HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2016 October 10.

Published in final edited form as:

Cancer Causes Control. 2015 April ; 26(4): 529–539. doi:10.1007/s10552-015-0530-7.

Statins and breast cancer stage and mortality in the Women's Health Initiative

Pinkal Desai,
Weill Cornell Medical College, New York, NY, USA

Amy Lehman,
Ohio State University, Columbus, OH, USA

Rowan T. Chlebowski,
Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, CA, USA

Marilyn L. Kwan,
Kaiser Permanente Northern California Division of Research, Oakland, CA, USA

Monica Arun,
Boston Medical Center, Boston, MA, USA

JoAnn E. Manson,
Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Sayeh Lavasani,
Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Sylvia Wasswertheil-Smoller,
Albert Einstein College of Medicine, Bronx, NY, USA

Gloria E. Sarto,
University of Wisconsin, Madison, WI, USA

Meryl LeBoff,
Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Jane Cauley,
University of Pittsburgh, Pittsburg, PA, USA

Michele Cote,
Barbara Ann Karmanos Cancer Institute, Wayne State University, 4100 John R, 4221 HWCRC, Detroit, MI, USA

Jennifer Beebe-Dimmer,
Barbara Ann Karmanos Cancer Institute, Wayne State University, 4100 John R, 4221 HWCRC, Detroit, MI

Allison Jay, and

Correspondence to: Michael S. Simon.

Result of the paper presented at the 2014 San Antonio Breast Cancer Conference (10–13 December 2014).

St. Johns Hospital and Medical Center, Detroit, MI, USA

Michael S. Simon
Barbara Ann Karmanos Cancer Institute, Wayne State University, 4100 John R, 4221 HWCRC, Detroit, MI, USA simonm@karmanos.org

Abstract

Purpose—To evaluate the association between statins and breast cancer stage and mortality in the Women's Health Initiative.

Methods—The study population included 128,675 post-menopausal women aged 50–79 years, out of which there were 7,883 newly diagnosed cases of in situ (19 %), local (61 %)-, regional (19 %)- and distant (1 %)-stage breast cancer and 401 deaths due to breast cancer after an average of 11.5 (SD = 3.7) years of follow-up. Stage was coded using SEER criteria and was stratified into early (in situ and local)- versus late (regional and distant)-stage disease. Information on statins and other risk factors were collected by self- and interviewer-administered questionnaires. Cause of death was based on medical record review. Multivariable-adjusted hazards ratios (HR) and 95 % confidence intervals (CIs) evaluating the relationship between statin use (at baseline only and in a time-dependent manner) and diagnosis of late-stage breast cancer and breast cancer-specific mortality were computed from Cox proportional hazards analyses after adjusting for appropriate confounders.

Results—Statins were used by 10,474 women (8 %) at baseline. In the multivariable-adjusted time-dependent model, use of lipophilic statins was associated with a reduction in diagnosis of late-stage breast cancer (HR 0.80, 95 % CI 0.64–0.98, $p = 0.035$) which was also significant among women with estrogen receptor-positive disease (HR 0.72, 95 % CI 0.56–0.93, $p = 0.012$). Breast cancer mortality was marginally lower in statin users compared with nonusers (HR 0.59, 95 % CI 0.32–1.06, $p = 0.075$).

Conclusions—Prior statin use is associated with lower breast cancer stage at diagnosis.

Keywords

Breast cancer; Cancer stage; Breast cancer mortality; Statins

Introduction

Statins are the most widely prescribed cholesterol-lowering drugs with approximately 25 % of US adults using statins in 2008 [1]. Statins are effective in preventing cardiovascular disease by lowering overall cholesterol levels [2] but have also been postulated to lower the risk of cardiovascular disease, stroke and cancer through cholesterol-independent mechanisms [3–5].

Statins act primarily as a competitive inhibitor of hydroxyl methyl glutaryl coenzyme A (HMG-CoA) reductase. Additionally, preclinical studies have identified antiproliferative effects [6], apoptotic [7–9] and anti-invasive properties. While early observational studies reported associations between statin use and lower breast cancer risk overall [10–12], a more recent analysis of data from the Women's Health Initiative (WHI) found no consistent

association [13]. Nonetheless, other analyses of the relationship between statins and breast cancer progression suggest that statins may be associated with earlier stage of disease at diagnosis [14], lower rates of recurrence [15–18] and lower breast cancer mortality [18, 19]. The purpose of the current analysis is to further address these questions using the extensive follow-up and outcome data available from the WHI. Based on findings in the epidemiologic literature, we predicted that prior statins would result in earlier stage at diagnosis, resulting in reduced morbidity of treatment associated with higher stage and as well as lower mortality rates.

Methods

Study population

The WHI includes an observational study (n = 93,676) and clinical trials (n = 68,132) of hormone therapy (estrogen alone or estrogen + progesterone), dietary modification (DM), and/or calcium and vitamin D supplementation in postmenopausal women of many races and ethnicities [20–22]. The current analysis included women enrolled in the observational study and clinical trial components of the WHI. Note that some study participants had less access to the medical care system, which might lead to a lower likelihood of receiving statins and/or a diagnosis of breast cancer at an earlier stage. We therefore excluded from the analysis women who did not report a mammogram within 5 years of study entry (16,687), those without health insurance (5,732) and women with no reported medical care provider (5,818). We also excluded 4,239 women with a prior history of breast cancer, 431 women with missing or no information on follow-up, 225 women with incident breast cancer who had missing information on cancer stage, and one with missing information on baseline statin use. The final analysis cohort consisted of 128,675 women.

Statin exposure

Baseline statin exposure was analyzed from both clinical trials and observational study participants, and information on statin intake was collected at years 1, 3, 6 and 9 in the clinical trials, and year 3 in the observational study [20– 22]. Participants were requested to bring all of their current prescription medications to their clinic visit, and report duration of medication use at the first screening interview as well as each follow-up period. Each medication name, but not the dose, was directly entered into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, CA) [20–22].

