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.

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).

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Key words: hydroxymethylglutaryl-CoA reductase inhibitors, colorectal neoplasm, neoplasm staging, hydrophobic, hydrophilic
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 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 4.7 years) 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 (3.2%), 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
To examine the impact of change in statin use over time, univariate and multivariable Cox models were created with univariate and multivariable models assessing the relationships between these variables and time to late stage CRC diagnosis.

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/m²)                                   |                                        |                                   |
| <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%)                       |
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 there is 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 significant relationship between lipophilic statin use and late stage CRC (HR=0.80, 95% CI, 0.66-0.98). 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.

**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 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

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\(^b\): 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\(^b\): 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 correlation between lipophilic statins and colorectal cancer stage.

**Acknowledgements**

We acknowledge the dedicated efforts of investigators and staff at the Women's Health Initiative (WHI) clinical centers, the WHI Clinical Coordinating Center, and the National Heart, Lung and Blood program office (listing available at http://www.whi.org). We also recognize the WHI participants for their extraordinary commitment to the WHI program. For a list of all the investigators who have contributed to WHI science, please visit: [http://www.whiscience.org/publications/WHI_investigators_longlist.pdf](http://www.whiscience.org/publications/WHI_investigators_longlist.pdf). This abstract was presented at the American Society of Clinical Oncology in Chicago, IL, USA on June 5th, 2017, and was published as Abstract no. 1540.

**Funding**

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221”, and the Cancer Center Support Grant NIH:NCI P30CA022453.

**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://biolinc-nhlbi.nih-gov/studies/whios/](https://biolinc-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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