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De novo post-diagnosis statin use, breast cancer-specific and overall mortality in women with stage I–III breast cancer

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Background: Prior evidence suggests a role for statins in the management of cancer. However, the benefit of statin use in the adjuvant setting remains uncertain. This study investigates associations between statin use initiated after a breast cancer diagnosis and mortality.

Methods: Women with stage I–III breast cancer were identified from the National Cancer Registry of Ireland ($N=4243$). Post-diagnostic statin initiators were identified from pharmacy claims data ($N=837$). Multivariate models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between *de novo* statin use and mortality.

Results: The median duration of statin use was 6.7 years. No association was found between post-diagnostic statin use and breast cancer-specific (HR 0.88, 95% CI 0.66, 1.17) or all-cause mortality (HR 1.00, 95% CI 0.82, 1.21).

Conclusions: The results from our study suggest that initiating statin use after a diagnosis of stage I–III breast cancer is not associated with a reduction in breast cancer-specific mortality.

Statins, or 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR) inhibitors, are prescribed for cholesterol reduction and cardiovascular disease prevention (Holmes and Chen, 2012); however, some epidemiological evidence suggests a role in breast cancer management (Kwan *et al*, 2008; Ahern *et al*, 2011; Chae *et al*, 2011; Nielsen *et al*, 2012; Nickels *et al*, 2013; Boudreau *et al*, 2014; Murtola *et al*, 2014; Cardwell *et al*, 2015; Desai *et al*, 2015). Uncertainty over the benefits of statins in the adjuvant breast cancer setting remain, as significant effects may be limited to reductions in locoregional recurrence, rather than distant recurrence (Ahern *et al*, 2011), and to date, no studies of statin use have reported reductions in breast cancer-specific mortality (Nickels *et al*, 2013; Cardwell *et al*, 2015; Desai *et al*, 2015). Previous studies have included women who initiated statin use prior to their breast cancer diagnosis, limiting their

utility in clinical decision making in the adjuvant setting (Ahern *et al*, 2011; Chae *et al*, 2011; Nickels *et al*, 2013; Boudreau *et al*, 2014; Cardwell *et al*, 2015; Desai *et al*, 2015). This study aimed to: (a) measure associations between statin use initiated after a breast cancer diagnosis (*de novo*), and breast cancer-specific and all-cause mortality, and (b) investigate whether these associations are modified by statin solubility or tumour characteristics.

MATERIALS AND METHODS

This study used patient records from the National Cancer Registry Ireland (NCRI), linked to individual-level prescription dispensing data from Ireland's Primary Care Reimbursement Services (PCRS),

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as described previously (Barron *et al*, 2014). The study included women diagnosed with stage I–III invasive breast cancer (ICD-10 C50) between 1 January 2001 and 31 December 2011, aged between 50–80 years at diagnosis, with GMS eligibility from at least 1 year prior to diagnosis and no history of invasive cancer, other than non-melanoma skin cancer. Women receiving statin therapy in the year prior to breast cancer diagnosis were excluded.

De novo post-diagnostic statin exposure was identified from prescriptions dispensed between breast cancer diagnosis and end of follow-up (death or 31 December 2012, whichever occurred first). The number of days' supply on each prescription was extracted and the statin dosing intensity was calculated on the basis of the number of days' statin supply in the prior year (Peterson *et al*, 2007). These exposure histories were used to define the following time varying exposure categories: (i) exposed (yes/no) from the date of their first statin prescription following diagnosis; (ii) within statin users, women were identified as having high-intensity exposure from the date they had received a statin at an intensity of $\geq 80\%$, for at least 1 year (e.g., at least 292 out of 365 days is considered high intensity). Once allocated to an exposure category, women remained in this category to the end of follow-up.