Statin use was defined as any HMG-CoA reductase inhibitor used at baseline or during participation in the WHI prior to diagnosis of breast cancer. Statins were further classified based on solubility in octanol as lipophilic or hydrophilic, and also by potency. Lipophilicity may modify the penetration of statins across cellular and mitochondrial membranes. Lovastatin, simvastatin, atorvastatin and fluvastatin are all lipophilic statins, whereas pravastatin is a hydrophilic statin. Fluvastatin and lovastatin are low-potency statins, pravastatin is a medium-potency statin, and simvastatin and atorvastatin are high-potency statins [23, 24]. Updated information on statin use collected at subsequent participant visits were used to measure statin use as a time-dependent exposure. The newer statins,

rosuvastatin and pitavastatin, were not used in the early years of the WHI and are, therefore, not included in this analysis.

Outcomes

Updates on breast cancer diagnoses were reported semi-annually in the clinical trials and annually in the observational study, and were confirmed by trained physician adjudicators after review of medical records using the Surveillance Epidemiology and End Results (SEER) coding system [25]. There were 7,883 centrally adjudicated and SEER-coded breast cancer cases [1,477 in situ (19 %), 4,831 localized stage (61 %), 1,499 regional stage (19 %) and 76 distant stage (1 %)] that were diagnosed from the start of the study through 30 September 2010, which was the end of the first WHI Extension Study for a total of 11.5 (SD 3.7) years of follow-up. For the purposes of this analysis, stage was stratified into early (in situ and local)-versus late (regional and distant)-stage disease. Cause of death, including breast cancer-specific mortality, was based on medical record review at the Clinical Coordinating Center. Estrogen receptor (ER) status was classified as ER positive (5,571) versus ER negative (1,039) or borderline [12]. For analyses that included ER status, 1,261 women with breast cancer with unknown or missing ER status were excluded.

Covariates

Table 1 lists the potentially confounding or modifying variables collected at baseline entry into the study [20–22]. These included socio-demographic and medical history variables that could have an impact on whether or not study participants were prescribed statins as well as breast cancer stage at diagnosis and/or breast cancer-specific mortality and other well-established risk factors for breast cancer. Physical activity was defined as expenditure of energy from recreational physical activity including walking as well as mild, moderate and strenuous physical activity in kcal/week/kg.

Statistical analysis

All demographic and clinical characteristics of women with and without a prior history of statin use at baseline were summarized separately. Separate univariable Cox proportional hazard models were first used to assess the relationship between statin use at baseline and the development of late-stage breast cancer as well as the relationship between statin use at baseline and death due to breast cancer. For the late-stage breast cancer models, women with early-stage breast cancer or those who died during follow-up were censored. Similarly, for models with death due to breast cancer as the primary endpoint, women who died due to other causes were censored. Statin use at baseline was characterized as yes/no, by type (lipophilic/ hydrophilic), and duration of use (<1 year, 1–3 years, 3+ years).

Next, to control for potential confounding variables, multivariable models were created using clinically relevant covariates determined a priori: race, education, smoking, BMI, waist circumference, mammogram in the past 2 years, Gail 5-year risk, female relative with breast cancer, age at menarche, number of live births, breast biopsy, hysterectomy, hormone use, oral contraceptive use, aspirin use and study component (hormone trial, dietary modification trial not in hormone trial, and observational study). All covariates in the multivariable models were categorized as shown in Table 1 and included as indicator

variables. The baseline hazard for both the univariable and multi-variable models was stratified by age stratum at randomization and WHI trial membership. All two-way interactions with statin use were checked for significance. In addition, the proportional hazard assumption was assessed graphically as well as by including interactions with time (natural log scale); no serious deviations were observed.

To evaluate the effects of change in statin use over time, univariable and multivariable Cox models with statin use (yes/no and by type) as time-dependent exposures, based on updated information on statin intake gathered at follow-up clinic visits, were next applied to the data. The same covariates from the baseline statin models were used in the time-dependent multivariable models; the baseline hazards were again stratified by age stratum at randomization and WHI trial membership.

Finally, all univariable and multivariable Cox models described above were stratified by ER status (positive vs. negative), and HR and 95 % CI from the baseline statin use, as well as time-dependent statin use, were calculated. All analyses were performed using SAS/STAT software version 9.2 (SAS Institute Inc., Cary, NC), Stata 13 (StataCorp LP, College Station, TX) and R 3.0.2.

Results

Table 1 describes the baseline demographic and clinical characteristics of WHI participants stratified by baseline statin use. There were 10,474 (8 %) women who reported statin use at baseline. The mean age of the study cohort was 63.4 years (SD = 7.2 years), and 84.6 % of the study population were white. Statin users were more likely than nonusers to be older, overweight or obese; however, family history of breast cancer, age at menarche, pregnancy history and age at first full-term pregnancy were relatively similar between the statin use groups. Table 2 describes the distribution of statin use at baseline by duration, type of statin used and other statin characteristics.

Table 3 shows the relationship between late-stage breast cancer at diagnosis and statin use. In the multivariable model, there was no significant association between statin use at baseline and late-stage breast cancer (HR = 0.93; 95 % CI 0.76–1.14; $p = 0.494$). In addition, there was no significant relationship between statin use and development of late-stage breast cancer by statin lipophilicity ($p = 0.777$), duration of use ($p = 0.926$, data not shown) or statin potency (data not shown). In the multivariable time-dependent analyses, statin use was associated with a modest, but nonsignificant reduction in late-stage breast cancer (HR = 0.84; 95 % CI 0.70–1.02; $p = 0.082$); however, there was a significantly lower hazard of late-stage breast cancer among women who used lipophilic statins compared to nonusers (HR = 0.80; 95 % CI 0.64–0.98; $p = 0.035$).

