The association between statins and colorectal cancer stage in the Women's Health Initiative

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Abstract. The anticarcinogenic effect of statins may reduce the metastatic potential of cancer cells leading to 'stage migration', with users more likely diagnosed with early rather than late stage cancer. The association between prior statin use and colorectal cancer (CRC) stage at diagnosis in the Women's Health Initiative (WHI) was investigated. The study population included 132,322 post-menopausal women, among which there were 2,628 pathologically confirmed cases of *in situ* (3.3%), localized (43.6%), regional (40.4%) and distant (12.7%) stage CRC, after an average of 13.9 (SD=4.7) years of follow-up. To reduce the possibility of detection bias among women more likely to be prescribed statins, women who did not report a mammogram within 5 years of study entry and who had no health insurance or medical care provider (n=28,237) were excluded from the study. Stage was coded using SEER criteria into early (*in situ* and local) vs. late (regional and distant) stage disease. Hazards ratios (HR) and 95% confidence intervals (CIs) evaluating the association between statin use and diagnosis of late-stage CRC both at baseline and in a time-dependent manner were computed from multivariable-adjusted Cox proportional hazards analyses. In the multivariable time-dependent analysis, there was a lower hazard of late stage CRC among users of lipophilic statins compared with non-users (HR=0.80, 95% CI 0.66-0.98, P=0.029) and a marginally lower hazard of late stage CRC among users of lipophilic vs. hydrophilic statins (HR=0.70, 95% CI 0.49-1.01, P=0.058). The use of lipophilic statins was associated with a reduction in the proportion of CRC cases that were late stage at the time of diagnosis.

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Introduction

Statins are widely prescribed in the United States with up to 25% of the population over age 45 estimated to use the medications from 2005 to 2008 (1). This is largely attributed to the demonstrated impact of statins on cardiovascular events and mortality in several randomized controlled trials (2-4). Over 62 million individuals are estimated to be statin-eligible based on guidelines from the ACC/AHA for statin use (5).

Statins are well known as inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase, the enzyme required for the conversion of HMG-CoA to mevalonic acid (6) and a number of cancers, including colorectal cancer (CRC), have molecular pathways which are potentially affected by the inhibition of mevalonic acid synthesis as well as through alternative pathways (7,8). Statins have also been shown to arrest cell cycle progression, to alter the adhesion and migration of tumor cells, and to induce tumor cell apoptosis potentially leading to a reduced risk of metastasis (9-11).

A number of epidemiologic studies, including one utilizing the Women's Health Initiative (WHI) database, have assessed the relationship between statins and CRC risk and have shown mixed results with some studies reporting a protective effect (12-14) and others no association (15,16). In particular, a previous study utilizing the WHI database has addressed the specific question of whether statins have an effect on the risk of CRC diagnosis and the results did show a benefit for the lipophilic sub-type of statins (12). Other studies including

two recent meta-analyses have revealed a generally weak influence of statin use on overall survival in patients with CRC with an inconsistent reduction in CRC specific mortality (17-19). There is only one prior study to date that has looked at the specific hypothesis of this study which is the relationship between statins and CRC stage at diagnosis. That study reported that 3 or more years of pre-diagnosis statin use was associated with lower AJCC tumor stage and lower prevalence of metastases compared to non-users (20).

In the current analysis, we evaluated whether prior statin use had an impact on CRC stage at the time of cancer diagnosis using data from the Women's Health Initiative (WHI) cohort. Our specific hypothesis for this study was to determine whether prior statin use had an impact on stage of CRC at diagnosis. The literature suggests that through the inhibition of cell migration and angiogenesis, along with reported pro-apoptotic effects, statins are hypothesized to have anti-invasive, anti-proliferative, and ultimately anti-metastatic effects (9-11,18,21-26). We hypothesized that the anticancer effects of statins would have a potential impact on CRC stage at diagnosis.