The following data were obtained from the NCRI database: age (years) at diagnosis, smoking status at diagnosis (never, past, current and unspecified), tumour stage (I, IIa, IIb, IIIa and IIIb–c), histologic tumour grade (low, intermediate, high and unspecified), oestrogen (ER), progesterone and human epidermal growth factor-2 (HER2) receptor status (positive, negative and unspecified), and chemotherapy (yes, no) in the year after diagnosis. The PCRS database was used to identify anti-oestrogen therapy in the year after breast cancer diagnosis (yes, no) and potentially confounding medication use in the year prior to diagnosis (exposed, unexposed); aspirin (Holmes *et al*, 2010), anti-diabetics (Holmes *et al*, 2010), non-steroidal anti-inflammatory drugs (Marshall *et al*, 2005) and bisphosphonates (Coleman *et al*, 2013). The number of drug classes (fourth level WHO-ATC classification) dispensed in the year before diagnosis was used as a proxy measure of comorbidity (Schneeweiss *et al*, 2001). Death certificates provided the date and cause of death (all-cause or breast cancer-specific). Breast cancer-specific deaths were identified using SEER definitions (Supplementary Table S1; Howlader *et al*, 2010).

Analyses were performed using SAS v9.3 (SAS Institute Inc, Cary, NC, USA). The proportion of post-diagnostic statin users was tabulated and differences in the rates of statin initiation across covariates were compared using Poisson regression (significance at a two-sided α -level of 0.05). Kaplan–Meier analysis was used to estimate the median duration of statin use from initiation to the last exposure (censored at the date of death or end of follow-up). The overall statin exposure intensity was calculated as the number of days' supply as a proportion of the number of days from initiation to last exposure.

For survival analyses, person time was calculated from the date of breast cancer diagnosis to the end of follow-up. Multivariate Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between post-diagnosis statin use, and breast cancer-specific and all-cause mortality. Statin exposure was lagged by 2 years to reduce the possibility that changes in breast cancer prognosis or treatment (i.e., cancer recurrence or approaching death) influenced statin initiation or continuation (Tevaarwerk *et al*, 2013; Chubak *et al*, 2013).

Subgroup analyses included stratification by: (a) high-/low-exposure intensity as a measure of drug adherence, (b) statin solubility: lipophilic (atorvastatin, fluvastatin and simvastatin), hydrophilic (pravastatin and rosuvastatin), or both, and (c) ER status (positive, negative and unspecified). An interaction term was included in the multivariable model to assess effect modification. In sensitivity analyses, we defined high-intensity statin exposure as

$\geq 80\%$ intensity for longer than two consecutive years, extended the time without pre-diagnostic statin exposure from 1 to 3 years, varied the lag time from 0 to 4 years and stratified lipophilic/hydrophilic statin use by high-/low-exposure intensity.

RESULTS

Cohort and exposure characteristics. For the 4243 eligible women, the median post-diagnostic follow-up was 4.9 years and their characteristics are described in Table 1. A study flow diagram is shown in Supplementary Figure S1. Within this cohort, 837 (19.7%) women initiated statin use after their breast cancer diagnosis. Rates of initiation were significantly higher in women with a history of diabetes, lower tumour stage at diagnosis and positive ER status. The median time from diagnosis to statin initiation was 2.1 years, the median duration of statin use was 6.7 years and the mean on-treatment exposure intensity was 86.3% (Table 2). Person time attributed to *de novo* statin users and non-users was 2426 and 12 369 years, respectively.

***De novo* statin use and mortality.** No significant association was found between *de novo* statin initiation, and breast cancer-specific (HR 0.88, 95% CI 0.66, 1.17) or all-cause mortality (HR 1.00, 95% CI 0.87, 1.18) (Table 2). Subgroup analyses in women taking statins at an intensity of $\geq 80\%$ for longer than 12 consecutive months also yielded null associations with breast cancer-specific mortality (HR 1.04, 95% CI 0.71, 1.51). The median length of time to statin initiation in this high-intensity exposure group was 2.0 years, the median duration of statin use was 8.5 years and the mean on-treatment exposure intensity was 89.2%. Our results were unchanged in sensitivity analyses (Table 3).

We found no statistically significant associations between hydrophilic or lipophilic statin use and breast cancer-specific mortality in subgroup analyses (Table 2). There was no evidence of effect modification by ER status ($P_{\text{interaction}} = 0.69$).

