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Article

ARTICLE

Statin Use and Survival After Colorectal Cancer: The Importance of Comprehensive Confounder Adjustment

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Abstract

Background: Statins have been associated with moderate reductions in mortality among colorectal cancer (CRC) patients, but these studies lacked adjustment for some potentially relevant factors associated with statin use. We aimed to provide more detailed results on this association from a population-based patient cohort study.

Methods: Use of statins and other risk or protective factors were assessed in standardized interviews with 2697 patients from southern Germany with a diagnosis of incident CRC between 2003 and 2009 (Darmkrebs: Chancen der Verhütung durch Screening [DACHS] study). Follow-up included assessment of therapy details, recurrence, vital status, and cause of death. Information about molecular pathological subtypes of CRC was available for 1209 patients. Cox proportional hazard regression models were used to estimate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical tests were two-sided.

Results: Patients were age 68 years on average, 412 used statins (15%), and 769 died during follow-up (29%). After a median follow-up time of 3.4 years, use of statins was not associated with overall (HR = 1.10, 95% CI = 0.85 to 1.41), CRC-specific (HR = 1.11, 95% CI = 0.82 to 1.50), or recurrence-free survival (HR = 0.90, 95% CI = 0.63 to 1.27). Analyses in relevant subgroups also showed no association of statin use with overall and CRC-specific survival, and no associations were observed after stratifying for major pathological subtypes. Among stage I and II patients, statin use was associated with better recurrence-free but not with better CRC-specific survival.

Conclusions: Statin use was not associated with reduced mortality among CRC patients. Effects reported in previous studies might reflect incomplete control for stage at diagnosis and other factors associated with the use of statins.

Statins function as inhibitors of 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase in the mevalonate pathway in the liver, and reduce endogenous cholesterol synthesis (1). They are widely used as drugs for reducing blood cholesterol levels and as standard medication for the prevention of cardiovascular disease in people at risk (2). In addition to HMG-CoA–dependent effects, statins seem to have HMG-CoA–independent or pleiotropic effects, which may contribute to cancer prevention and influence apoptotic, angiogenic, proliferative, and inflammatory processes (2,3).

A considerable number of studies have investigated the association of statins with colorectal cancer (CRC) risk (4–20). However, no clinically relevant protective effect was found with the use of statins after pooling results in a meta-analysis

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(relative risk = 0.92, 95% confidence interval [CI] = 0.87 to 0.97) (21).

In contrast to studies on CRC risk, only few studies have investigated the effect of statins on survival and recurrence after a diagnosis of CRC. The largest study thus far of pre-diagnostic statin use is a nationwide registry-based follow-up study from Denmark including more than 43000 CRC patients that found a 21% reduction in cancer-related mortality 2.6 years after diagnosis (22), but the analyses lacked comprehensive adjustment for some of the potentially relevant confounders including CRC stage, which was missing for most patients in the study (23). Postdiagnostic statin use was investigated in another registry-based study with comprehensive adjustment for potential confounders that observed a 29% reduction of cancer-specific mortality five years after diagnosis (24).

The objective of the present study was to provide more detailed results from a large population-based cohort of CRC patients and to analyze associations of statin use with overall, CRC-specific and recurrence-free survival according to clinical and pathological patient characteristics, active ingredient, and duration of use.

Methods

Study Design and Study Population

This prospective patient cohort study included patients from the Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study, an ongoing population-based case-control study on CRC with follow-up of patients from the Rhine-Neckar region in the southwest of Germany. All 22 hospitals in the study region offering CRC surgery participated in the recruitment of patients for this study. Patients in this study were diagnosed between 2003 and 2009 and were eligible to participate if they had a first diagnosis of primary CRC, were able to speak German, were at least 30 years old (no upper age limit), and were physically and mentally able to participate in an interview of about one hour. More details of the study design have been reported previously (25,26). The study was approved by the ethical committees of the Medical Faculty of the University of Heidelberg and the Medical Chambers of Baden-Württemberg and Rhineland-Palatinate.

