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Pre-diagnostic statin use, lymph node status and mortality in women with stages I–III breast cancer

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Background: Recent meta-analyses suggest that pre-diagnostic statin use is associated with reduced breast cancer-specific mortality. Studies have shown that high breast tumour expression of the statin target (3-hydroxy-3-methylglutaryl coenzyme-A reductase) is associated with lymph-node negative cancer. Therefore, we examined the association between pre-diagnostic statin use and; lymph node status, breast cancer-specific and all-cause mortality.

Methods: Women with stages I–III breast cancer were identified from the National Cancer Registry of Ireland ($N=6314$). Pre-diagnostic statin users were identified from linked prescription claims data ($N=2082$). Relative risks were estimated for associations between pre-diagnostic statin use and lymph node status. Hazard ratios (HR) were estimated for associations between pre-diagnostic statin use and breast cancer-specific and all-cause mortality.

Results: Pre-diagnostic statin use was not associated with lymph node negative status at diagnosis. In multivariate analyses, pre-diagnostic statin use was associated with reduced all-cause (HR 0.78 95% confidence interval (CI) 0.69, 0.89) and breast cancer-specific mortality (HR 0.81 95% CI 0.68, 0.96). This reduction in cancer-specific mortality was greatest in statin-users with oestrogen (ER) receptor-positive tumours (HR 0.69 95% CI 0.55, 0.85).

Conclusion: Patients with pre-diagnostic statin exposure had a significant reduction in breast cancer-specific mortality, which was even more pronounced in women with ER+ tumours.

Statins are widely used for the prevention of cardiovascular disease through reduction of serum cholesterol (Holmes and Chen, 2012). Up to 30% of Americans over the age of 40 receive statins, and utilisation is similar across Europe (Walley *et al*, 2004; Robinson and Booth, 2010). Statins bind to 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR); inhibiting the rate-limiting step of the cholesterol biosynthesis pathway, leading to reduced levels of mevalonate and downstream products (Tobert, 2003). Potentially anti-cancer effects of statins involve the reduction of these downstream products, which have important roles in cellular processes such as membrane integrity, protein synthesis, and cell signalling (Chan *et al*, 2003; Jakobisiak and Golab, 2003). In addition, a recent study suggests that statin treatment may have breast tumour anti-proliferative properties due to effects on cell cycle regulators P21 and P27 (Feldt *et al*, 2015). A window-of-opportunity study has shown that treatment of breast cancer patients with short duration, high-dose atorvastatin (80 mg per day) results in decreased tumour proliferation and an increase in tumour HMGCR expression (Bjarnadottir *et al*, 2013). Interestingly, Brennan *et al* (2011) found that breast cancer

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patients with high-tumour HMGCR expression were more likely to have smaller, node negative cancer. However, this study did not record information on prescribed medications in these patients, and could not assess the potential effect of statin use.

A recent meta-analysis suggests that pre-diagnostic statin use is associated with significantly improved cancer-specific (HR 0.73 95% CI 0.61, 0.89) survival in women with breast cancer (Zhong *et al*, 2015). In a study by Ahern *et al* (2011) statin use was associated with reduced breast cancer recurrence; this benefit was observed only in women with ER+ tumours (HR 0.69, 95% CI 0.55, 0.88) and not in women with ER- tumours (HR 0.75 95% 0.47, 1.2) (Ahern *et al*, 2011). This effect modification by ER status has not yet been observed in studies investigating statin exposure and breast cancer-specific survival (Mc Menamin *et al*, 2016).

In our study, we investigate associations between pre-diagnostic statin use and: (i) lymph node status at diagnosis; (ii) breast cancer-specific and all-cause mortality; and (iii) whether any associations were modified by oestrogen (ER) receptor status, in a cohort of Irish women with newly diagnosed breast cancer.

METHODS

Setting and data sources. This cohort study was carried out using records from the National Cancer Registry Ireland (NCRI), which are linked to individual-level prescription dispensing data from Ireland's Primary Care Reimbursement Services (PCRS) pharmacy claims database, as described previously (Barron *et al*, 2014). Information on date and cause of death are obtained from linkage to death certificates. The completeness of cancer registration is estimated to be at least 97% (Data Quality and Completeness at the Irish National Cancer Registry, 2012). The use for research of anonymised data held by the NCRI is covered by the Health (Provision of Information) Act 1997.