Table 4 shows the relationship between statins and late-stage breast cancer stratified by ER status. In the baseline statin use model, there was a nonsignificant trend toward a lower risk of late-stage ER-positive breast cancer among users of statins (HR = 0.85; 95 % CI 0.67–1.08; $p = 0.191$ from the multivariable model); however, in the time-dependent analysis, there was a significantly lower risk of late-stage ER-positive breast cancer (HR = 0.79; 95 %

CI 0.63–0.99; $p = 0.044$). This association was also seen among women using lipophilic statins compared to nonusers (HR = 0.72; 95 % CI 0.56–0.93; $p = 0.012$).

Table 5 shows the relationship between statins and breast cancer-specific mortality. There were 401 deaths with breast cancer recorded as cause of death, 15,882 other deaths and 112,692 women with no recorded death. In the multivariable model, there was no significant relationship between statin use and breast cancer-specific mortality (HR = 0.91; 95 % CI 0.60–1.37; $p = 0.648$) and, in addition, no significant relationship between type of statin ($p = 0.254$) and duration of statin use ($p = 0.827$, data not shown). In the multivariable time-dependent analysis, statin use (yes vs. no) was associated with a decreased, albeit not statistically significant risk of breast cancer mortality over time (HR = 0.59, 95 % CI 0.32–1.06; $p = 0.075$). In addition, there was no significant relationship between statin use and breast cancer mortality stratified by ER status (data not shown).

Several sensitivity analyses were performed. First, we checked for possible selection bias by repeating our time-varying multivariable models for late-stage breast cancer without any exclusions for healthcare access; indicator variables for the original inclusion criteria (mammogram in the past 5 years, current health insurance, current healthcare provider and no prior breast cancer) were added as additional covariates in the multivariable models. The hazard ratio for statin use over time (yes vs. no) from the multivariable model using the extended cohort was 0.85 (95 % CI 0.71, 1.01), compared to the original hazard ratio shown in Table 3 of 0.84 (95 % CI 0.84, 1.02). Similarly, the hazard ratios comparing types of statin use over time were extremely similar to the original results (data not shown). Next, multiple imputation using chained equations was performed in order to assess the impact of the missing covariate data (female relative with breast cancer, hysterectomy, oral contraceptive use, aspirin, waist circumference, ethnicity, smoking status, education, BMI, age at menarche, number of live births, breast biopsy and hormone use) for the multivariable late-stage breast cancer models. A total of 17,329/128,676 observations had one or more missing covariate values; imputation using logistic and multinomial logistic models was performed. In addition to the covariates listed above, age, trial membership and outcome were used to fill in missing data. Using 20 imputed datasets, changes to the Cox model HR and CI from the complete case model results were assessed. Again, results from the imputation procedure were similar to our original complete case results (data not shown). Finally, we checked both the univariable and multivariable baseline statin use models using a competing risk approach as described by Fine and Gray [26]. For late-stage breast cancer, early-stage breast cancer and death were treated as competing risks instead of being censored (the ‘naïve’ models). Similarly, for death due to breast cancer, death due to other causes was treated as a competing risk. For late-stage breast cancer, the differences between the competing risks models and the naïve models were minimal: The HR for baseline statin use (yes vs. no) from the multivariable competing risks model was 0.93 (95 % CI 0.76–1.14), compared with 0.93 (95 % CI 0.76–1.14) from the naïve model. Similarly, for death due to breast cancer, differences in the hazard ratio and CI for baseline statin use between the multivariable competing risks model (HR = 0.92; 95 % CI 0.62–1.37) and the naïve model (HR = 0.91; 95 % CI 0.60–1.37) were slight. Univariable results for both outcomes between the naïve and competing risks models were also very similar (data not shown).

Discussion

Although prior analysis of data from the WHI revealed no significant relationship between prior statin use and breast cancer incidence [13], we hypothesized that prior statin use was protective against late-stage breast cancer and breast cancer-specific mortality. Our results revealed no significant relationship between statin use measured at baseline and stage or breast cancer-related mortality; however, when accounting for statin use over time, we found a significantly lower risk of late-stage breast cancer among women who used lipophilic statins, which was even more pronounced for women with ER-positive breast cancer. Furthermore, in the time-dependent analysis, prior statin use was associated with a lower breast cancer-specific mortality, albeit not statistically significant.

Anti-invasive properties of statins have been postulated to result from inhibition of farnesyl diphosphate (FFP) and geranylgeranyldipohsphate (GGPP), which are downstream products of the mevalonate pathway and are both involved in posttranslational modification of many proteins [3, 5, 27–29]. GGPP is involved in geranylgeranylation of rho proteins, which are involved in various cellular functions including gene expression, actin cytoskeleton migration, adhesion and contractility of cells [29]. Thus, by inhibiting the production of GGPP, statins may reduce cell migration and have anti-proliferative and anti-invasive properties. Other potential mechanisms include reduction in nuclear factor kappa B (NFkB) along with rho A inhibition, resulting in a decrease in matrix metalloproteinase 9 (MMP9) and urokinase levels which are important in cell migration [30] as well as inhibition of angiogenesis [31, 32]. Statins can also induce cellular arrest in the G1- to S-phase transition [33]. Finally, reduction in the metastatic potential after treatment with statins has been demonstrated in breast cancer cell lines as well as in mouse models [34, 35].