Data Collection and Follow-up

The patients provided information during a face-to-face interview. The interviews were conducted by trained interviewers and were based on a standardized questionnaire. All questions referred to the time up to their diagnosis of CRC. In addition, discharge letters, pathology reports, and reports of previous large bowel endoscopies were collected.

About three years after diagnosis, we requested standardized information on CRC therapy, intermittent diagnoses of concomitant diseases, and CRC recurrence from the physicians of the patients. About five years after diagnosis, additional information was collected from the patients alive, again including questions on newly diagnosed diseases and recurrences. New diagnoses and cancer recurrences were verified through medical records of the attending physicians. Data on vital status and date of death were obtained from the population registries.

Causes of death were verified by death certificates obtained from the health authorities in the Rhine-Neckar region and coded according to World Health Organization standards. Follow-up time was calculated as the time between the date of diagnosis and the date of event or censoring. Follow-up time of patients with no event of interest (death, recurrence, metastasis) was censored at the date of the last follow-up.

Assessment of Statins

Current regular use of drugs (more than once per week, up to CRC diagnosis) and year of initiation were ascertained during the interview for a variety of indications, including cardiovascular disease prevention and lowering of blood lipids (15). All drugs were coded according to the Anatomical Therapeutic Chemical/Defined Daily Dose Classification (ATC/DDD) (27,28). Use of statins in this analysis comprised the following ATC codes: C10AA01-C10AA08, C10BA, C10BX.

Study Exclusions and Multiple Imputation of Missing Data

Patients with missing information on medication against heart problems or hyperlipidemia and patients with missing information on follow-up time were excluded. Following these exclusions, we performed multiple imputations using the Markov-Chain Monte Carlo method to fill in missing data (n = 10 imputed datasets, SAS procedure PROC MI).

Tumor Tissue Analyses

For a subsample of the patients, results from molecular tumor tissue analyses were available (n = 1209, diagnosed 2003–2007, median follow-up time = 5.0 years, for details see [29]). Microsatellite instability (MSI-high) was determined using a mononucleotide marker panel (BAT25, BAT26, CAT25) in sections of the tumor block (30). Using DNA of the same tumor tissue samples, we furthermore screened for presence of *KRAS* mutations by using a single-stranded conformational polymorphism technique (SSCP) (31) and analyzed CpG Island methylator phenotype (CIMP) after DNA bisulfite conversion (32), as previously described. In brief, CIMP-negative, CIMP-low, and CIMP-high were classified if none, less than three, and three or more out of the five investigated gene loci (*MGMT*, *MLH1*, *MINT1*, *MINT2*, *MINT31*) showed methylation, respectively. Estrogen receptor (ER)–beta expression status (negative, moderate, high) was determined by immunohistochemical analyses in sections of tissue microarray blocks (for details see [33]).

Statistical Analyses

We first compared the distribution of patient characteristics among users and nonusers of statins and assessed differences between the two groups by chi-square tests, and included differentially distributed factors ($P < .05$) as covariates in the multivariable Cox regression model. Adjusted hazard ratios (HRs) of statin use (yes vs no) with overall, CRC-specific and, among stage I-III patients, recurrence-free survival were estimated using Cox proportional-hazards regression models. The assumption of proportionality was verified by testing for time-dependent effects of statin use or any of the covariates included in the adjusted model. Models were adjusted for age at diagnosis, sex, cancer stage, location of CRC, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, body mass index, lifetime pack-years of active smoking, physical activity, diabetes, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) including

aspirin, ever use of hormone replacement therapy (HRT) among women, previous large bowel endoscopy, hypercholesterolemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, and for a time-dependent effect of chemotherapy (chemotherapy*log(time); no time-dependant effects were observed for the other covariates in the adjusted model). All survival analyses were also adjusted for late entry into the study, because interviews were mostly conducted after diagnosis (median time: 31 days, interquartile range = 10–251 days). We conducted multinomial logistic regression analyses to estimate adjusted odds ratios of the association of statin use and CRC stage at diagnosis.