The PCRS is responsible for reimbursement of dispensed medication claims made under the General Medical Services (GMS) scheme. The GMS scheme provides subsidised healthcare, including prescription medications at no/minimal cost, to approximately one third of the Irish population. Eligibility for the scheme is assessed by a combination of age and means test; therefore the data set may have an overrepresentation of older people and those with lower socioeconomic status. The PCRS database records details, including quantity and dose, of prescription drugs dispensed to patients availing of the GMS scheme. This includes all statins, which are prescription-only. Drugs are coded according to WHO–ATC classifications (WHOCC–ATC/DDD Index).

Cohort and exposure definitions. The study population comprised of women diagnosed with stages I–III breast cancer (ICD-10 C50) between 1 January 2001 and 31 December 2011. Women were included in the study population if they were aged 50–80 years at diagnosis; had GMS coverage from at least 1 year before diagnosis; and no history of invasive cancer, other than non-melanoma skin cancer. The study population was restricted by age because younger women are less likely to be prescribed statins and older women are less likely to receive definitive cancer staging/treatment (Hillner *et al*, 1996).

We identified pre-diagnostic statin prescriptions dispensed to the women in the study cohort from the PCRS database using WHO-ATC classifications (Supplementary Table 1). For each day of follow-up, we calculated statin dosing intensity from the number of days' supply of statin received in the prior year (Peterson *et al*, 2007). These statin exposure histories were used to define the following time-varying exposure categories: (i) women were identified as exposed (yes/no) from the date they received their first statin prescription; (ii) women were identified as having high-intensity exposure once they had taken a statin at an intensity of $\geqslant$80%, for at least 1 year (e.g., a statin supply for at least 292 out of a 365 day period was considered high intensity; Supplementary Figure 1). The overall intensity of statin exposure while on treatment was calculated by expressing the number of days' supply received as a proportion of the number of days from initiation to last exposure. Once allocated to an exposure category, women remained in this category to the end of follow-up. Patients with *de-novo* post-diagnostic statin use were excluded from analyses, so as to determine the effect of statin use in patients with pre-diagnostic use.

Covariates and outcomes. The NCRI database was used to identify lymph node status at diagnosis (positive and negative). Women were lymph node positive if they had a nodal status of N1/2/3. The following information was also obtained from the NCRI database: age (years) at diagnosis, smoking status at diagnosis (never, past, current and unspecified), tumour presentation (organised screening, opportunistic screening, incidental, symptomatic and unknown), tumour size (T1, T2, T3 and T4), tumour stage (I, IIa, IIb, IIIa and IIIb-c), histologic tumour grade (low, intermediate, high and unspecified), ER, progesterone (PR), human epidermal growth factor-2 (HER-2) receptor status (positive, negative and unspecified) and receipt of chemotherapy (yes, no) in the year after diagnosis. Anti-ER therapy started in the year after breast cancer diagnosis (yes, no) was identified using the PCRS database (WHO-ATC classifications–Supplementary Table 1). The PCRS database was also used to identify other potentially confounding medication use in the year before 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 co-morbidity (Schneeweiss *et al*, 2001). Death certificates were used to determine the date and cause of death. Breast cancer-specific deaths were identified using SEER definitions (Supplementary Table 1; Howlader *et al*, 2010).

Statistical analysis. The proportion of statin-users and non-users was tabulated for each covariate and differences in the rates of statin use across covariates were compared using univariate Poisson regression. Univariate and multivariate log-binomial models were used to estimate relative risks (RR) and 95% confidence intervals (CI's) for associations between pre-diagnostic statin use and lymph node negative breast cancer at diagnosis.

In survival analyses, multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% CI's for associations between pre-diagnostic statin use and breast cancer-specific and all-cause mortality. Women were categorised as statin exposed (yes/no) from the time they received their first statin prescription. These exposures were lagged by 1 year in survival analyses to reduce the possibility that changes in breast cancer prognosis or treatment, for example a breast cancer recurrence or approaching death, influenced a patient's or prescriber's decision to initiate or continue statin therapy (Chubak *et al*, 2013; Smith *et al*, 2017). The previously described covariates were selected for inclusion in multivariable analyses, based on prior knowledge of patient and clinical characteristics associated with breast cancer-specific mortality.

The following pre-planned subgroup analyses were applied to both lymph-node status analyses and survival analyses. Firstly, analyses were stratified by ER status (positive, negative, unspecified). In survival analyses, the presence of effect modification by ER status was assessed with the inclusion of an interaction term in the

multivariable model. Secondly, as prior studies have suggested that only lipophilic statin use is associated with improved breast cancer outcomes (Ahern *et al*, 2011) analyses were also stratified by statin solubility: lipophilic (atorvastatin, fluvastatin, simvastatin), hydrophilic (pravastatin, rosuvastatin), both (Gazzerro *et al*, 2012). Finally, we stratified analyses by high/low exposure intensity.

