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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 $\geqslant$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 $\geqslant$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 $\geqslant$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 Dietschy, 2000;

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

	De novo statin use post breast cancer diagnosis[a,b]			
Characteristic	**Non-user (*N* = 2759)**	**User (*N* = 837)**	**Initiation rate (per 1000 person years), associated *P*-value**	
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.

[a] No 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.

[b] Patients identified as statin users/non-users after lagging exposure by 2 years.

[c] In the year prior to breast cancer diagnosis.

[d] Difference in statin initiation rate $P < 0.05$ (Poisson regression).

[e] AJCC Cancer Staging Manual 6th Edition. Springer, 2002.

[f] In the year post breast cancer diagnosis.

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

						All-cause mortality			Breast cancer-specific 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)**	**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	—	—	—	12369	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	—	—	—	12369	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	—	—	—	12369	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	—	—	—	12369	692 (55.9)	Ref	Ref	398 (32.1)	Ref	Ref
Hydrophilic statin user											
Low intensity	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)
High intensity[d]	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											
Low intensity	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]
High intensity[d]	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)
Both	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.

[a]Deaths per 1000 person years.

[b]Adjusted 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).

[c]Statin exposure lagged by 2 years in analysis.

[d]Statin dosing intensity of $\geqslant$80% for $\geqslant$12 consecutive months defined as high dosing intensity. All other statin exposures defined as low-dosing intensity.

[e]Analysis conducted *post hoc*.

[f]*P*-value $<$ 0.05.

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

						All-cause mortality			Breast cancer-specific 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)**	**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
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)
Statin exposure – yes/no (lag 1 year)											
Non-user	3058	—	—	—	15 291	804 (52.6)	Ref	Ref	482 (31.5)	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)
Statin exposure – yes/no (lag 3 years)											
Non-user	2425	—	—	—	9776	564 (57.7)	Ref	Ref	308 (31.5)	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)
Statin exposure – yes/no (lag 4 years)											
Non-user	2046	—	—	—	7540	427 (56.6)	Ref	Ref	221 (29.3)	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)
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
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)
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)
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
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)

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

[a]Deaths per 1000 person years.

[b]Adjusted 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).

[c]Statin exposure lagged by 2 years in analysis.

Brookhart *et al*, 2007; Dormuth *et al*, 2009) and have a better breast cancer prognoses (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.

REFERENCES

Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, Sørensen HT, Lash TL (2011) Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. *J Natl Cancer Inst* **103**: 1461–1468.

Barron TI, Flahavan EM, Sharp L, Bennett K, Visvanathan K (2014) Recent prediagnostic aspirin use, lymph node involvement, and 5-year mortality in women with stage I–III breast cancer: a nationwide population-based cohort study. *Cancer Res* **74**: 4065–4077.

Bjarnadottir O, Kimbung S, Johansson I, Veerla S, Jönsson M, Bendahl P-O, Grabau D, Hedenfalk I, Borgquist S (2015) Global transcriptional changes following statin treatment in breast cancer. *Clin Cancer Res* **21**: 3402–3411.

Bjarnadottir O, Romero Q, Bendahl P-O, Jirström K, Rydén L, Loman N, Uhlén M, Johannesson H, Rose C, Grabau D, Borgquist S (2013) Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. *Breast Cancer Res Treat* **138**: 499–508.

Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJA, Fujii M, Buist DSM (2014) Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. *Breast Cancer Res Treat* **144**: 405–416.

Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, Solomon DH (2007) Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol* **166**: 348–354.

Cardwell CR, Hicks BM, Hughes C, Murray LJ (2015) Statin use after diagnosis of breast cancer and survival: a population-based cohort study. *Epidemiology* **26**: 68–78.

Chae YK, Valsecchi ME, Kim J, Bianchi AL, Khemasuwan D, Desai A, Tester W (2011) Reduced risk of breast cancer recurrence in patients using ACE inhibitors, ARBs, and/or statins. *Cancer Invest* **29**: 585–593.

Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS (2013) Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. *J Natl Cancer Inst* **105**: 1456–1462.

Coleman R, Gnant M, Paterson A, Powles T, von Minckwitz G, Pritchard K, Bergh J, Bliss J, Gralow J, Anderson S, Evans V, Pan H, Bradley R, Davies C, Gray R (2013) Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: a meta-analysis of individual patient data from randomised trials. *Cancer Res* **73**(24 Supplement): S4–07.