In sensitivity analyses, the association of statin use and survival was analyzed in patients with assessment of use at least three and six months after diagnosis of CRC, respectively. Also, we assessed postdiagnostic consistency of statin use by comparing statin use at baseline and at five-year follow-up among survivors providing both questionnaires. All analyses were performed with SAS, software version 9.2 (SAS Institute Inc., Cary, NC). Statistical tests were two-sided, using an alpha level of .05.

Results

Of 2822 patients with CRC, 124 (4%) were excluded because of missing information on medication for heart problems or hyperlipidemia, and one patient because information on follow-up time was missing. In the remaining study population of 2697 patients with CRC, mean age was 68 years and 40% were women. Four hundred and twelve used statins (15%), and 769 died during follow-up (29%). Median follow-up time after diagnosis of CRC was 3.4 years (interquartile range = 2.3–5.0 years).

Use of statins was associated with higher age, male sex, lower cancer stage, higher BMI, higher amount of pack-years of smoking, and with more frequent use of NSAIDs (Table 1). Also, use of statins was associated with higher participation rate in general health check-ups, with a history of diabetes, myocardial infarction, stroke, heart failure, and hypercholesterolemia (88% vs 21% among nonusers of statins).

Simvastatin was the statin used most frequently (56%), followed by atorvastatin (22%), pravastatin (11%), and fluvastatin (7%). Other statins, active ingredients, or combinations of statins with other ingredients were used by only 5% of the statin users (Supplementary Table 1, available online).

In multivariable analyses adjusting for major clinical and epidemiological factors, use of statins was not associated with overall survival (HR = 1.10, 95% CI = 0.85 to 1.41), CRC-specific survival (HR = 1.11, 95% CI = 0.82 to 1.50), and recurrence-free survival (HR = 0.90, 95% CI = 0.63 to 1.27), respectively (Table 2). Controlling for current regular use of acetylsalicylic acid (ASA) instead of NSAIDs yielded very similar results in

Table 1. Characteristics of patients with colorectal cancer by use of statins*

Characteristics	Use of statins: Yes (n = 412) No. (%)	Use of statins: No (n = 2285) No. (%)	P
Age at diagnosis, mean (SD)	70.3 (8.4)	67.6 (11.0)	<.001
No. (%) women	140 (34)	944 (41)	.005
Colorectal cancer diagnosis and therapy			
Stage at diagnosis (UICC)			
I	116 (28)	482 (21)	
II	127 (31)	683 (30)	
III	126 (31)	771 (34)	
IV	43 (10)	350 (15)	.002
Cancer site			
Proximal colon	145 (35)	704 (31)	
Distal colon	111 (27)	633 (28)	
Rectum (C19, C20)	156 (38)	948 (41)	.19
Surgery	401 (97)	2,223 (97)	.96
Chemotherapy	164 (40)	1,132 (50)	<.001
Radiotherapy	56 (14)	408 (18)	.03
Lifestyle, health behaviour and medication up to diagnosis			
Body mass index, kg/m^2, mean (SD)	27.3 (4.2)	26.3 (4.4)	<.001
Active smoking, lifetime pack-years, mean (SD)	14.9 (19.4)	10.7 (16.5)	<.01
Alcohol, lifetime ethanol, g/d, mean (SD)	18.4 (20.5)	17.8 (22.4)	.64
Physical activity, lifetime MET h/wk,mean (SD)	209.4 (114.6)	230.8 (133.0)	.001
Participation in health check-up	379 (92)	1,872 (82)	<.001
Previous large bowel endoscopy	115 (28)	497 (22)	.006
Regular use of NSAIDs	208 (50)	428 (19)	<.001
Use of HRT (women only)	49 (35)	279 (30)	.17
Comorbidity up to diagnosis			
Hyperlipidemia	363 (88)	486 (21)	<.001
Diabetes	137 (33)	346 (15)	<.001
Myocardial infarction	117 (28)	93 (4)	<.001
Stroke	35 (9)	109 (5)	.002
Heart failure	114 (28)	230 (10)	<.001

* HRT = hormone replacement therapy; MET = metabolic equivalent of task; NSAID = nonsteroidal anti-inflammatory drug; UICC = Union Internationale Contre le Cancer.

the multivariable analyses (data not shown). Analyses by active ingredient and duration of use as well as sex- and age-specific analyses suggested no risk reduction. Also, no site-specific effects of statins on survival were observed. However, we observed an association of statin use and recurrence-free survival in early-stage carcinomas (stage I+II: HR = 0.50, 95% CI = 0.26 to 0.95) (Table 3).