We conducted the following sensitivity analyses: (i) associations between pre-diagnostic statin use and lymph node status, all-cause and cancer-specific mortality were assessed with stratification by mode of tumour presentation; (ii) in survival analyses, high-intensity statin exposure was defined as $\geqslant$80% intensity for longer than two consecutive years; and (iii) in survival analyses, statin exposure lag time was varied (0, 6 months, 2 years) to account for possible reverse causation bias, as mentioned above. All analyses were performed using SAS v9.3 (SAS Institute Inc, Cary, NC, USA). Results were regarded as significant at a two-sided α-level of 0.05.

RESULTS

Cohort and exposure characteristics. We identified 6314 women eligible for inclusion in the study (Figure 1). The characteristics of pre-diagnostic statin-users ($n=2082$) and non-users ($n=4232$) are presented in Table 1. Statin-users were significantly older and had a significantly higher comorbidity score than non-users. Statin-users were also significantly more likely to be prescribed aspirin, NSAIDs, anti-diabetics and bisphosphonates.

Pre-diagnostic statin use and lymph node status. Relative risks for associations between pre-diagnostic statin use and lymph node negative breast cancer are presented in Table 2. The proportion of women with node-negative status in the statin-user and non-user groups was 54% and 53%, respectively. No significant association was found between pre-diagnostic statin use and lymph node negative status at diagnosis, in both univariate (RR 1.01 95% CI 0.96, 1.06) and multivariate adjusted analyses (RR 1.00 95% 0.98, 1.03; Table 2). Analyses stratified by; high-intensity statin use, duration of statin use, and type of statin received, also yielded null

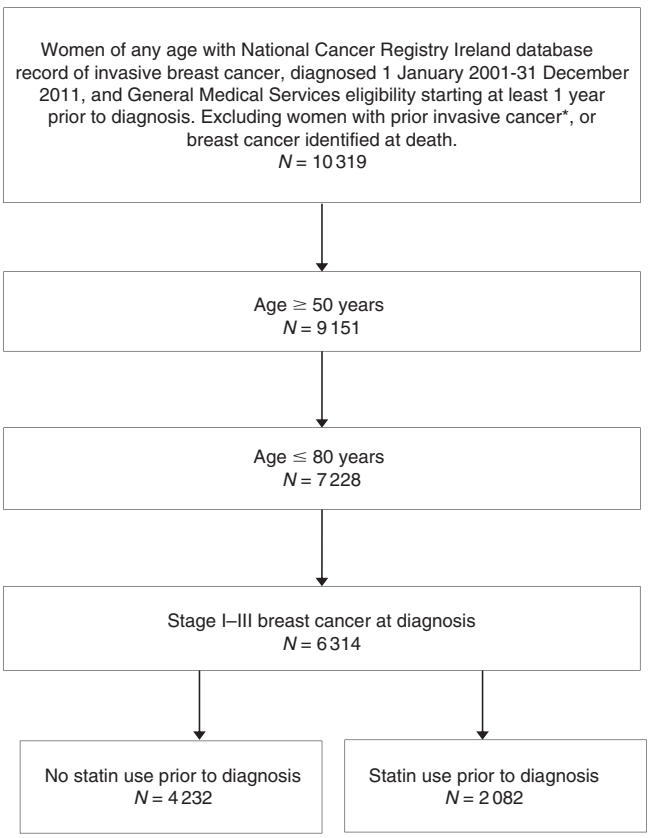

Figure 1. Flowchart for study cohort inclusion and exclusion criteria. *With the exception of non-melanoma skin cancer.