DISCUSSION

This study sought to address the clinically relevant question of whether there is a benefit associated with statin initiation for women following a breast cancer diagnosis. We observed no significant association between *de novo* post-diagnostic statin exposure and breast cancer-specific mortality in a cancer registry-based cohort of 4243 women newly diagnosed with stage I–III breast cancer. Within statin initiators, we observed long treatment durations and high treatment intensity, suggesting that our results are unlikely to be due to inadequate statin exposure. A statistically significant association with reduced all-cause and breast cancer-specific mortality was observed in the low-intensity lipophilic statin subgroup. However, this finding is very unlikely to be causal, as the median duration of exposure in this subgroup was only 6 months and high-intensity lipophilic statin use was not associated with a reduction in breast cancer-specific mortality.

Several studies have examined post-diagnostic statin use in women who initiated statin treatment prior to their breast cancer diagnosis (Ahern *et al*, 2011; Chae *et al*, 2011; Nickels *et al*, 2013; Boudreau *et al*, 2014; Murtola *et al*, 2014; Cardwell *et al*, 2015; Desai *et al*, 2015), with some reporting large reductions in breast cancer recurrence, in particular for lipophilic statin users (Ahern *et al*, 2011; Murtola *et al*, 2014). However, these findings may be at least partly attributable to residual confounding due to statin-prescribing patterns and healthy user effects. There is evidence that statins are preferentially prescribed for, and taken by, patients who make better healthcare choices, engage in healthier behaviours and have superior health outcomes (Evans *et al*, 1995; Haley and Dietsch, 2000;

Table 1. Characteristics of women included in the study cohort, by post-diagnosis statin exposure, with statin initiation rate

| Characteristic | De novo statin use post breast cancer diagnosis ^{a,b} | | | Initiation rate (per 1000 person years), associated P-value |
|--|--|----------------|------|---|
| | Non-user (N = 2759) | User (N = 837) | | |
| Age in years | | | | |
| Median (IQR) | 66 (58, 73) | 65 (58, 72) | | — |
| Comorbidity score^c | | | | |
| Median (IQR) | 6 (3, 11) | 7 (3, 11) | | — |
| Smoking (%) | | | | |
| Current | 583 (21.1) | 171 (20.4) | 41.3 | 0.53 |
| Past | 306 (11.1) | 106 (12.7) | 47.5 | |
| Never | 1324 (48.0) | 422 (50.4) | 43.8 | |
| Unspecified | 546 (19.8) | 138 (16.5) | 38.8 | |
| Aspirin (%)^c | | | | |
| Yes | 432 (15.7) | 153 (18.3) | 49.2 | 0.06 |
| No | 2327 (84.3) | 684 (81.7) | 41.6 | |
| NSAID (%)^c | | | | |
| Yes | 1178 (42.7) | 384 (45.9) | 44.8 | 0.22 |
| No | 1581 (57.3) | 453 (54.1) | 41.2 | |
| Anti-diabetic (%)^{c,d} | | | | |
| Yes | 60 (2.2) | 38 (4.5) | 74.7 | 0.001 |
| No | 2699 (97.8) | 799 (95.5) | 41.9 | |
| Bisphosphonate (%)^c | | | | |
| Yes | 198 (7.2) | 46 (5.5) | 39.4 | 0.40 |
| No | 2561 (92.8) | 791 (94.5) | 43.0 | |
| Tumour stage (%)^{d,e} | | | | |
| I | 917 (33.2) | 297 (35.5) | 44.1 | 0.02 |
| IIa | 843 (30.6) | 297 (35.5) | 47.5 | |
| IIb | 610 (22.1) | 162 (19.4) | 38.0 | |
| IIIa | 166 (6.0) | 40 (4.8) | 39.6 | |
| IIIb–c | 223 (8.1) | 41 (4.9) | 31.7 | |
| Tumour grade (%) | | | | |
| Low | 301 (10.9) | 101 (12.1) | 44.8 | 0.18 |
| Intermediate | 1357 (49.2) | 416 (49.7) | 43.9 | |
| High | 866 (31.4) | 254 (30.4) | 42.4 | |
| Unspecified | 235 (8.5) | 66 (7.9) | 35.8 | |
| ER (%)^d | | | | |
| Negative | 471 (17.1) | 110 (13.1) | 35.3 | 0.01 |
| Positive | 2028 (73.5) | 610 (72.9) | 43.7 | |
| Unspecified | 260 (9.4) | 117 (14.0) | 47.5 | |
| PR (%) | | | | |
| Negative | 717 (26.0) | 179 (21.4) | 39.2 | 0.22 |
| Positive | 1393 (50.5) | 415 (49.6) | 44.7 | |
| Unspecified | 649 (23.5) | 243 (29.0) | 42.7 | |
| HER2 (%) | | | | |
| Negative | 1679 (60.9) | 419 (50.1) | 40.8 | 0.06 |
| Positive | 339 (12.3) | 99 (11.8) | 44.7 | |
| Unspecified | 741 (26.9) | 319 (38.1) | 45.1 | |
| Chemotherapy (%)^f | | | | |
| Yes | 1123 (40.7) | 344 (41.1) | 43.2 | 0.78 |
| No | 1636 (59.3) | 493 (58.9) | 42.5 | |
| Anti-oestrogen (%)^f | | | | |
| Yes | 2065 (74.9) | 642 (76.7) | 43.8 | 0.25 |
| No | 694 (25.1) | 195 (23.3) | 39.9 | |