Among patients with incident CRC, statin use was not differentially associated with prevalence of any of the molecular pathological subtypes investigated (Table 4). Analyses stratified by molecular subtypes of CRC suggested no association of statins and overall survival among patients with the more common tumor subtypes (microsatellite stable [MSS] tumors, CIMP-low/-negative tumors, tumors with negative or moderate expression of ER-beta, *KRAS*–wild-type and *KRAS*-mutated tumors). Because of the low numbers, associations with less common subtypes could not be analyzed.

For comparisons with previous studies we analyzed the overall association of statins and survival after CRC with different levels of adjustment (Table 5; Supplementary Table 2, available online). Compared with the basic model adjusting for age and sex, additional adjustment for stage removed or attenuated any apparent protective effect and yielded hazard ratios similar to the fully adjusted model. Further analyses of baseline data showed that use of statins was associated with a strongly reduced probability of late-stage diagnosis even if this association was somewhat less pronounced and not statistically significant in the fully adjusted model, which included variables potentially reflecting the degree of adherence to screening measures, such as previous large bowel endoscopy or participation in general health check-ups (Table 6).

In sensitivity analyses, we restricted our analyses to patients with assessment of statin use more than three months and more than six months after diagnosis, and obtained results similar to those of the overall analyses (Supplementary Table 3, available online). Among survivors who provided information on medication in the five-year follow-up questionnaire and at baseline, the concordance rate for use of statins was 88% (Supplementary Table 4, available online).

Discussion

In this population-based patient cohort study from Germany on the association of statin use and survival after CRC, we assessed major clinical and lifestyle factors, relevant comedication, comorbidities, and health-related behavior. After a median follow-up time of 3.4 years, we observed no association of statin use and survival. Subgroup analyses according to duration of use, active ingredient, and by age, sex, CRC stage and location, and by conduct of chemotherapy also suggested no improvement of overall or CRC-specific survival with the use of statins. Furthermore, analyses by the more common forms of major molecular pathological subtypes of CRC (MSI, CIMP, *KRAS*, and ER-beta expression) did not indicate an association of statin use with improved survival.

Statin use was, however, associated with better recurrence-free survival in our study among patients with early-stage CRC. An association with lower risk of recurrence (including relapse, progression, and death) in patients with stage I and II has not been reported before. Given the lack of association with CRC-specific survival and the large number of analyses in this study, this could also be a chance finding.

The largest study thus far on the association of prediagnostic statin use and survival after CRC comes from Denmark. In a nationwide approach, all cancer case patients between 1995 and 2007 were followed up for a median time of 2.6 years (22). Among 43<thin space>487 patients with CRC, statin use was associated with a 21% reduction in cancer-specific mortality in multivariable analysis (22<thin space>838 deaths, HR = 0.79, 95% CI = 0.74 to 0.85) (see their Supplementary Appendix, Figure S14). Yet, no adjustment was possible in this study for some potentially relevant confounders including comedication, lifestyle factors, and health-related behavior. Also, information on stage of CRC was missing for most patients in that study, hindering effective control for this important covariate. Stage was a major confounder in our analyses, and use of statins was associated with diagnosis at an earlier stage. The latter association has been reported in another large case-control study (16) too, suggesting that if information on stage is limited the observed effect of statins could actually be because of the better prognosis of CRC detected at an early stage. The diagnosis at an earlier stage could be because of

Table 2. Association of statin use with overall, colorectal cancer–specific, and recurrence-free survival