Materials and methods

Study population. The study population included 161,806 women enrolled in either the WHI clinical trials (CT) (n=68,132) or observational study (OS) (n=93,676) and included women with newly diagnosed incident invasive and *in situ* CRC through the end of the first WHI Extension Study. The CT consisted of randomized trials of hormone therapy, dietary modification, and/or calcium and vitamin D supplementation (27,28). More information related to the WHI trials including the study's design, procedures, and components can be found at the WHI website (29). In order to reduce the possibility of detection bias among women more likely to be prescribed statins, we excluded from the analysis women who did not report a mammogram within 5 years of study entry (16,686), women with no health insurance at baseline (5,732), and women with no reported medical care provider (5,818). We also excluded women who had a prior history of CRC (813) and women with missing information on baseline statin use (2) resulting in a total of 29,051 women who were excluded from the analysis. We did not exclude participants based on whether or not they had a colonoscopy within the past 10 years as this was thought to limit the size of the study population number in a time period where alternative methods of CRC screening such as sigmoidoscopy were part of the standard of care. In total, there were 132,757 women included in the analysis who were followed for an average of 13.9 (SD 4.72) years.

Statin exposure. Statin use was defined as use of any HMG-CoA reductase inhibitor. Statins are classified as either lipophilic or hydrophilic. This classification is based on their solubility in octanol (lipophilicity) or water (hydrophilicity). Corresponding to their solubility properties, lipophilic statins penetrate the plasma membrane while hydrophilic statins do not (30).

Statin exposure was defined as statin use for any duration of time before the diagnosis of CRC. We analyzed baseline statin exposure from CT and OS participants as well as follow-up information on statin use determined at year 3 in the OS and years 1, 3, 6 and 9 in the CT, and statin use at the start of the 2nd extension study for both (27,28). At baseline and each follow-up period, participants were asked to bring all of their current prescription medications to the clinic visit (or first interview at baseline). At those times, study personnel entered each medication name directly from the medication containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc.). At the time of the visit, women also reported duration of use for each current medication. Information related to statin use at subsequent visits continued to be ascertained throughout the study and was used to develop a time dependent measure of statin exposure in this study.

Covariates. Variables within the study population that can affect risk of CRC may have an effect on the stage migration and were assessed as potential confounding variables and are listed in Table I. Information on these variables was collected on the baseline WHI study questionnaires and included participant socio-demographics, medical history and other information on established risk factors for CRC (17,27,28).

Outcomes. Cancer diagnoses were updated by telephone questionnaires and/or by mail semi-annually in the CT and annually in the OS. Centrally trained physician adjudicators were utilized to verify participant or next of kin reports of CRC through careful review of pathology reports and supporting medical records in conjunction with the Surveillance Epidemiology and End Results (SEER) coding system. Information on the frequency of screening tests, including fecal occult blood tests, rectal examinations, and sigmoidoscopy or colonoscopy was collected at baseline and updated every 6 months in the CT and every 12 months in the OS. Corresponding to the goals of this study, stage was stratified as either early-stage disease (*in situ* and local) versus late-stage (regional and distant) disease. There was a total of 13.9 years of follow-up (SD 4.7 years) from the start through the end of the first WHI Extension Study with (n=2,628) centrally adjudicated and SEER-coded CRC cases [89 *in situ* (3.25%), 1,145 localized stage (42.8%), 1,062 regional stage (39.6%) and 334 distant stage (12.4%).

Statistical analysis. Univariate and multivariable Cox models were fit to assess the relationship between each of overall statin use at baseline, type of statin use at baseline, and duration of statin use at baseline respectively with time to late stage CRC diagnosis as the outcome. Women who died during follow-up in the study or presented with early stage CRC were treated as censored in all of the main analyses' models. The baseline hazard for the univariate and multivariable models was stratified both by WHI trial membership and age stratum. Multivariable models were created using the following clinically relevant covariates determined a priori as covariates: race, education, smoking, alcohol, body mass index (BMI), mammogram in the past 2 years, aspirin use, and history of colonoscopy or sigmoidoscopy.