Table 1. Characteristics of women selected for inclusion in study cohort

Characteristic	Statin use before diagnosis: Non-user N = 4232	Statin use before diagnosis: User N = 2082
Age in years[a]		
Median (IQR)	67 (58, 74)	71 (63, 75)
Comorbidity score[a]		
Median (IQR)	7 (3, 11)	11 (7, 16)
Smoking (%)		
Current	885 (20.9)	381 (18.3)
Past	490 (11.6)	262 (12.6)
Never	2009 (47.5)	994 (47.7)
Unspecified	848 (20.0)	445 (21.4)
Tumour presentation (%)		
Screening; organised	750 (17.7)	324 (15.6)
Screening; opportunistic	51 (1.2)	28 (1.3)
Screening; unspecified	151 (3.8)	86 (4.1)
Incidental	87 (2.1)	46 (2.2)
Symptomatic	2990 (70.7)	1476 (70.9)
Unspecified	203 (4.8)	122 (5.9)
Tumour morphology (%)		
Lobular	527 (12.5)	273 (13.1)
Ductal	3098 (73.2)	1543 (74.1)
Other	607 (14.3)	266 (12.8)
Aspirin (%)[a]		
Yes	713 (16.9)	1061 (51.0)
No	3519 (83.1)	1021 (49.0)
NSAID (%)[a]		
Yes	1848 (43.7)	988 (47.5)
No	2384 (56.3)	1094 (52.5)
Anti-diabetic (%)[a]		
Yes	143 (3.4)	330 (15.9)
No	4089 (96.6)	1752 (84.1)
Chemotherapy (%)[a,b]		
Yes	1685 (39.8)	718 (34.5)
No	2547 (60.2)	1364 (65.5)
Anti-ER (%)[a,b]		
Yes	3131 (74.0)	1630 (78.3)
No	1101 (26.0)	452 (21.7)
Bisphosphonate (%)[a]		
Yes	326 (7.7)	283 (13.6)
No	3906 (92.3)	1799 (86.4)
Nodal status (%)		
Positive	1756 (41.7)	847 (40.7)
Negative	2261 (53.4)	1125 (54.0)
Unspecified	215 (5.1)	110 (5.3)
Tumour size (%)		
T0	31 (0.7)	18 (0.9)
T1	1796 (42.4)	907 (43.6)
T2	1850 (43.7)	919 (44.1)
T3	262 (6.2)	134 (6.4)
T4	283 (6.7)	98 (4.7)
Unspecified	10 (0.2)	6 (0.3)

Table 1. (Continued)

Characteristic	Statin use before diagnosis: Non-user N = 4232	User N = 2082
Tumour stage (%)[a]		
I	1366 (32.3)	687 (33.0)
IIa	1333 (31.5)	675 (32.4)
IIb	882 (20.8)	428 (20.6)
IIIa	263 (6.2)	140 (6.7)
IIIb-c	388 (9.2)	152 (7.3)
Tumour grade (%)[a]		
Low	454 (10.7)	201 (9.7)
Intermediate	2079 (49.1)	1087 (52.2)
High	1352 (32.0)	673 (32.3)
Unspecified	347 (8.2)	121 (5.8)
ER (%)[a]		
Negative	720 (17.0)	326 (15.7)
Positive	3066 (72.5)	1605 (77.1)
Unspecified	446 (10.5)	151 (7.3)
PR (%)[a]		
Negative	1109 (26.2)	534 (25.7)
Positive	2108 (49.8)	1170 (56.2)
Unspecified	1015 (24.0)	378 (18.2)
HER2 (%)[a]		
Negative	2511 (59.3)	1460 (70.1)
Positive	530 (12.5)	246 (11.8)
Unspecified	1191 (28.1)	376 (18.1)

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; NSAID = non-steroidal anti-inflammatory drug; PR = progesterone receptor.
[a]Difference in statin use $P < 0.05$ (Poisson regression).
[b]In the year after diagnosis.

findings (Table 2). No effect modification was observed by ER status, or mode of tumour presentation (Table 2). In univariate analyses, statin-users with breast cancers diagnosed through mammography screening were significantly more likely to be lymph node negative (RR 1.32, 95% CI 1.23, 1.43); however, this effect was non-significant in multivariable adjusted analyses (RR 1.01, 95% CI 0.95, 1.08) (Table 2).

Pre-diagnostic statin use and mortality. After lagging statin exposure by 1 year, we identified 2024 women with pre-diagnostic statin use. In multivariable adjusted survival analyses, pre-diagnostic statin use was associated with a significant, 19% reduction in breast cancer-specific mortality (HR 0.81 95% CI 0.68, 0.96) and a significant 22% reduction in all-cause mortality (HR 0.78 95% CI 0.69, 0.89; Table 3). This cancer-specific survival benefit was observed in women with high-intensity use (HR 0.70 95% CI 0.52, 0.94) but not in those with low-intensity statin use (HR 0.90 95% CI 0.67, 1.2). In analyses stratified by type of statin received (hydrophilic, lipophilic, both), survival benefit was significant in women who received a lipophilic statin (HR 0.76 95% CI 0.61, 0.95) but not hydrophilic statin.

In multivariable survival analyses stratified by mode of tumour presentation, a similar effect on all-cause (HR 0.78 95% CI 0.68, 0.90) and breast cancer-specific (HR 0.83 95% CI 0.68, 1.00) mortality was seen in those with tumours diagnosed through symptomatic presentation. This effect was not seen in women with tumours diagnosed through organised screening; however, this may be due to fewer numbers of women in this subgroup (Table 3).