Statin use	Overall survival			CRC-specific survival		Recurrence-free survival*		
	No.	Events No. (%)	HR (95% CI)†	Events No. (%)	HR (95% CI)†	No.	Events No. (%)	HR (95% CI)†
No statin use	2285	651 (28)	1.00 (Ref.)	483 (21)	1.00 (Ref.)	1937	413 (21)	1.00 (Ref.)
Any statin use	412	118 (29)	1.10 (0.85 to 1.41)	80 (19)	1.11 (0.82 to 1.50)	367	64 (17)	0.90 (0.63 to 1.27)
Active ingredient								
Simvastatin	231	70 (30)	1.21 (0.91 to 1.61)	46 (20)	1.15 (0.81 to 1.64)	204	29 (14)	0.78 (0.50 to 1.22)
Atorvastatin	90	27 (30)	1.16 (0.75 to 1.81)	21 (23)	1.38 (0.82 to 2.30)	80	21 (26)	1.38 (0.82 to 2.33)
Pravastatin	44	13 (30)	1.00 (0.56 to 1.80)	8 (18)	0.87 (0.41 to 1.83)	41	8 (20)	0.90 (0.41 to 1.98)
Duration of statin use, y								
0–2	117	32 (27)	0.92 (0.62 to 1.35)	24 (21)	0.93 (0.59 to 1.45)	102	15 (15)	0.64 (0.35 to 1.16)
3–6	124	40 (32)	1.23 (0.85 to 1.76)	26 (21)	1.22 (0.78 to 1.93)	113	22 (19)	1.13 (0.69 to 1.85)
7+	145	37 (26)	1.13 (0.77 to 1.67)	24 (17)	1.33 (0.70 to 1.82)	133	25 (19)	1.01 (0.61 to 1.68)

* Stage IV patients were excluded in the analyses on recurrence. Recurrence includes relapse, metastases, or death because of colorectal cancer. CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio.

† Cox proportional hazards model adjusted for age at diagnosis, sex, Union Internationale Contre le Cancer stage, location of CRC, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, body mass index, lifetime pack-years of active smoking, average lifetime physical activity, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), ever use of hormone replacement therapy (women), previous large bowel endoscopy, diabetes, hyperlipidemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, and for a time-dependent effect of chemotherapy (chemotherapy*log[time]). All statistical tests were two-sided.

Table 3. Association of statin use at diagnosis with overall, colorectal cancer-specific, and recurrence-free survival stratified by age, sex, stage and location of colorectal cancer at diagnosis, and by conduct of chemotherapy