All covariates in the multivariable models were categorized as seen in Table I. Statin use at baseline was categorized by use vs. non-use, type (lipophilic vs. hydrophilic), and duration of use (<1 year, 1-3 years, and 3+ years) for each of the respective

Table I. Selected demographics and clinical characteristics by baseline statin use in the Women's Health Initiative.

Variable	No baseline statin use n=121,889 (92%)	Baseline statin use n=10,868 (8%)
Age group at enrollment (years)		
50-54	16,414 (13%)	575 (5%)
55-59	24,166 (20%)	1,346 (12%)
60-69	54,527 (45%)	5,694 (52%)
70-79+	26,782 (22%)	3,253 (30%)
Ethnicity		
Native American/Alaskan native	464 (0%)	34 (0%)
Asian or Pacific Islander	3,135 (3%)	434 (4%)
Black or African American	9,801 (8%)	904 (8%)
Hispanic or Latino	3,578 (3%)	289 (3%)
White (not of Hispanic origin)	103,292 (85%)	9,057 (83%)
Other	1,320 (1%)	121 (1%)
Education		
None to some HS	4,877 (4%)	636 (6%)
HS diploma/GED	19,925 (16%)	2,268 (21%)
Vocational, training school, some college or associate degree	45,397 (37%)	4,197 (39%)
College graduate or more	50,996 (42%)	3,708 (34%)
BMI (kg/m^2)		
<25	44,560 (37%)	2,723 (25%)
25-29	41,804 (34%)	4,318 (40%)
>30	34,464 (28%)	3,737 (34%)
Smoking		
Never smoked	61,771 (51%)	5,263 (48%)
Past smoker	51,463 (42%)	4,852 (45%)
Current smoker	7,189 (6%)	605 (6%)
Alcohol use		
Non-drinker or past drinker	33,733 (28%)	3,628 (33%)
<1 drink/month to <7 drinks per week	72,460 (59%)	6,137 (56%)
7+ drinks per week	14,892 (12%)	1,037 (10%)
Overall physical activity		
None	17,191 (14%)	1,501 (14%)
>0 to 3.75 MET-hours/week	16,344 (13%)	1,614 (15%)
3.75-8.75 MET-hours/week	23,759 (19%)	2,318 (21%)
8.75-17.5 MET-hours/week	27,095 (22%)	2,515 (23%)
>17.5 MET-hours/week	31,793 (26%)	2,658 (24%)
Aspirin use		
No	98,423 (81%)	7,122 (66%)
Yes	23,466 (19%)	3,746 (34%)
Mammogram within 2 years		
No	10,709 (9%)	744 (7%)
Yes	111,180 (91%)	10,124 (93%)
Colon screening		
Yes, <5 years ago	40,693 (35%)	4,154 (40%)
Yes, >5 years ago	22,221 (19.2%)	2,159 (20%)
Never	52,606 (46%)	4,228 (40%)

univariate and multivariable models assessing the relationships between these variables and time to late stage CRC diagnosis.

To examine the impact of change in statin use over time, univariate and multivariable Cox models were created with

Table II. Characteristics of statin use and CRC outcomes.

Characteristic	Number (%)
Baseline statin use:	
No	121,889 (92%)
Yes	10,868 (8%)
Baseline statin duration[a]:	
No baseline statin use	121,889 (92%)
<1 year	3,541 (3%)
1-3 years	3,711 (3%)
3+ years	3,616 (3%)
Baseline statin name:	
No baseline statin use	121,889 (92%)
Atorvastatin calcium	837 (1%)
Fluvastatin sodium	1,330 (1%)
Lovastatin	2,955 (2%)
Pravastatin sodium	2,456 (2%)
Simvastatin	3,290 (2%)
Baseline statin type:	
None	121,889 (92%)
Lipophilic	8,412 (6%)
Hydrophilic	2,456 (2%)