While early epidemiologic studies suggest an association between statins and lower breast cancer risk [10–12, 36, 37], our recent update of data from the WHI showed no significant relationship [13] which has been confirmed in two large meta-analyses [38, 2]. The goal of the current analysis was to evaluate whether prior statin intake is protective against late-stage disease and/or mortality due to breast cancer. Others have evaluated the relationship between statins and breast cancer stage, recurrence risk, and mortality [14–19]. In a retrospective analysis from the Kaiser Permanente Northern California Cancer Registry, statin use of 1 year or greater before breast cancer diagnosis was associated with a lower risk of ER/PR-negative breast cancer (OR 0.63; 95 % CI 0.43–0.92) and a higher likelihood of low-grade and earlier-stage disease [14]. Use of statins has also been associated with a lower risk of breast cancer recurrence, as in a retrospective cohort of 703 women with stage II or III breast cancer [15] and in a prospective cohort of 1,945 women with stage I–III breast cancer [16]. In a study of 18,769 women with stage I–III breast cancer, lower risk of recurrence [16] was only seen among women with ER-positive breast cancer [17]. Further, in a population-based cohort of 3,024 women with stage I–III breast cancer, lipid-lowering drugs (including statins) were associated with a decreased risk of recurrence (HR = 0.83; 95 % CI 0.54–1.24). Lastly, in a large population-based study in Denmark, statin users compared with nonusers had lower overall cancer mortality rates (HR = 0.85; 95 % CI 0.82–0.87) as well as lower breast cancer-specific mortality (HR = 0.87; 95 % CI 0.79–0.99, $p = 0.03$) although it is not

clear whether the reduction in breast cancer-specific mortality was due to a shift in stage at diagnosis or to other causes [19].

While data on breast cancer recurrence is not available in the WHI, our findings suggest an influence of lipophilic statins on stage at diagnosis among women with ER-sensitive cancers and are consistent with results of another study which showed a lower risk of breast cancer recurrence, also among women with ER-positive disease [16]. The preferential effect of lipophilic statins on breast cancer stage at diagnosis may be due to increased penetration across cellular membranes; however, this finding warrants further investigation. Mendelian randomization designs using genetic variation affecting the cellular uptake of statins could be considered to investigate the causal relationship between statin use and breast cancer staging. Lastly, while the relationship between statins and lower breast cancer mortality was not significant in the WHI analysis, our findings are consistent with those of other reports [15, 17, 18] and again warrant further study. It is possible that our results were not significant in regard to mortality due to the small number of deaths from breast cancer in the WHI.

The strengths of this analysis include the comprehensive demographic and cancer risk factor assessment, as well as central review of cancer diagnoses with a long follow-up period and detailed capture of statin use over time by inperson assessment of medication use. Limitations include the low prevalence of statin use at baseline in the WHI compared to current use, and lack of information on medication compliance among study participants. Another limitation is that this was an observational analysis of statins and breast cancer stage, and therefore, baseline risk-factor status, surveillance for breast cancer and other factors that predict either use of statins or diagnosis of breast cancer may have differed between statin users and nonusers. Also, we were not able to use the TNM classification of breast cancer stage due to missing data on the number of affected lymph nodes at the time of diagnosis, and we also excluded 225 women diagnosed with breast cancer due to missing SEER staging which may have had an impact on the power of our study. Other limitations included the relatively modest number of breast cancer deaths and the lack of information on cancer-related treatments.

In conclusion, our results from one of the largest studies to date suggest that lipophilic statins use may reduce the frequency of late stage in favor of earlier-stage breast cancer and may result in lower breast cancer mortality. Further studies should leverage large datasets with longer follow-up and information on specific types of statins used and cancer-directed therapy.

Acknowledgments

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. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US 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.

References

1. www.cdc.gov/nchs/data/hus/hus10.pdf#fig17
2. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366(9493):1267–1278. [PubMed: 16214597]
3. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature. 1990; 343(6257):425–430. [PubMed: 1967820]
4. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005; 45:89–118. [PubMed: 15822172]
5. Liao JK. Isoprenoids as mediators of the biological effects of statins. J Clin Invest. 2002; 110(3): 285–288. [PubMed: 12163444]
6. Wachtershauser A, Akoglu B, Stein J. HMG-CoA reductase inhibitor mevastatin enhances the growth inhibitory effect of butyrate in the colorectal carcinoma cell line Caco-2. Carcinogenesis. 2001; 22(7):1061–1067. [PubMed: 11408350]
7. Agarwal B, Halmos B, Feoktistov AS, et al. Mechanism of lovastatin-induced apoptosis in intestinal epithelial cells. Carcinogenesis. 2002; 23(3):521–528. [PubMed: 11895868]
8. Spampanato C, De MS, Sarnataro M, et al. Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of Bax and down-regulation of BCL-2 gene expression. Int J Oncol. 2012; 40(4):935–941. [PubMed: 22134829]
9. Cho SJ, Kim JS, Kim JM, Lee JY, Jung HC, Song IS. Simvastatin induces apoptosis in human colon cancer cells and in tumor xenografts, and attenuates colitis-associated colon cancer in mice. Int J Cancer. 2008; 123(4):951–957. [PubMed: 18521906]
10. Cauley JA, McTiernan A, Rodabough RJ, et al. Statin use and breast cancer: prospective results from the women's health initiative. J Natl Cancer Inst. 2006; 98(10):700–707. [PubMed: 16705124]
11. Pocobelli G, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Hampton JM, Egan KM. Statin use and risk of breast cancer. Cancer. 2008; 112(1):27–33. [PubMed: 18008366]
12. Haukka J, Sankila R, Klaukka T, et al. Incidence of cancer and statin usage—record linkage study. Int J Cancer. 2010; 126(1):279–284. [PubMed: 19739258]
13. Desai P, Chlebowski R, Cauley JA, et al. Prospective analysis of association between statin use and breast cancer risk in the women's health initiative. Cancer Epidemiol Biomarkers Prev. 2013; 22(10):1868–1876. [PubMed: 23975947]
14. Kumar AS, Benz CC, Shim V, Minami CA, Moore DH, Esserman LJ. Estrogen receptor-negative breast cancer is less likely to arise among lipophilic statin users. Cancer Epidemiol Biomark Prev. 2008; 17(5):1028–1033.
15. Chae YK, Valsecchi ME, Kim J, et al. Reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs, and/or statins. Cancer Invest. 2011; 29(9):585–593. [PubMed: 21936625]
16. Kwan ML, Habel LA, Flick ED, Quesenberry CP, Caan B. Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. Breast Cancer Res Treat. 2008; 109(3):573–579. [PubMed: 17674197]
17. Ahern TP, Pedersen L, Tarp M, et al. Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. J Natl Cancer Inst. 2011; 103(19):1461–1468. [PubMed: 21813413]
18. Nickels S, Vrieling A, Seibold P, et al. Mortality and recurrence risk in relation to the use of lipid-lowering drugs in a prospective breast cancer patient cohort. PLoS ONE. 2013; 8(9):e75088. [PubMed: 24086446]
19. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. 2012; 367(19):1792–1802. [PubMed: 23134381]
20. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998; 19(1):61–109. [PubMed: 9492970]
21. Anderson GL, Manson J, Wallace R, et al. Implementation of the women's health initiative study design. Ann Epidemiol. 2003; 13(9 Suppl):S5–S17. [PubMed: 14575938]

22. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA. 2002; 288(3):321–333. [PubMed: 12117397]
23. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005; 19(1):117–125. [PubMed: 15660968]
24. Fong CW. Statins in therapy: understanding their hydrophilicity, lipophilicity, binding to 3-hydroxy-3-methylglutaryl-CoA reductase, ability to cross the blood brain barrier and metabolic stability based on electrostatic molecular orbital studies. Eur J Med Chem. 2014; 85:661–674. [PubMed: 25128668]
25. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the women's health initiative. Ann Epidemiol. 2003; 13(9 Suppl):S122–S128. [PubMed: 14575944]
26. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999; 94(446):496–509.
27. Holstein SA, Wohlford-Lenane CL, Hohl RJ. Isoprenoids influence expression of Ras and Ras-related proteins. Biochemistry. 2002; 41(46):13698–13704. [PubMed: 12427032]
28. Duncan RE, El-Sohemy A, Archer MC. Statins and cancer development. Cancer Epidemiol Biomarkers Prev. 2005; 14(8):1897–1898. [PubMed: 16103434]
29. Seasholtz TM, Majumdar M, Brown JH. Rho as a mediator of G protein-coupled receptor signaling. Mol Pharmacol. 1999; 55(6):949–956. [PubMed: 10347235]
30. Denoyelle C, Vasse M, Korner M, et al. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. Carcinogenesis. 2001; 22(8):1139–1148. [PubMed: 11470741]
31. Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut. 2010; 59(11): 1572–1585. [PubMed: 20660702]
32. Asakage M, Tsuno NH, Kitayama J, et al. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (pravastatin) inhibits endothelial cell proliferation dependent on G1 cell cycle arrest. Anticancer Drugs. 2004; 15(6):625–632. [PubMed: 15205608]
33. Keyomarsi K, Sandoval L, Band V, Pardee AB. Synchronization of tumor and normal cells from G1 to multiple cell cycles by lovastatin. Cancer Res. 1991; 51(13):3602–3609. [PubMed: 1711413]
34. Alonso DF, Farina HG, Skilton G, Gabri MR, De Lorenzo MS, Gomez DE. Reduction of mouse mammary tumor formation and metastasis by lovastatin, an inhibitor of the mevalonate pathway of cholesterol synthesis. Breast Cancer Res Treat. 1998; 50(1):83–93. [PubMed: 9802623]
35. Farina HG, Bublik DR, Alonso DF, Gomez DE. Lovastatin alters cytoskeleton organization and inhibits experimental metastasis of mammary carcinoma cells. Clin Exp Metastasis. 2002; 19(6): 551–559. [PubMed: 12405293]
36. Cauley JA, Zmuda JM, Lui LY, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt). 2003; 12(8):749–756. [PubMed: 14588125]
37. Boudreau DM, Gardner JS, Malone KE, Heckbert SR, Blough DK, Daling JR. The association between 3-hydroxy-3-methylglutaryl coenzyme A inhibitor use and breast carcinoma risk among postmenopausal women: a case-control study. Cancer. 2004; 100(11):2308–2316. [PubMed: 15160333]
38. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J Clin Oncol. 2005; 23(34): 8606–8612. [PubMed: 16260694]

Table 1

Demographics and clinical characteristics by baseline statin use in the Women's Health Initiative