Subgroup	Statin use	Overall survival			CRC-specific survival		Recurrence-free survival*		
		No.	Events No. (%)	HR (95% CI)†	Events No. (%)	HR (95% CI)†	No.	Events No. (%)	HR (95% CI)†
Age at diagnosis, y									
<70	No	1257	290 (23)	1.00 (Ref.)	237 (19)	1.00 (Ref.)	1057	202 (19)	1.00 (Ref.)
	Yes	184	40 (22)	1.10 (0.70 to 1.74)	31 (17)	1.28 (0.77 to 2.15)	164	25 (15)	1.15 (0.65 to 2.03)
≥70	No	1028	361 (35)	1.00 (Ref.)	246 (24)	1.00 (Ref.)	880	211 (24)	1.00 (Ref.)
	Yes	228	78 (34)	1.19 (0.87 to 1.61)	49 (21)	1.13 (0.77 to 1.65)	204	39 (19)	0.85 (0.55 to 1.32)
Sex									
Male	No	1341	380 (28)	1.00 (Ref.)	276 (21)	1.00 (Ref.)	1125	237 (21)	1.00 (Ref.)
	Yes	272	74 (27)	1.00 (0.71 to 1.39)	46 (17)	0.93 (0.62 to 1.41)	243	37 (15)	0.80 (0.49 to 1.30)
Female	No	944	271 (29)	1.00 (Ref.)	207 (22)	1.00 (Ref.)	812	176 (22)	1.00 (Ref.)
	Yes	140	44 (31)	1.32 (0.89 to 1.96)	34 (24)	1.49 (0.94 to 2.35)	125	27 (22)	1.11 (0.66 to 1.84)
UICC stage									
Stage I + II	No	1165	174 (15)	1.00 (Ref.)	82 (7)	1.00 (Ref.)	1165	158 (14)	1.00 (Ref.)
	Yes	243	34 (14)	1.07 (0.66 to 1.72)	10 (4)	0.97 (0.43 to 2.19)	241	16 (7)	0.50 (0.26 to 0.95)
Stage III	No	771	210 (27)	1.00 (Ref.)	155 (20)	1.00 (Ref.)	771	255 (33)	1.00 (Ref.)
	Yes	126	48 (38)	1.14 (0.75 to 1.75)	35 (28)	1.22 (0.75 to 2.00)	126	48 (38)	1.25 (0.82 to 1.92)
Stage IV	No	348	267 (77)	1.00 (Ref.)	246 (71)	1.00 (Ref.)	--	--	--
	Yes	43	36 (84)	1.04 (0.67 to 1.63)	35 (81)	1.07 (0.68 to 1.70)	--	--	--
Location of CRC									
Proximal colon	No	701	205 (29)	1.00 (Ref.)	141 (20)	1.00 (Ref.)	604	110 (18)	1.00 (Ref.)
	Yes	145	47 (32)	1.08 (0.71 to 1.64)	32 (22)	1.01 (0.60 to 1.69)	124	18 (15)	0.78 (0.48 to 1.26)
Distal colon	No	631	175 (28)	1.00 (Ref.)	129 (20)	1.00 (Ref.)	523	103 (20)	1.00 (Ref.)
	Yes	110	27 (25)	0.95 (0. 57 to 1.59)	17 (15)	1.01 (0.53 to 1.95)	98	17 (17)	1.24 (0.71 to 2.14)
Rectum	No	946	267 (28)	1.00 (Ref.)	209 (22)	1.00 (Ref.)	805	198 (25)	1.00 (Ref.)
	Yes	156	44 (28)	1.25 (0.84 to 1.87)	31 (20)	1.35 (0.84 to 2.15)	145	29 (27)	1.16 (0.76 to 1.76)
Chemotherapy									
No	No	1325	330 (25)	1.00 (Ref.)	221 (17)	1.00 (Ref.)	1195	199 (17)	1.00 (Ref.)
	Yes	272	66 (24)	1.29 (0.93 to 1.79)	36 (13)	1.26 (0.82 to 1.93)	256	30 (12)	0.99 (0.67 to 1.47)
Yes	No	954	317 (33)	1.00 (Ref.)	258 (27)	1.00 (Ref.)	738	212 (29)	1.00 (Ref.)
	Yes	139	52 (37)	1.03 (0.69 to 1.52)	44 (32)	1.08 (0.70 to 1.67)	112	34 (30)	1.21 (0.82 to 1.78)

* Stage IV patients were excluded in the analyses on recurrence. Recurrence includes relapse, metastases, or death because of colorectal cancer. CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio; UICC = Union Internationale Contre le Cancer.

† Cox proportional hazards model adjusted for age at diagnosis, sex, UICC stage, location of CRC, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, body mass index, lifetime pack-years of active smoking, average lifetime physical activity, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), ever use of hormone replacement therapy (women), previous large bowel endoscopy, diabetes, hyperlipidemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, and for a time-dependent effect of chemotherapy (chemotherapy*log[time]). All statistical tests were two-sided.

Table 4. Association of statin use with molecular pathological subtypes of colorectal cancer at diagnosis and with subtype-specific overall survival

Molecular pathological subtype	Association with subtypes		P	Overall survival		
	Statin use No. (%)	No statin use No. (%)		Events (users) No. (%)	Events (nonusers) No. (%)	HR (95% CI)*
MSS	146 (92)	898 (91)		48 (33)	313 (35)	0.90 (0.57 to 1.42)
MSI-high	12 (8)	93 (9)	.47	3 (25)	21 (23)	n.a.
CIMP low/negative	153 (92)	900 (88)		49 (32)	308 (34)	0.97 (0.61 to 1.55)
CIMP high	14 (8)	123 (12)	.17	6 (43)	38 (31)	n.a.
ER-beta expression neg./moderate	117 (81)	749 (83)		39 (33)	261 (35)	0.91 (0.55 to 1.51)
ER-beta expression high	27 (19)	153 (17)	.60	8 (30)	41 (27)	n.a.
KRAS wildtype	102 (68)	625 (71)		33 (32)	206 (33)	0.97 (0.55 to 1.70)
KRAS mutated	48 (32)	255 (29)	.45	14 (29)	99 (39)	1.05 (0.44 to 2.47)