In analyses of effect-modification by ER status, pre-diagnostic statin use was associated with a more marked, statistically significant, 31% reduction in breast cancer-specific mortality in patients with ER+ tumours (HR 0.69 95% CI 0.55, 0.85)

Table 2. Univariate and multivariate RRs for associations between pre-diagnostic statin use and lymph node negative breast cancer

					Node negative breast cancer			
	Node +	(%)	Node –	(%)	Univariate RR (95% CI)		Multivariate RR (95% CI)[a]	
Statin exposure								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Prediagnostic statin-user	847	40.7	1125	54.0	1.01	0.96, 1.06	1.00	0.98, 1.03
Hydro/lipophilic								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Hydrophilic statin-user	216	36.9	335	57.2	1.07	1.00, 1.16	1.00	0.97, 1.04
Lipophilic statin-user	444	41.9	562	53.0	0.99	0.93, 1.05	1.00	0.97, 1.03
Both	186	43.0	226	52.2	0.97	0.89, 1.07	1.01	0.97, 1.05
Dosing intensity								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Low-intensity user	163	41.3	204	51.7	0.96	0.87, 1.06	0.98	0.94, 1.02
High-intensity user	684	40.6	921	54.6	1.03	0.97, 1.09	1.01	0.99, 1.04
Effect modification ER+								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Pre-diagnostic statin-user	636	39.6	883	55.0	1.04	0.98, 1.09	1.01	0.97, 1.06
Symptomatic presentation								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Pre-diagnostic statin-user	659	44.7	735	49.8	0.91	0.86, 0.96	1.00	0.97, 1.03
Screening presentation								
Non-user	1756	41.5	2261	53.4	Ref	–	Ref	–
Pre-diagnostic statin-user	95	29.3	227	70.1	1.32	1.23, 1.43	1.01	0.95, 1.08

Abbreviations: CI = confidence interval; ER = oestrogen receptor; HR = hazard ratio; NSAID = non-steroidal anti-inflammatory drug; Ref = referent group.
[a]Adjusted for age at diagnosis (years); smoking status (never, past, current, unspecified); comorbidity score, tumour stage (I, IIa, IIb, IIIa, IIIb-c); tumour grade (low, intermediate, high, unspecified); ER, PR and HER2 receptor status (positive, negative, unspecified); chemotherapy in year post diagnosis (yes, no); anti-ER therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID and anti-diabetic medication use (yes, no), mode of tumour presentation (screening, incidental, symptomatic, unspecified), tumour morphology (ductal, lobular, other).

Table 3. Univariate and multivariate hazard ratios for associations between pre-diagnostic statin use and mortality

		All-cause mortality			Breast cancer-specific mortality		
Statin exposure definitions	***N***	**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	4069	1002 55.0	Ref –	Ref –	575 31.5	Ref –	Ref –
Statin-user	2024	379 49.6	1.01 (0.90, 1.13)	**0.78 (0.69, 0.89)**	198 25.9	0.88 (0.75, 1.03)	**0.81 (0.68, 0.96)**
Dosing intensity[c]							
Non-user	4069	1002 55.0	Ref –	Ref –	575 31.5	Ref –	Ref –
Statin-user–low intensity	166	34 8.9	1.10 (0.95, 1.27)	0.78 (0.66, 0.92)	20 5.2	0.92 (0.75, 1.12)	0.90 (0.67, 1.20)
Statin-user–high intensity[d]	1858	345 30.7	0.94 (0.81, 1.09)	**0.79 (0.67, 0.92)**	178 15.8	0.85 (0.70, 1.04)	**0.70 (0.52, 0.94)**
Hydro/lipophilic[c]							
Non-user	4069	1002 55.0	Ref –	Ref –	575 31.5	Ref –	Ref –
Hydrophilic statin-user	572	114 48.1	0.92 (0.83, 1.19)	**0.79 (0.65, 0.95)**	56 23.6	0.85 (0.66, 1.09)	0.79 (0.61, 1.03)
Lipophilic statin-user	1031	181 46.2	0.96 (0.83, 1.12)	**0.73 (0.63, 0.86)**	102 26.0	0.87 (0.71, 1.07)	**0.76 (0.61, 0.95)**
Both	421	84 61.9	1.19 (0.96, 1.48)	0.84 (0.67, 1.05)	40 29.5	0.97 (0.72, 1.32)	0.82 (0.60, 1.13)
Symptomatic presentation[c]							
Non-user	2859	854 65.1	Ref –	Ref –	503 38.4	Ref –	Ref –
Statin-user	1422	304 55.2	0.99 (0.87, 1.12)	**0.78 (0.68, 0.90)**	167 30.3	0.88 (0.74, 1.04)	0.83 (0.68, 1.00)
Screening presentation[c]							
Non-user	746	40 13.6	Ref –	Ref –	19 6.5	Ref –	Ref –
Statin-user	320	21 18.6	1.48 (0.87, 2.51)	0.64 (0.32, 1.27)	10 8.8	1.41 (0.65, 3.07)	0.65 (0.23, 1.81)
Effect modification–ER status[c]							
ER+	1573						**0.69 (0.55, 0.85)**
ER–	303						1.10 (0.81, 1.49)
ER unspecified	148						0.96 (0.61, 1.53)