Variables	Level	No baseline statin use (*n* = 118,201)	Baseline statin use (*n* = 10,474)
Trial membership	OS	68,294 (58 %)	6,500 (62 %)
	E-alone	4,631 (4 %)	516 (5 %)
	E + P trial	7,915 (7 %)	753 (7 %)
	DM	32,122 (27 %)	2,334 (22 %)
	E-alone/E + P trial + DM	5,239 (4 %)	371 (4 %)
Age group at screening	<50–59	39,446 (33 %)	1,865 (18 %)
	60–69	52,942 (45 %)	5,469 (52 %)
	70–79+	25,813 (22 %)	3,140 (30 %)
Age stratum at randomization or enrollment	50–54	15,967 (14 %)	565 (5 %)
	55–59	23,482 (20 %)	1,301 (12 %)
	60–69	52,936 (45 %)	5,466 (52 %)
	70–79	25,816 (22 %)	3,142 (30 %)
Ethnicity	Missing	286 (<1 %)	29 (<1 %)
	American Indian or Alaskan Native	449 (<1 %)	33 (<1 %)
	Asian or Pacific Islander	3,068 (3 %)	424 (4 %)
	Black or African–American	9,457 (8 %)	875 (8 %)
	Hispanic/Latino	3,461 (3 %)	274 (3 %)
	White (not of Hispanic origin)	100,194 (85 %)	8,719 (83 %)
	Other	1,286 (1 %)	120 (1 %)
Education	Missing	672 (1 %)	58 (1 %)
	None to some HS	4,733 (4 %)	608 (6 %)
	HS diploma/GED	19,365 (16 %)	2,199 (21 %)
	Vocational, training school, some college or associate degree	44,119 (37 %)	4,046 (39 %)
	College graduate or more	49,312 (42 %)	3,563 (34 %)
Smoking	Missing	1,411 (1 %)	134 (1 %)
	Never smoked	59,923 (51 %)	5,078 (48 %)
	Past smoker	49,887 (42 %)	4,670 (45 %)
	Current smoker	6,980 (6 %)	592 (6 %)
Alcohol use	Missing	779 (1 %)	63 (1 %)
	Nondrinker or past drinker	32,614 (28 %)	3,511 (34 %)
	<1 drink/month to<7 drinks per week	70,410 (60 %)	5,897 (56 %)
	7+ drinks a week	14,398 (12 %)	1,003 (10 %)
Physical activity	Missing	5,668 (5 %)	259 (2 %)
	None	16,676 (14 %)	1,454 (14 %)
	>0–3.75 MET-h/week	15,803 (13 %)	1,557 (15 %)
	3.75–8.75 MET-h/week	23,071 (20 %)	2,252 (22 %)
	8.75–17.5 MET-h/week	26,238 (22 %)	2,417 (23 %)

Variables	Level	No baseline statin use (*n* = 118,201)	Baseline statin use (*n* = 10,474)
	≥17.5 MET-h/week	30,745 (26 %)	2,535 (24 %)
% Calories from fat	Missing	204 (<1 %)	15 (<1 %)
	<30 % calories from fat	42,688 (36 %)	4,634 (44 %)
	≥30 % calories from fat	75,309 (64 %)	5,825 (56 %)
BMI	Missing	1,003 (1 %)	87 (1 %)
	<25	43,150 (37 %)	2,614 (25 %)
	25–29	40,598 (34 %)	4,160 (40 %)
	≥30	33,450 (28 %)	3,613 (34 %)
Waist circumference	Missing	548 (<1 %)	52 (<1 %)
	≤88 cm	71,447 (60 %)	5,108 (49 %)
	>88 cm	46,206 (39 %)	5,314 (51 %)
Mammogram within 2 years of screening	Yes	107,682 (91 %)	9,754 (93 %)
	No	10,519 (9 %)	720 (7 %)
Gail risk of breast cancer	<1.67 %	68,434 (58 %)	5,429 (52 %)
	≤1.67 %	49,767 (42 %)	5,045 (48 %)
Female relative had breast cancer?	Missing	6,167 (5 %)	585 (6 %)
	No	90,935 (77 %)	8,005 (76 %)
	Yes	21,099 (18 %)	1,884 (18 %)
Age at menarche	Missing	409 (<1 %)	33 (<1 %)
	≤11	25,813 (22 %)	2,341 (22 %)
	12–13	65,509 (55 %)	5,768 (55 %)
	14+	26,470 (22 %)	2,332 (22 %)
Ever been pregnant?	Missing	276 (<1 %)	25 (<1 %)
	No	10,729 (9 %)	983 (9 %)
	Yes	107,196 (91 %)	9,466 (90 %)
Age at end of first full-term (at least 6 months) pregnancy	Missing	10,687 (9 %)	1,080 (10 %)
	Never pregnant	10,729 (9 %)	983 (9 %)
	Never had a term pregnancy	2,963 (3 %)	247 (2 %)
	<20	13,791 (12 %)	1,261 (12 %)
	20–29	71,220 (60 %)	6,146 (59 %)
	30+	8,811 (7 %)	757 (7 %)
Number of live births	Missing	691 (1 %)	61 (1 %)
	Never pregnant	10,729 (9 %)	983 (9 %)
	None	3,138 (3 %)	260 (2 %)
	1–2	41,301 (35 %)	3,481 (33 %)
	3+	62,342 (53 %)	5,689 (54 %)
Breast biopsy	Missing	6,363 (5 %)	322 (3 %)
	None	86,508 (73 %)	7,737 (74 %)
	1	17,711 (15 %)	1,648 (16 %)
	2+	7,619 (6 %)	767 (7 %)