[a]>100% due to rounding. CRC, colorectal cancer.

statin use (by type and by use vs. non-use) as time dependent exposures. Time varying statin use models (overall and by statin type) were based on updates on statin intake obtained at follow-up clinic visits. The time varying models were also categorized by age stratum at randomization and WHI trial membership, and used the same covariates as the baseline models. All analyses were performed using SAS/STAT software version 9.4 (SAS Institute Inc). P-values less than 0.05 were considered to be statistically significant. We also fit competing risk models treating both diagnosis of early stage CRC and death as competing risks respectively as sensitivity analyses for all of the main analyses' models described above.

Results

The study consisted of 10,868 women who reported statin use at baseline and 121,889 who reported no statin use at baseline. The mean age of the postmenopausal population was ~63 years old and 84.6% of the study participants were white. Table I describes the demographic and clinical characteristics of the study cohort. Statin users were more likely than non-users to be older, diabetic, overweight or obese; however, family history of CRC, tobacco use, and alcohol use were relatively similar between the two groups. Statin users were also slightly more likely to have had a screening colonoscopy and to be taking aspirin or an NSAID. Table II describes the distribution of statin use at baseline by duration, type of statin used, and other statin characteristics. Additionally, Table II lists the number of CRC cases both by severity and also in association with statin use at baseline. It is important to note however that the data in Table II is included to demonstrate the baseline data on statin use by stage of CRC, and does not include data pertinent to the time dependent analysis.

Table III shows the relationship between late-stage CRC at diagnosis and statin use. In the multivariable model, there was no significant association between statin use at baseline and late-stage CRC (HR=1.08; 95% CI, (0.86-1.36, P=0.498). Table IV shows the relationship between late-stage CRC and statin use in a time-dependent model. In the multivariable time-dependent analyses, overall statin use (regardless of type) was not associated with a significant reduction in late-stage CRC (HR=0.87, 95% CI, 0.73-1.03, P=0.109). However, when statin type was assessed, there was found to be a significant relationship between lipophilic statin use and late stage CRC (HR=0.80, 95% CI, 0.66-0.98, P=0.029) compared to no statin use over time. When comparing lipophilic vs. hydrophilic statin use there was a marginally decreased risk of late stage CRC for users of lipophilic statins, however these differences were not statistically significant (HR=0.70, 95% CI, 0.49-1.01, P=0.058).

Several sensitivity analyses were performed. First, we checked for possible selection bias by repeating our baseline statin use multivariable models for late-stage CRC without any exclusion for healthcare access; indicator variables for the original inclusion criteria (mammogram in the past 5 years, current health insurance, current healthcare provider and no personal history of CRC) were added as additional covariates in the multivariable models. The hazard ratio for statin use at baseline (yes vs. no) from the multivariable model using the extended cohort was 1.02 compared to the original hazard ratio show in Table III of 1.08. We further assessed whether treating diagnosis of early stage CRC or death as competing risks would have an effect on the cox model estimates, and found the hazard ratios to be similar to the initial models.

Discussion

The primary goal of this study was to determine whether prior statin use is associated with earlier stage CRC at the time of cancer diagnosis. While our analysis of statin use at baseline alone showed no significant association, after taking into account subsequent exposure to statins captured in a time-dependent analysis, we found a significant reduction in the proportion of cancer diagnoses that were consistent with late stage disease among users of statins. Our findings appeared to depend on the type of statin used, as specifically users of lipophilic statins were found to have decreased risk for late stage disease when analyzed independently compared to non-users. The impact of hydrophilic statins which, in contrast, did not have a protective association, is likely responsible for the aggregate statin group results lack of a statistically significant association. In a similar analysis, we reported a reduction in late stage breast cancer among prior users of statins as well as a marginally lower risk of death from breast cancer among users of lipophilic statins (31). In another previous WHI analysis assessing the overall risk of CRC in statin users, a significant reduction in CRC risk for lovastatin, a lipophilic statin, was observed (12). Given our prior findings, the present study was designed to specifically focus on the hypothesis that there is a reduced likelihood of advanced stage CRC in statin users at

Table III. CRC stage migration by baseline statin use.