Abbreviations: CI = confidence interval; HR = hazard ratio; ER = oestrogen; NSAID = non-steroidal anti-inflammatory drug; Ref = referent group.
Bold text indicates significant results at $P<0.05$.
[a]Deaths/1000 person years.
[b]Adjusted for age at diagnosis (years); smoking status (never, past, current, unspecified); comorbidity score, tumour stage (I, IIa, IIb, IIIa, IIIb-c); tumour grade (low, intermediate, high, unspecified); ER, PR & HER2 receptor status (positive, negative, unspecified); chemotherapy in year post diagnosis (yes, no); anti-ER therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID and anti-diabetic medication use (yes, no), mode of tumour presentation (screening, incidental, symptomatic, unspecified), tumour morphology (ductal, lobular, other).
[c]Statin exposure lagged by 1 year in analysis.
[d]Statin dosing intensity of ⩾80% for ⩾12 consecutive months defined as high dosing intensity. All other statin exposures defined as low dosing intensity.

(*P*interaction < 0.01) (Table 3). This survival benefit was not observed in women with ER- tumours (HR 1.10 95% CI 0.81, 1.10; Table 3).

In sensitivity analyses, a similar reduction in breast cancer-specific mortality was observed when high-intensity exposure window was increased to 2 years (HR 0.67 95% CI 0.47, 0.94) (Table 4). Again, a similar effect was seen when varying the statin exposure lag time in survival analyses (Table 4).

DISCUSSION

In this study of 6314 women with stage I-III breast cancer, pre-diagnostic statin use was not significantly associated with lymph node status at diagnosis but was associated with a statistically significant reduction in all-cause and breast cancer-specific mortality, even when adjusting for major prognostic factors. The survival benefit was even more pronounced in women with ER+ tumours.

The survival benefit observed is similar to findings from a meta-analysis of studies investigating statin use and breast cancer-specific mortality by Zhong *et al* (2015) (HR 0.73, 95% CI 0.62, 0.86), and another by Mansourian *et al* (2016) (HR 0.85 95% CI 0.83, 0.87) (Mansourian *et al*, 2016). Our study showed cancer-specific survival benefit was strongest among women receiving lipophilic statins (HR 0.76), and in those with high-intensity statin exposure (HR 0.70). The exact cause of reductions in breast cancer mortality is still largely unknown. However, possible mechanisms have been suggested; pre-clinical studies have shown effects on cell signalling through stabilisation of cyclin-dependent kinase inhibitors p21 and p27 (Denoyelle *et al*, 2001). Statins have also been shown to exhibit immunomodulatory properties; cerivastatin was shown to enhance tumour CD8+ T-cell infiltration and induced tumour associated macrophages to an M1-like phenotype; creating an anti-tumour environment (Mira *et al*, 2013).

Table 4. Sensitivity analyses–univariate and multivariate hazard ratios for associations between statin use and mortality