Variables	Level	No baseline statin use (*n* = 118,201)	Baseline statin use (*n* = 10,474)
Hysterectomy ever	Missing	63 (<1 %)	9 (<1 %)
	No	68,623 (58 %)	5,706 (54 %)
	Yes	49,515 (42 %)	4,759 (45 %)
Bilateral oophorectomy	Missing	2,492 (2 %)	273 (3 %)
	No	92,207 (78 %)	7,908 (76 %)
	Yes	23,502 (20 %)	2,293 (22 %)
Hormone use	Missing	98 (<1 %)	13 (<1 %)
	Never	46,433 (39 %)	4,591 (44 %)
	Past user	17,773 (15 %)	1,797 (17 %)
	Current user <5 years	15,067 (13 %)	1,122 (11 %)
	Current user 5–<10 years	13,424 (11 %)	915 (9 %)
	Current user ≥10 years	25,406 (21 %)	2,036 (19 %)
Current estrogen/progesterone use	Missing	98 (<1 %)	13 (<1 %)
	Never used either E-alone or E + P	46,433 (39 %)	4,591 (44 %)
	Past user of either E-alone or E + P	17,773 (15 %)	1,797 (17 %)
	Current user E-alone	29,911 (25 %)	2,522 (24 %)
	Current user E + P	23,986 (20 %)	1,551 (15 %)
Oral contraceptive use ever	Missing	2 (<1 %)	0 (<1 %)
	No	67,591 (57 %)	6,910 (66 %)
	Yes	50,608 (43 %)	3,564 (34 %)
Aspirin use	No	95,405 (81 %)	6,862 (66 %)
	Yes	22,796 (19 %)	3,612 (34 %)
NSAID use	No	80,283 (68 %)	5,757 (55 %)
	Yes	37,918 (32 %)	4,717 (45 %)
In general, would you say your health is…	Missing	639 (1 %)	65 (1 %)
	Excellent	21,413 (18 %)	817 (8 %)
	Very good	50,174 (42 %)	3,634 (35 %)
	Good	36,968 (31 %)	4,530 (43 %)
	Fair/poor	9,007 (8 %)	1,428 (14 %)
Diabetes ever	Missing	79 (<1 %)	11 (<1 %)
	No	111,944 (95 %)	9,266 (88 %)
	Yes	6,178 (5 %)	1,197 (11 %)
High cholesterol requiring pills ever	Missing	7,033 (6 %)	294 (3 %)
	No	103,091 (87 %)	348 (3 %)
	Yes	8,077 (7 %)	9,832 (94 %)
MI ever	Missing	54 (<1 %)	10 (<1 %)
	No	116,211 (98 %)	9,571 (91 %)
	Yes	1,936 (2 %)	893 (9 %)
Angina ever	Missing	732 (1 %)	80 (1 %)
	No	112,050 (95 %)	8,697 (83 %)

Variables	Level	No baseline statin use (*n* = 118,201)	Baseline statin use (*n* = 10,474)
	Yes	5,419 (5 %)	1,697 (16 %)

Table 2

Characteristics of statin use

Characteristics	*n* (%)
Baseline statin use	
No	118,201 (92 %)
Yes	10,474 (8 %)
Baseline statin duration[a]	
<1 year	3,432 (33 %)
1–3 years	3,565 (34 %)
3+ years	3,477 (33 %)
Baseline statin name[a]	
Atorvastatin calcium	797 (8 %)
Fluvastatin sodium	1,282 (12 %)
Lovastatin	2,846 (27 %)
Pravastatin sodium	2,377 (23 %)
Simvastatin	3,172 (30 %)
Baseline statin type[a]	
Lipophilic	7,300 (70 %)
Hydrophilic	3,174 (30 %)

[a]Among those who reported baseline statin use

Table 3

Associations of statin use with late-stage breast cancer

Comparison	Model type	HR	95 % CI	*p* value
Baseline statin: yes versus no	Univariable	0.87	(0.71, 1.06)	0.163
	Multivariable[a]	0.93	(0.76, 1.14)	0.494
Baseline statin: by type[b]	Univariable			
Lipophilic versus none		0.85	(0.68, 1.07)	0.158
Hydrophilic versus none		0.93	(0.63, 1.37)	0.722
Lipophilic versus hydrophilic	Multivariable	0.91	(0.59, 1.42)	0.686
Lipophilic versus none		0.92	(0.73, 1.16)	0.486
Hydrophilic versus none		0.97	(0.64, 1.45)	0.868
Lipophilic versus hydrophilic		0.95	(0.50, 1.51)	0.841
Statin use over time: yes versus no	Univariable	0.83	(0.69, 0.99)	0.037
	Multivariable[a]	0.84	(0.70, 1.02)	0.082
Statin use over time: by type[b]	Univariable			
Lipophilic versus none		0.80	(0.65, 0.97)	0.022
Hydrophilic versus none		0.96	(0.65, 1.43)	0.845
Unclassified versus none		1.48	(0.61, 3.57)	0.381
Lipophilic versus hydrophilic	Multivariable[a]	0.83	(0.54, 1.28)	0.390
Lipophilic versus none		0.80	(0.64, 0.98)	0.035
Hydrophilic versus none		1.06	(0.70, 1.59)	0.784
Unclassified versus none		1.57	(0.65, 3.78)	0.320
Lipophilic versus hydrophilic		0.75	(0.48, 1.17)	0.210

[a]Adjusted for race (American Indian or Alaskan Native; Asian or Pacific Islander; Black or African–American; Hispanic/Latino; White), education (none to some HS; HS diploma/GED; vocational, training school, some college or associate degree; college degree or more), smoking (never smoked; past smoker; current smoker), BMI (<25; 25–29; ≥30), waist circumference (≤88 cm;>88 cm), mammogram in the past 2 years (no; yes), Gail 5-year risk (<1.67 %; ≥1.67 %), female relative with breast cancer(no; yes), age at menarche (≤11, 12–13; 14+), number of live births (never pregnant; none; 1–2; 3+), breast biopsy (no; yes), hysterectomy (no; yes), hormone use (never; past user; current user <5 years; current user 5 to <10 years; current user ≥10 years), oral contraceptive (no; yes), aspirin use (no; yes) and study component (observational study; estrogen alone clinical trial, estrogen + progesterone clinical trial; dietary modification clinical trial; estrogen/estrogen + progesterone and dietary modification clinical trial)

[b]Lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin), hydrophilic (pravastatin)