* Cox proportional hazards model adjusted for age at diagnosis, sex, Union Internationale Contre le Cancer stage, location of colorectal cancer, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, body mass index, lifetime pack-years of active smoking, average lifetime physical activity, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), ever use of hormone replacement therapy (women), previous large bowel endoscopy, diabetes, hyperlipidemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, and for a time-dependent effect of chemotherapy (chemotherapy*log[time]). All statistical tests were two-sided. CI = confidence interval; ER-beta = estrogen receptor–beta; HR = hazard ratio; MSI-high = high-level microsatellite instability; MSS = microsatellite-stable.

Table 5. Association of statin use at diagnosis with overall, colorectal cancer–specific, and recurrence-free survival

	Overall survival	CRC-specific survival	Recurrence-free survival*
Statin use	HR (95% CI)	HR (95% CI)	HR (95% CI)
No statin use	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Any statin use, adjustment for			
Age, sex	0.97 (0.80 to 1.19)	0.90 (0.71 to 1.14)	0.83 (0.63 to 1.10)
Age, sex, stage	1.11 (0.91 to 1.36)	1.09 (0.86 to 1.39)	0.90 (0.68 to 1.19)
Full adjustment†	1.10 (0.85 to 1.41)	1.11 (0.82 to 1.50)	0.90 (0.63 to 1.27)

* Stage IV patients were excluded in the analyses on recurrence. Recurrence includes relapse, metastases, or death because of colorectal cancer. CI = confidence interval; CRC = colorectal cancer; HR = hazard ratio.

† Cox proportional hazards model adjusted for age at diagnosis, sex, Union Internationale Contre le Cancer stage, location of CRC, surgery, neoadjuvant treatment, chemotherapy, radiotherapy, body mass index, lifetime pack-years of active smoking, average lifetime physical activity, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), ever use of hormone replacement therapy (women), previous large bowel endoscopy, diabetes, hyperlipidemia, myocardial infarction, stroke, heart failure, participation in general health check-ups, and for a time-dependent effect of chemotherapy (chemotherapy*log(time)). All statistical tests were two-sided.

Table 6. Association of statin use with stage of colorectal cancer at diagnosis

		Adjusted for age, sex	Full adjustment
Stage	Statin use No. (%)	OR (95% CI)*	OR (95% CI)†
Stage I	116 (19)	1.00 (Ref.)	1.00 (Ref.)
Stage II	127 (16)	0.77 (0.58 to 1.02)	0.98 (0.69 to 1.41)
Stage III	126 (14)	0.73 (0.55 to 0.97)	0.87 (0.61 to 1.23)
Stage IV	43 (11)	0.53 (0.36 to 0.77)	0.66 (0.41 to 1.06)
Per increase in stage of CRC		0.72 (0.59 to 0.87)	0.81 (0.64 to 1.03)

* Multinomial logistic regression model adjusted for age at diagnosis, sex. CI = confidence interval; CRC = colorectal cancer; OR = odds ratio.

† Multinomial logistic regression model adjusted for age at diagnosis, sex, body mass index, lifetime pack-years of active smoking, average lifetime physical activity, ever regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), ever use of hormone replacement therapy (women), previous large bowel endoscopy, diabetes, hyperlipidemia, myocardial infarction, stroke, heart failure, participation in general health check-ups. All statistical tests were two-sided.

better medical surveillance of statin users in general or because of more common use of CRC screening measures, as reflected in the higher proportion of statin users with a previous colonoscopy or previous general health examinations in our study. The attenuation of the association of statin use with earlier stage at diagnosis after controlling for these factors is in line with this potential explanation.

Another retrospective cohort study including 1309 male CRC patients from the United States observed 27% lower CRC-specific mortality five years after diagnosis with the use of statins (34). This study, which was based on prescription information, lacked adjustment for comorbidities and health behavior, but also found an association of statin use with lower tumor stage at diagnosis. The longer survival time demonstrated by a univariate log-rank test could again be because of a more favorable stage distribution among statin users. In a smaller case-control study from Scotland using drug prescription data, statin use was non-significantly associated with reduced overall and CRC-specific mortality after adjustment for age, sex, and stage of CRC, but case numbers were too low to detect even strong effects (35).