		All-cause mortality			Breast cancer-specific mortality		
Statin exposure definitions	***N***	**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: varied exposure lag times							
Statin exposure–yes/no (lag 0 years)							
Non-user	4232	1165 48.1	Ref –	Ref –	682 28.2	Ref –	Ref –
Statin-user	2082	437 55.5	1.01 (0.92, 1.13)	**0.77 (0.68, 0.87)**	230 29.2	0.87 (0.75, 1.00)	**0.77 (0.66, 0.90)**
Statin exposure–yes/no (lag 6 months)							
Non-user	4149	1082 51.1	Ref –	Ref –	630 29.7	Ref –	Ref –
Statin-user	2052	407 52.5	1.00 (0.90, 1.12)	**0.77 (0.68, 0.88)**	217 28.0	0.88 (0.76, 1.03)	**0.80 (0.68, 0.95)**
Statin exposure–yes/no (lag 1 year, included for reference)							
Non-user	4069	1002 55.0	Ref –	Ref –	575 31.5	Ref –	Ref –
Statin-user	2024	379 49.6	1.01 (0.90, 1.13)	**0.78 (0.69, 0.89)**	198 25.9	0.88 (0.75, 1.03)	**0.81 (0.68, 0.96)**
Statin exposure–yes/no (lag 2 years)							
Non-user	3566	832 58.8	Ref –	Ref –	462 32.6	Ref –	Ref –
Statin-user	1701	301 50.0	1.03 (0.90, 1.17)	**0.81 (0.70, 0.93)**	148 24.5	0.87 (0.73, 1.04)	**0.81 (0.66, 0.98)**
Sensitivity analysis: high-intensity exposure ⩾80% for ⩾24 consecutive months[c]							
Non-user	4069	1002	Ref –	Ref –	575 53.1	Ref –	Ref –
Statin-user–low intensity	302	64	1.08 (0.95, 1.23	**0.81 (0.70, 0.94)**	35	0.92 (0.77, 1.11)	0.87 (0.67, 1.13)
Statin-user–high intensity	1722	315	0.89 (0.74, 1.07)	**0.73 (0.61, 0.89)**	163	0.80 (0.63, 1.03)	**0.67 (0.47, 0.94)**

Abbreviations: CI = confidence interval; ER = oestrogen; HR = hazard ratio; NSAID = non-steroidal anti-inflammatory drug; Ref = referent group.
Bold text indicates significant results at $P<0.05$.
[a]Deaths/1000 person years.
[b]Adjusted for age at diagnosis (years); smoking status (never, past, current, unspecified); comorbidity score, tumour stage (I, IIa, IIb, IIIa, IIIb-c); tumour grade (low, intermediate, high, unspecified); ER, PR and HER2 receptor status (positive, negative, unspecified); chemotherapy in year post diagnosis (yes, no); anti-ER therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID and anti-diabetic medication use (yes, no), mode of tumour presentation (screening, incidental, symptomatic, unspecified), tumour morphology (ductal, lobular, other).
[c]Statin exposure lagged by 1 year in analysis.

A number of studies have been published investigating associations between pre and/or post-diagnostic statin exposure and breast cancer outcomes (Kwan *et al*, 2008; Ahern *et al*, 2011; Chae *et al*, 2011; Brewer *et al*, 2013; Nickels *et al*, 2013; Murtola *et al*, 2014; Cardwell *et al*, 2015; Desai *et al*, 2015; Zhong *et al*, 2015; Mansourian *et al*, 2016; Manthravadi *et al*, 2016; Smith *et al*, 2016). To our knowledge, this is the first study investigating associations between pre-diagnostic statin use and lymph node status at diagnosis. In our study, pre-diagnostic statin use was not associated with lymph node negativity in multivariable adjusted analyses. Relative risks remained unchanged after stratification by statin type and statin intensity. In a clinical trial in which breast cancer patients were administered short-term high-dose (80 mg per day) atorvastatin; post-treatment tumour biopsies had significantly increased expression of HMGCR, the target enzyme for statins (Bjarnadottir *et al*, 2013). Interestingly, moderate/strong HMGCR expression in breast tumour biopsies has been shown to be associated with a less aggressive tumour phenotype; lymph node negativity, lower grade and ER/PR positivity (Gustbée *et al*, 2015). Although we did not observe an association between pre-diagnostic statin exposure and lymph node negativity in our study, it is possible that there may be specific subgroups of patients, for example; those with tumour expression of HMGCR, for whom statin treatment may be beneficial. In this study, we do not have access to reliable recurrence information, and it is possible that reductions in breast cancer specific mortality in statin-users are due to a reduction in cancer recurrence. Interestingly, Brennan *et al* (2011) showed that tumour HMGCR protein expression was associated with tamoxifen response in a cohort of over 500 women. We found a more marked reduction in breast cancer mortality for users of lipophilic statins (HR 0.76), which is in keeping with previous studies (Campbell *et al*, 2006; Ghosh-Choudhury *et al*, 2010; Ahern *et al*, 2011; Cardwell *et al*, 2015). However, it should be noted that the numbers of patients receiving a hydrophilic statin were much lower than lipophilic, and any association may be under-powered. In addition, atorvastatin is considered hydrophilic in the study by Ahern *et al* (2011), which is unlike the other previously mentioned studies. Studies have shown that lipophilic statins can inhibit breast cancer cell survival and cell proliferation through effects on p-MEK1/2 and NF-κB (Campbell *et al*, 2006). Lipophilic statins have been shown to inhibit anti-apoptotic Bcl-XL expression and induce the expression of pro-apoptotic/anti-proliferative PTEN (Ghosh-Choudhury *et al*, 2010). In addition, lipophilic statin use was associated with reduced breast cancer recurrence in a Danish cohort of women with breast cancer (Ahern *et al*, 2011). A possible explanation for the differential effect by statin structure is due to lipophilic statins being more widely distributed throughout the body and their ability to penetrate the plasma membrane passively (Matusewicz *et al*, 2015). Hydrophilic statins, however, require uptake by the

OATP1B1 transporter which is mainly found in the liver (Matusewicz *et al*, 2015).