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; NSAID = non-steroidal anti-inflammatory drug; PR = progesterone receptor.

^aNo statin use in the year prior to diagnosis and at least one statin prescription received between diagnosis and the end of follow-up, 31 December 2011.

^bPatients identified as statin users/non-users after lagging exposure by 2 years.

^cIn the year prior to breast cancer diagnosis.

^dDifference in statin initiation rate $P < 0.05$ (Poisson regression).

^eAJCC Cancer Staging Manual 6th Edition. Springer, 2002.

^fIn the year post breast cancer diagnosis.

Table 2. Univariate and multivariate hazard ratios for association between de novo post-diagnostic statin use and mortality

| De novo post-diagnostic definitions | N | Years to treatment initiation (median) | Years on treatment (median) | On-treatment exposure intensity (mean %) | Follow-up (person years) | All-cause mortality | | | Breast cancer-specific mortality | | | |
|--|------|--|-----------------------------|--|--------------------------|----------------------------|------------------------|---------------------------------------|----------------------------------|------------------------|---------------------------------------|--|
| | | | | | | Deaths (rate) ^a | Univariate HR (95% CI) | Multivariate HR (95% CI) ^b | Deaths (rate) ^a | Univariate HR (95% CI) | Multivariate HR (95% CI) ^b | |
| Statin exposure – yes/no^c | | | | | | | | | | | | |
| Non-user | 2759 | — | — | — | 12 369 | 692 (55.9) | Ref | Ref | 398 (32.2) | Ref | Ref | |
| Statin user | 837 | 2.1 | 6.7 | 86.3 | 2426 | 128 (52.8) | 0.93 (0.77, 1.14) | 1.00 (0.82, 1.21) | 56 (23.1) | 0.79 (0.59, 1.06) | 0.88 (0.66, 1.17) | |
| Dosing intensity^c | | | | | | | | | | | | |
| Non-user | 2759 | — | — | — | 12 369 | 692 (55.9) | Ref | Ref | 398 (32.2) | Ref | Ref | |
| Statin user – low intensity | 346 | 2.4 | 0.7 | 82.1 | 1165 | 54 (46.4) | 0.82 (0.62, 1.08) | 0.88 (0.67, 1.17) | 24 (20.6) | 0.68 (0.45, 1.02) | 0.76 (0.50, 1.15) | |
| Statin user – high intensity ^d | 491 | 2.0 | 8.5 | 89.2 | 1261 | 74 (58.7) | 1.05 (0.82, 1.35) | 1.11 (0.86, 1.43) | 32 (25.4) | 0.92 (0.63, 1.34) | 1.03 (0.71, 1.50) | |
| Hydro/lipophilic^c | | | | | | | | | | | | |
| Non-user | 2759 | — | — | — | 12 369 | 692 (55.9) | Ref | Ref | 398 (32.1) | Ref | Ref | |
