manuscript.

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