Model type	Comparison	HR	95% CI	P-value
Univariable: baseline statin (Y/N)	Baseline statin (yes vs. no)	1.06	(0.85, 1.32)	0.628
Univariable: baseline statin duration	Baseline statin: <1 year vs. none	0.88	(0.58, 1.33)	0.548
	Baseline statin: 1-3 years vs. none	1.32	(0.95, 1.83)	0.100
	Baseline statin: 3+ years vs. none	0.96	(0.65, 1.41)	0.830
	Baseline statin: <1 year vs. 1-3 years	0.67	(0.40, 1.12)	0.129
	Baseline statin: <1 year vs. 3+ years	0.92	(0.53, 1.60)	0.764
	Baseline statin: 1-3 years vs. 3+ years	1.38	(0.84, 2.26)	0.208
Univariable: baseline statin type	Baseline statin: lipophilic vs. none	0.96	(0.74, 1.24)	0.733
	Baseline statin: hydrophilic vs. none	1.41	(0.95, 2.08)	0.088
	Baseline statin: lipophilic vs. hydrophilic	0.68	(0.43, 1.08)	0.100
Multivariable[a]	Baseline statin (yes vs. no)	1.08	(0.86, 1.36)	0.498
Multivariable: baseline statin duration	Baseline statin: <1 year vs. none	0.86	(0.56, 1.33)	0.490
	Baseline statin: 1-3 years vs. none	1.43	(1.02, 1.99)	0.036
	Baseline statin: 3+ years vs. none	0.95	(0.64, 1.42)	0.814
	Baseline statin: <1 year vs. 1-3 years	0.60	(0.35, 1.03)	0.063
	Baseline statin: <1 year vs. 3+ years	0.90	(0.50, 1.61)	0.723
	Baseline statin: 1 -3 years vs. 3+ years	1.50	(0.90, 2.49)	0.120
Multivariable[a]: baseline statin type	Baseline statin: lipophilic vs. none	1.01	(0.78, 1.32)	0.943
	Baseline statin: hydrophilic vs. none	1.33	(0.88, 2.02)	0.177
	Baseline statin: lipophilic vs. hydrophilic	0.76	(0.47, 1.23)	0.259

[a]Adjusted for race, education, smoking, BMI, mammogram in the past 2 years, aspirin use, and history or colonoscopy. History of colonoscopy is a categorical variable that has the following categories (no, yes, within the past 5 years; yes, more than 5 years ago). CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval.

Table IV. Association of statin use over time and late stage CRC stratified by type of statin.

Model type	Comparison	HR	95% CI	P-value
Univariable: Statin use over time (Y/N)	Statin use over time (yes vs. no)	0.85	(0.72, 1.01)	0.064
Multivariable[a]	Statin use over time (yes vs. no)	0.87	(0.73, 1.03)	0.109
Univariable: Statin use over time: by type	Statin use over time: lipophilic vs. none	0.79	(0.66, 0.96)	0.016
	Statin use over time: hydrophilic vs. none	1.18	(0.86, 1.61)	0.303
	Statin use over time: lipophilic vs. hydrophilic	0.67	(0.48, 0.96)	0.027
Multivariable[a]: Statin use over time: by type	Statin use over time: lipophilic vs. none	0.80	(0.66, 0.98)	0.029
	Statin use over time: hydrophilic vs. none	1.14	(0.83, 1.59)	0.419
	Statin use over time: lipophilic vs. hydrophilic	0.70	(0.49, 1.01)	0.058

[a]Adjusted for race, education, smoking, BMI, mammogram in the past 2 years, aspirin use, and history or colonoscopy. CRC, colorectal cancer; HR, hazard ratio; CI, confidence interval.

the time of diagnosis due to the anticarcinogenic molecular pathways associated with statin use. The results from our prior work adds evidence to the hypothesis of a preferential effect of lipophilic statins compared to hydrophilic statins possibly related to the increased permeability of lipophilic statins across the cell membrane.