A 30% risk reduction in breast cancer mortality was observed in women with high-intensity statin exposure. When the minimum period with high-intensity exposure was extended to 2 years in a sensitivity analysis (i.e., receiving a statin for at least 584 days in a 730 day period), the cancer-specific survival benefit was even greater (HR 0.67). This suggests a possible dose-response relationship between statin exposure and improved breast cancer survival. However, it should be noted that over 85% of statin-users were high-intensity users.

To our knowledge, this is the first study to report a significant reduction in breast cancer mortality, stratified by ER status. In a study investigating statin use and breast cancer stage, lipophilic statin-users were significantly less likely to present with late-stage breast cancer at diagnosis (HR 0.80), and this was more marked in those with ER+ tumours (HR 0.72) (Desai *et al*, 2015). Ahern *et al* (2011) found that significant reductions in breast cancer recurrence in lipophilic statin-users were confined to ER+ patients (HR 0.69); however, it should be noted that over 70% of women had ER+ tumours (Ahern *et al*, 2011). Unfortunately, we did not have access to recurrence information and cannot determine whether reductions in breast cancer mortality in our study are due to reduced recurrence in statin-users. In a recent randomised, phase III, double-blind clinical trial, concomitant cholesterol-lowering medication and aromatase inhibitors was associated with improved disease-free survival (HR 0.76, 95% CI 0.60, 0.97) in women with early stage, hormone-receptor-positive breast cancer (Borgquist *et al*, 2017). It is known that 27-hydroxycholesterol (27HC) is cholesterol metabolite and a selective ER receptor modulator (SERM) capable of promoting proliferation in ER+ cells (McDonnell *et al*, 2014). As statins decrease the level of cholesterol in the circulation, and subsequent level of 27HC, it is possible that this leads to a decrease in ER+ tumour cell profileration (Kimbung *et al*, 2016). As mentioned, tumour expression of HMGCR may have an important role in the anticancer properties of statins. Interestingly, in studies investigating the prognostic role of breast tumour HMGCR expression, a combination of both HMGCR and ER positivity was associated with improved response to tamoxifen (Brennan *et al*, 2011), breast cancer-specific survival and recurrence free survival (Borgquist *et al*, 2008). As literature accumulates, it is clear that there may be important clinical implications for statin-use and breast cancer outcomes. However, there may be specific subgroups of women which may benefit, and the complex interplay between statin exposure, HMGCR expression, ER status, and subsequent cancer outcomes warrant further investigation.

Our study has a number of strengths, including the use of accurate cancer outcome and prescription refill data. However, there are some limitations. We could not verify whether women took the medication and non-compliance may have resulted in exposure misclassification. However, we expect that women are unlikely to continue filling prescriptions for medication they no longer take. It is important to consider that statins may be preferentially prescribed for, and taken by, patients who engage in healthier behaviours and have superior health outcomes (Evans *et al*, 1995; Brookhart *et al*, 2007; Flahavan *et al*, 2014). This is known as healthy-user bias and may cause an overestimation of any beneficial effect of statins (Glynn *et al*, 2006). In our study, the rates of breast cancers detected through mammography screening were similar in statin-users and non-users, suggesting that healthy-user bias may be minimal (Brookhart *et al*, 2007). We did not have information on all lifestyle factors that may influence disease progression, for example, BMI, and the potential for residual confounding in our analyses should be considered. Up to 28% of women have an unspecified HER2 status; these women may have been diagnosed before the introduction of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 testing guidelines in 2007 (Tchrakian *et al*, 2015). Finally, when generalising our results, it should be noted that our study population was a subset of breast cancer cases defined by eligibility for the GMS scheme.

To conclude, the results from our study suggest that pre-diagnostic statin use in women with stages I–III breast cancer is associated with a significant reduction in both breast cancer-specific and all-cause mortality, particularly in those with ER+ breast cancer, but is not significantly associated with lymph node status at diagnosis. In future studies, we suggest that the association between statin exposure, tumour HMGCR expression, and breast cancer outcomes be explored further.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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