In a recent registry-based cohort study from the United Kingdom, pre- and postdiagnostic use of statins were associated with improved cancer-specific survival among 7657 CRC stage I-III patients (HR = 0.91, 95% CI = 0.83 to 0.99 and HR = 0.71, 95% CI = 0.61 to 0.84, respectively) (24). By linking information from several databases, the authors were able to adjust for many potentially relevant confounders. However, analyses on prediagnostic use of statins lacked adjustment for stage and results were similar to our results when omitting stage in the model. The authors' reasoning that stage could be on the causal pathway would rather be an argument for the adjustment for stage, when the intention was to assess an independent effect on survival. Another major difference with our study was that 17% of the patients with less than one year of follow-up time were excluded from analyses on postdiagnostic use, as it was assumed that use of statins for therapeutic purposes will not be able to affect death rates in the first year. It remains unclear why administration of statins should not be effective in the first year in a cohort of nonmetastatic patients with reasonable to very good chances of survival.

In line with our results, an observational follow-up study including 842 stage III CRC patients of a randomized chemotherapy trial from the United States found no beneficial effect with the use of statins during or after chemotherapy (median follow-up time = 6.5 years) (36), and subgroup analyses by *KRAS* mutation status did not alter the results.

To our knowledge, the present study is the first to report associations of statin use and survival by pathological subtype in an unselected cohort of CRC patients. We observed no reduction in mortality for any of the molecular pathological subtypes investigated (see above).

Recently, American expert groups have extended the indications for statin therapy in their guidelines and lowered low density lipoprotein (LDL) cholesterol limits for certain risk groups (37). It was estimated that patients eligible for statin therapy will increase from 43 million to 56 million adults in the United States because of these changes (38). Existing studies suggest that statin use has no major adverse effects even after long-term use (39). If statin use would reduce mortality in CRC patients who use statins because of cardiovascular disease prevention, this would be important because an increasing proportion of CRC patients might benefit. However, our study results do not support this association observed in previous studies.

Our study has potential limitations that require discussion. The results refer to use of statins up to diagnosis and do not include use that was discontinued in the years prior to diagnosis. Discontinued use would introduce misclassification of statin use and underestimation of hazard ratios in case previous use of statins had an effect on survival. However, we observed no duration effects, and, once prescribed, statins are usually taken continuously in this age group. Also, statin use and the year of initiation were self-reported and may have led to (nondifferential) misclassification of some of the patients. As we had no reliable information on the dose and frequency of statin use, dose-response effects could not be estimated. Despite the high consistency of reported prediagnostic and postdiagnostic statin use, this may not apply to other exposures controlled for in the adjusted model, such as physical activity.

Although the current cohort study included more than 2600 patients, the study power was not sufficient to detect potential weak effects of statins and, depending on the size of the subgroup, analyses in subgroups were even more limited. Although inclusion of 1209 patients represents a large study compared with other existing studies including molecular characterization of tumors, even larger studies or consortia are needed to investigate patient groups with less common subtypes such as high-level MSI.

In conclusion, in this prospective patient cohort study statin use was not associated with reduced mortality among CRC patients. The results of the present study do not support suggestions of beneficial effects of statins for CRC prognosis derived from registry-based studies and suggest that such effects reported in previous studies might partly reflect the lack of or incomplete control for stage at diagnosis and other factors associated with the use of statins such as better medical surveillance. Our finding of better recurrence-free survival associated with use of statins among early-stage patients may be because of chance and needs to be confirmed. Before results from a first ongoing randomized trial become available (40), additional large observational cohort studies with prospective, comprehensive clinical and epidemiological assessment are required to clarify the currently uncertain effect of statins on survival of CRC patients and to inform future planning of clinical trials.

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Notes

The authors had full responsibilities for the design of the study, the collection of the data, the analysis and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication.

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