| Hydrophilic statin user | 221 | 1.8 | 5.0 | 88.9 | 610 | 41 (67.2) | 1.18 (0.68, 1.63) | 1.43 (1.04, 1.97) ^f | 21 (34.4) | 1.16 (0.74, 1.81) | 1.35 (0.86, 2.11) | |
| Lipophilic statin user | 509 | 2.2 | 5.8 | 88.2 | 1579 | 74 (46.9) | 0.83 (0.65, 1.06) | 0.83 (0.65, 1.06) | 31 (19.6) | 0.67 (0.46, 0.97) | 0.72 (0.49, 1.04) | |
| Both | 107 | 2.3 | 7.9 | 71.6 | 236 | 13 (55.0) | 0.98 (0.56, 1.70) | 1.21 (0.69, 2.11) | 4 (16.9) | 0.62 (0.23, 1.66) | 0.77 (0.28, 2.08) | |
| Hydro/lipophilic – dosing intensity^{c,e} | | | | | | | | | | | | |
| Non-user | 2759 | — | — | — | 12 369 | 692 (55.9) | Ref | Ref | 398 (32.1) | Ref | Ref | |
| Hydrophilic statin user | 103 | 1.8 | 0.7 | 85.5 | 290 | 22 (75.9) | 1.33 (0.87, 2.03) | 1.60 (1.05, 2.46) ^f | 13 (44.8) | 1.44 (0.83, 2.51) | 1.68 (0.96, 2.94) | |
| Low intensity | 118 | 1.8 | 8.5 | 91.9 | 320 | 19 (59.3) | 1.03 (0.65, 1.61) | 1.23 (0.78, 1.92) | 8 (25.0) | 0.92 (0.47, 1.80) | 1.07 (0.55, 2.10) | |
| Lipophilic statin user | 217 | 2.4 | 0.5 | 85.2 | 805 | 28 (34.8) | 0.62 (0.42, 0.90) | 0.63 (0.43, 0.92) ^f | 9 (11.2) | 0.37 (0.19, 0.72) | 0.39 (0.20, 0.76) ^f | |
| Low intensity | 292 | 2.1 | 8.9 | 90.4 | 774 | 46 (59.4) | 1.07 (0.80, 1.44) | 1.06 (0.79, 1.44) | 22 (28.4) | 0.95 (0.61, 1.48) | 1.05 (0.67, 1.63) | |
| High intensity ^d | 107 | 2.3 | 7.9 | 71.6 | 236 | 13 (55.0) | 0.96 (0.48, 1.93) | 1.23 (0.61, 2.48) | 4 (16.9) | 0.72 (0.23, 2.26) | 0.91 (0.29, 2.86) | |

Abbreviations: CI = confidence interval; HR = hazard ratio; Ref = referent group.

^aDeaths per 1000 person years.

^bAdjusted for age at diagnosis (years); smoking status (never, past, current and unspecified); comorbidity score, tumour grade (I, IIa, IIb, IIIa and IIIb–c); tumour stage (I, IIa, IIb, IIIa and IIIb–c); tumour grade (low, intermediate, high and unspecified); ER, PR and HER2 receptor status (positive, negative and unspecified); chemotherapy in year post diagnosis (yes, no); anti-oestrogen therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID and anti-diabetic medication use (yes, no).

^cStatin exposure lagged by 2 years in analysis.

^dStatin dosing intensity of $\geq 80\%$ for ≥ 12 consecutive months defined as high dosing intensity. All other statin exposures defined as low-dosing intensity.

^eAnalysis conducted post hoc.

^fP-value < 0.05.