Desai P, Lehman A, Chlebowski RT, Kwan ML, Arun M, Manson JE, Lavasani S, Wasswertheil-Smoller S, Sarto GE, LeBoff M, Cauley J, Cote M, Beebe-Dimmer J, Jay A, Simon MS (2015) Statins and breast cancer stage and mortality in the Women's Health Initiative. *Cancer Causes Control* **26**: 529.

Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, Brookhart MA (2009) Statin adherence and risk of accidents: a cautionary tale. *Circulation* **119**: 2051–2057.

Evans JS, Harries C, Dennis I, Dean J (1995) General practitioners' tacit and stated policies in the prescription of lipid lowering agents. *Br J Gen Pract* **45**: 15–18.

Garwood ER, Kumar AS, Baehner FL, Moore DH, Au A, Hylton N, Flowers CI, Garber J, Lesnikoski B-A, Hwang ES, Olopade O, Port ER, Campbell M, Esserman LJ (2010) Fluvastatin reduces proliferation and increases apoptosis

in women with high grade breast cancer. *Breast Cancer Res Treat* **119**: 137–144.

Glynn RJ, Knight EL, Levin R, Avorn J (2001) Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology* **12**: 682–689.

Glynn RJ, Schneeweiss S, Wang PS, Levin R, Avorn J (2006) Selective prescribing led to overestimation of the benefits of lipid-lowering drugs . *J Clin Epidemiol* **59**: 819–828.

Haley RW, Dietschy JM (2000) Is there a connection between the concentration of cholesterol circulating in plasma and the rate of neuritic plaque formation in Alzheimer disease? *Arch Neurol* **57**: 1410–1412.

Holmes MD, Chen WY (2012) Hiding in plain view: the potential for commonly used drugs to reduce breast cancer mortality. *Breast Cancer Res* **14**: 216.

Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE (2010) Aspirin intake and survival after breast cancer. *J Clin Oncol* **28**: 1467–1472.

Howlader N, Ries LAG, Mariotto AB, Reichman ME, Ruhl J, Cronin KA (2010) Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst* **102**: 1584–1598.

Kwan ML, Habel LA, Flick ED, Quesenberry CP, Caan B (2008) Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. *Breast Cancer Res Treat* **109**: 573–579.

Marshall SF, Bernstein L, Anton-Culver H, Deapen D, Horn-Ross PL, Mohrenweiser H, Peel D, Pinder R, Purdie DM, Reynolds P, Stram D, West D, Wright WE, Ziogas A, Ross RK (2005) Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. *J Natl Cancer Inst* **97**: 805–812.

Murtola TJ, Visvanathan K, Artama M, Vainio H, Pukkala E (2014) Statin use and breast cancer survival: a nationwide cohort study from Finland. *PLoS One* **9**: e110231.

Nickels S, Vrieling A, Seibold P, Heinz J, Obi N, Flesch-Janys D, Chang-Claude J (2013) Mortality and recurrence risk in relation to the use of lipid-lowering drugs in a prospective breast cancer patient cohort. *PLoS One* **8**: e75088.

Nielsen SF, Nordestgaard BG, Bojesen SE (2012) Statin use and reduced cancer-related mortality. *N Engl J Med* **367**: 1792–1802.

Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M (2007) A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* **10**: 3–12.

Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ (2001) Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* **154**: 854–864.

Snyder CF, Frick KD, Kantsiper ME, Peairs KS, Herbert RJ, Blackford AL, Wolff AC, Earle CC (2009a) Prevention, screening, and surveillance care for breast cancer survivors compared with controls: changes from 1998 to 2002. *J Clin Oncol* **27**: 1054–1061.

Snyder CF, Frick KD, Peairs KS, Kantsiper ME, Herbert RJ, Blackford AL, Wolff AC, Earle CC (2009b) Comparing care for breast cancer survivors to non-cancer controls: a five-year longitudinal study. *J Gen Intern Med* **24**: 469–474.

Tevaarwerk AJ, Gray R, Schneider BP, Smith ML, Wagner LI, Fetting J, Davidson N, Goldstein L, Miller KD, Sparano JA (2013) Survival in metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence for improvement over the past three decades. *Cancer* **119**: 1140–1148.

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