Table 4

Associations of statins use with late-stage breast cancer by ER status

ER status	Comparison	Model type	HR	95 % CI	*p* value
ER positive	Baseline statin: yes versus no	Univariable	0.80	(0.63, 1.01)	0.062
		Multivariable[a]	0.85	(0.67, 1.08)	0.191
	Baseline statin: by type[b]	Univariable			
	Lipophilic versus none		0.79	(0.60, 1.03)	0.080
	Hydrophilic versus none		0.85	(0.53, 1.35)	0.484
	Lipophilic versus hydrophilic	Multivariable	0.93	(0.55, 1.58)	0.783
	Lipophilic versus none		0.85	(0.65, 1.12)	0.244
	Hydrophilic versus none		0.85	(0.52, 1.40)	0.521
	Lipophilic versus hydrophilic		1.00	(0.57, 1.74)	0.998
	Statin use over time: yes versus no	Univariable	0.78	(0.63, 0.96)	0.018
		Multivariable	0.79	(0.63, 0.99)	0.044
	Statin use over time: by type[b]	Univariable			
	Lipophilic versus none		0.73	(0.58, 0.92)	0.009
	Hydrophilic versus none		0.87	(0.54, 1.41)	0.549
	Lipophilic versus hydrophilic	Multivariable[a]	0.84	(0.50, 1.42)	0.511
	Lipophilic versus none		0.72	(0.56, 0.93)	0.012
	Hydrophilic versus none		1.01	(0.62, 1.63)	0.978
	Lipophilic versus hydrophilic		0.72	(0.42, 1.22)	0.218
ER negative/borderline	Baseline statin: yes versus no	Univariable	1.15	(0.74, 1.78)	0.536
		Multivariable[a]	1.29	(0.82, 2.02)	0.266
	Baseline statin: by type[b]	Univariable			
	Lipophilic versus none		1.08	(0.65, 1.80)	0.763
	Hydrophilic versus none		1.38	(0.61, 3.11)	0.436
	Lipophilic versus hydrophilic	Multivariable	0.78	(0.31, 2.00)	0.609
	Lipophilic versus none		1.21	(0.72, 2.03)	0.468
	Hydrophilic versus none		1.56	(0.69, 3.53)	0.287
	Lipophilic versus hydrophilic		0.78	(0.30, 1.99)	0.598

ER status	Comparison	Model type	HR	95 % CI	*p* value
	Statin use over time: yes versus no	Univariable	0.98	(0.65, 1.48)	0.911
		Multivariable	0.96	(0.61, 1.51)	0.848
	Statin use over time: by type[b]	Univariable			
	Lipophilic versus none		0.96	(0.61, 1.52)	0.870
	Hydrophilic versus none		1.46	(0.64, 3.30)	0.366
	Lipophilic versus hydrophilic	Multivariable[a]	0.66	(0.27, 1.63)	0.368
	Lipophilic versus none		0.96	(0.59, 1.58)	0.877
	Hydrophilic versus none		1.39	(0.56, 3.40)	0.478
	Lipophilic versus hydrophilic		0.69	(0.26, 1.86)	0.469

[a]Adjusted for race (American Indian or Alaskan Native; Asian or Pacific Islander; Black or African–American; Hispanic/Latino; White), education (none to some HS; HS diploma/GED; vocational, training school, some college or associate degree; college degree or more), smoking (never smoked; past smoker; current smoker), BMI (<25; 25–29; ≥30), waist circumference (≤88 cm;>88 cm), mammogram in the past 2 years (no; yes), Gail 5-year risk (<1.67 %; ≥1.67 %), female relative with breast cancer(no; yes), age at menarche (≤11, 12–13; 14+), number of live births (never pregnant; none; 1–2; 3+), breast biopsy (no; yes), hysterectomy (no; yes), hormone use (never; past user; current user <5 years; current user 5 to <10 years; current user ≥10 years), oral contraceptive (no; yes), aspirin use (no; yes) and study component (observational study; estrogen alone clinical trial, estrogen + progesterone clinical trial; dietary modification clinical trial; estrogen/estrogen + progesterone and dietary modification clinical trial)

[b]Lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin), hydrophilic (pravastatin)

Table 5

Associations of statin use with breast cancer mortality

Comparison	Model type	HR	95 % CI	*p* value
Baseline statin: yes versus no	Univariable	0.85	(0.56, 1.25)	0.435
	Multivariable[a]	0.91	(0.60, 1.37)	0.648
Baseline statin: by type[b]	Univariable			
Lipophilic versus none		0.72	(0.44, 1.17)	0.188
Hydrophilic versus none		1.31	(0.68, 2.54)	0.425
Lipophilic versus hydrophilic	Multivariable[a]	0.55	(0.25, 1.23)	0.147
Lipophilic versus none		0.75	(0.45, 1.25)	0.269
Hydrophilic versus none		1.49	(0.77, 2.90)	0.241
Lipophilic versus hydrophilic		0.50	(0.22, 1.14)	0.100
Statin use over time: yes versus no	Univariable	0.64	(0.38, 1.08)	0.095
	Multivariable[a]	0.59	(0.32, 1.06)	0.075

[a]Adjusted for race (American Indian or Alaskan Native; Asian or Pacific Islander; Black or African–American; Hispanic/Latino; White), education (none to some HS; HS diploma/GED; vocational, training school, some college or associate degree; college degree or more), smoking (never smoked; past smoker; current smoker), BMI (<25; 25–29; ≥30), waist circumference (≤88 cm;>88 cm), mammogram in the past 2 years (no; yes), Gail 5-year risk (<1.67 %; ≥1.67 %), female relative with breast cancer(no; yes), age at menarche (≤11, 12–13; 14+), number of live births (never pregnant; none; 1–2; 3+, breast biopsy (no; yes), hysterectomy (no; yes), hormone use (never; past user; current user <5 years; current user 5 to <10 years; current user ≥10 years), oral contraceptive (no; yes), aspirin use (no; yes) and study component (observational study; estrogen alone clinical trial, estrogen + progesterone clinical trial; dietary modification clinical trial; estrogen/estrogen + progesterone and dietary modification clinical trial)

[b]Lipophilic (lovastatin, simvastatin, fluvastatin, atorvastatin), hydrophilic (pravastatin)