Table 3. Sensitivity analyses – univariate and multivariate hazard ratios for association between de novo post-diagnostic statin use and mortality

| De novo post-diagnostic statin exposure definitions | N | Years to treatment initiation (median) | Years on treatment (median) | On-treatment exposure intensity (mean %) | Follow-up (person years) | All-cause mortality | | | Breast cancer-specific mortality | | | |
|--|------|--|-----------------------------|--|--------------------------|----------------------------|------------------------|---------------------------------------|----------------------------------|------------------------|---------------------------------------|-------------------|
| | | | | | | Deaths (rate) ^a | Univariate HR (95% CI) | Multivariate HR (95% CI) ^b | Deaths (rate) ^a | Univariate HR (95% CI) | Multivariate HR (95% CI) ^b | |
| Sensitivity analysis: yes/no exposure lagged by 0, 1, 3 and 4 years | | | | | | | | | | | | |
| Statin exposure – yes/no (lag 0 years) | | | | | | | | | | | | |
| Non-user | 3038 | — | — | — | 18 339 | 909 (49.6) | Ref | Ref | 562 (30.7) | Ref | Ref | Ref |
| Statin user | 1205 | 2.5 | 5.7 | 85.6 | 4496 | 230 (51.5) | 0.94 (0.81, 1.09) | 1.01 (0.87, 1.18) | 107 (23.9) | 0.78 (0.63, 0.97) | 0.86 (0.69, 1.07) | 0.86 (0.69, 1.07) |
| Statin exposure – yes/no (lag 1 year) | | | | | | | | | | | | |
| Non-user | 3058 | — | — | — | 15 291 | 804 (52.6) | Ref | Ref | 482 (31.5) | Ref | Ref | Ref |
| Statin user | 1033 | 2.3 | 6.7 | 86.0 | 3354 | 183 (54.6) | 0.99 (0.84, 1.17) | 1.06 (0.89, 1.25) | 85 (25.3) | 0.85 (0.67, 1.08) | 0.94 (0.74, 1.19) | 0.94 (0.74, 1.19) |
| Statin exposure – yes/no (lag 3 years) | | | | | | | | | | | | |
| Non-user | 2425 | — | — | — | 9776 | 564 (57.7) | Ref | Ref | 308 (31.5) | Ref | Ref | Ref |
| Statin user | 640 | 1.9 | 6.1 | 85.9 | 1686 | 93 (55.2) | 0.99 (0.79, 1.25) | 1.06 (0.84, 1.33) | 40 (23.7) | 0.87 (0.62, 1.22) | 0.96 (0.68, 1.34) | 0.96 (0.68, 1.34) |
| Statin exposure – yes/no (lag 4 years) | | | | | | | | | | | | |
| Non-user | 2046 | — | — | — | 7540 | 427 (56.6) | Ref | Ref | 221 (29.3) | Ref | Ref | Ref |
| Statin user | 492 | 1.7 | 6.1 | 85.7 | 1117 | 59 (52.8) | 0.96 (0.73, 1.27) | 0.99 (0.74, 1.31) | 25 (22.4) | 0.88 (0.57, 1.35) | 0.95 (0.62, 1.46) | 0.95 (0.62, 1.46) |
| Sensitivity analysis: high-intensity exposure ≥ 80% for ≥ 24 consecutive months^c | | | | | | | | | | | | |
| Non-user | 2759 | — | — | — | 12 369 | 692 (55.9) | Ref | Ref | 398 (32.2) | Ref | Ref | Ref |
| Statin user – low intensity | 480 | 2.5 | 1.6 | 82.8 | 1613 | 83 (51.5) | 0.91 (0.72, 1.14) | 0.96 (0.76, 1.21) | 37 (22.9) | 0.76 (0.54, 1.06) | 0.84 (0.60, 1.18) | 0.84 (0.60, 1.18) |
| Statin user – high intensity | 357 | 1.8 | 8.5 | 91.0 | 813 | 45 (55.3) | 1.00 (0.73, 1.36) | 1.07 (0.78, 1.47) | 19 (23.4) | 0.88 (0.55, 1.42) | 1.02 (0.63, 1.65) | 1.02 (0.63, 1.65) |
| Sensitivity analysis: no statin exposure in 3 years prior to diagnosis | | | | | | | | | | | | |
| Statin exposure – yes/no^c | | | | | | | | | | | | |
| Non-user | 2670 | — | — | — | 12 096 | 677 (56.0) | Ref | Ref | 392 (32.4) | Ref | Ref | Ref |
| Statin user | 796 | 2.2 | 6.7 | 86.1 | 2307 | 124 (53.8) | 0.96 (0.78, 1.17) | 1.03 (0.84, 1.25) | 55 (23.8) | 0.82 (0.61, 1.10) | 0.90 (0.67, 1.21) | 0.90 (0.67, 1.21) |

^aAbbreviations: CI = confidence interval; HR = hazard ratio; Ref = referent group.