In order to have a beneficial impact on CRC outcomes, it is desirable to identify strategies to either prevent or down-stage disease at diagnosis (32,33). Through the inhibition of cell migration and angiogenesis, along with reported pro-apoptotic effects, statins are hypothesized to have anti-invasive, anti-proliferative, and ultimately anti-metastatic effects (9-11,18,21-26). There has only been one other population-based study that has looked at the relationship between statin use and CRC stage at diagnosis however others have also assessed the impact of statins on response to adjuvant or neoadjuvant chemotherapy (18,19,34-36). Among 1,309 male veterans with CRC, use of 3 or more years of pre-diagnosis

statins was associated with a lower mean AJCC tumor stage (2.2 for users vs. 2.6 for non-users; P<0.01) and lower prevalence of metastases [OR =0.7 (0.4-0.9, 95%CI); P<0.01] (20). Also, in an analysis of 407 individuals with primary rectal cancer, statin use was significantly associated with improved response to chemotherapy as measured by the AJCC tumor regression grading system which itself was associated with improved oncologic outcomes (35) results of which were collaborated by others (34). The results of our study are consistent with others in the literature suggesting the possibility that, through their previously described inhibition of the mevalonic acid pathway, statins may have a mitigatory effect on the severity or stage of cancer found at the time of diagnosis.

The strengths of our analysis include the WHI protocol for comprehensive assessment and central review of cancer diagnoses with accompanying information related to demographics and cancer risk factors. Limitations include an inability to utilize the TNM classification system for staging due to missing data on the number of involved lymph nodes at the time of diagnosis. Notably, in addition there was a much lower prevalence of statin use at the study's inception as compared with predicted current use (1) and we were unable to confirm medication start dates or compliance. There is also the potential for other biases given that statin users may be more likely to have had better medical care and to have exposure to CRC screening which may account for earlier stage at diagnosis among statin users. We attempted to control for bias related to access to care by only including women in the analysis who had a mammogram in the past 5 years and who had health insurance and a regular medical provider and we also adjusted our results for past reported colon cancer screening. However, the dataset was not comprehensive in relation to the frequency of or indication for colonoscopic evaluation. Without additional information on screening colonoscopy, we were unable to construct a meaningful time-dependent control for screening colonoscopy. The difficulties with both construction of a comprehensive medication use history as well as construction of a detailed history of screening colonoscopy reflect the retrospective nature of our analysis within the setting of an observational study. In light of these limitations, in our view the results of the study should be viewed primarily as exploratory and hypothesis provoking. Further investigation by clinical trial would aid in a more definitive conclusion.

In summary, our results suggest that lipophilic statins use may be associated with an anticarcinogenic effect corresponding with a lower likelihood of developing late stage CRC which may have future implications for CRC prevention and management.

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Availability of data and materials

The data that support the findings of this study are available from the National Heart, Lung and Blood Institute (https://biolincc-nhlbi-nih-gov/studies/whios/), but restrictions apply to the availability of these data. Data are however available from the WHI upon reasonable request.

Authors' contributions

BPR and MSS were responsible for the conception, design, and interpretation of data analysis and drafting of the manuscript. MAR was responsible for the data analysis. PD, SL, JL, RN, QL and MA made substantial contributions to the analysis and interpretation of the data along with being responsible for the revisions and critical review of the drafts. All authors have approved the final version of this manuscript.

Ethics approval and consent to participate

The Women's Health Initiative was overseen by ethics committee at all 40 clinical centers, and an independent data and safety monitoring board for the clinical trials. Each institution obtained human subjects committee approval. Each participant provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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