^bDeaths per 1000 person years.

^cAdjusted for age at diagnosis (years); smoking status (never, past, current and unspecified); comorbidity score, tumour stage (I, IIa, IIb, IIIa and IIIb-c); tumour grade (low, intermediate, high and unspecified); ER, PR and HER2 receptor status (positive, negative and unspecified); chemotherapy in year post diagnosis (yes, no); anti-oestrogen therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID and anti-diabetic medication use (yes, no).

^dStatin exposure lagged by 2 years in analysis.

Brookhart *et al*, 2007; Dormuth *et al*, 2009) and have a better breast cancer prognosis (Snyder *et al*, 2009a, b). If unaccounted for in analyses, this residual confounding can lead to an overestimation of any beneficial effect of statins (Glynn *et al*, 2001, 2006). Moreover, these studies included women who initiated statin use prior to their breast cancer diagnosis, limiting the relevance of their findings to clinical decision making in the adjuvant setting.

Although our study is larger and more methodologically robust, our results are consistent with those from the small number of studies that have specifically examined *de novo* post-diagnostic statin use and breast cancer-specific mortality (Kwan *et al*, 2008; Cardwell *et al*, 2015). In these studies, statin use initiated after diagnosis was not associated with an improvement in breast cancer outcomes. In a study by Murtola *et al* (Murtola *et al*, 2014) investigating statin use and breast cancer survival, a sensitivity analysis was carried out that limited their analysis to *de novo* statin users. A large reduction in breast cancer mortality was observed (HR 0.31, 95% CI 0.22, 0.44), however, this association lacked a clear dose response. In addition, this study did not employ a lagged statin exposure, thereby, increasing the risk of reverse causation bias (Chubak *et al*, 2013). Although we observed no overall association between *de novo* statin use and breast cancer-specific mortality in an unselected population, experimental studies suggest there may be specific subgroups of patients for whom statin treatment could be beneficial (Garwood *et al*, 2010; Bjarnadottir *et al*, 2013, 2015). In a study by Bjarnadottir *et al* (Bjarnadottir *et al*, 2013, 2015), in which women received atorvastatin (80 mg per day) for 2 weeks between diagnosis and surgical resection of their breast tumour, statin treatment was associated with a statistically significant reduction in Ki67 proliferation index among women with tumours expressing HMGCR. It would be worthwhile to evaluate tumour expression of HMGCR as a predictor of response to statin treatment in future studies.

Study strengths include the use of prospectively collected outcome and statin exposure data, whereas limitations include the potential for (a) residual confounding owing to a lack of information on lifestyle factors that could influence disease progression (i.e., obesity) and (b) misclassification bias owing to non-adherence (although the risk is small, as women are unlikely to continue filling a prescription they are no longer taking). A limitation of this study is the unavailability of reliable cancer recurrence data. Finally, the generalisability of study findings is limited by the use of the GMS-eligible population, which is constrained by age and socioeconomic status.

In conclusion, the results from our study suggest that initiating statin use after a diagnosis of stage I–III breast cancer is not significantly associated with a reduction in breast cancer-specific mortality. We observed no evidence of effect modification by statin solubility or hormone receptor characteristics.

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CONFLICT OF INTEREST

LS reports receiving commercial research support from Sanofi-Aventis for a project on treatment and outcomes in breast cancer; 2011–2012. WMG holds a part-time role as Chief Scientific Officer in OncoMark Limited, and was a co-founder and current shareholder of the same. The remaining authors declare no conflict of interest.

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