Smith A, Murphy L, Sharp L, O'Connor D, Gallagher WM, Bennett K, Barron TI. *De novo* post-diagnosis statin use, breast cancer-specific and overall mortality in women with stage I-III breast cancer. *British Journal of Cancer* 2016, 115(5), 592-598.

TITLE

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

AUTHORS

Amelia Smith [1]	smitha25@tcd.ie
Laura Murphy [1]	laura.murphy@tcd.ie
Linda Sharp [2]	linda.sharp@ncl.ac.uk
Darran O'Connor [3]	darran.oconnor@ucd.ie
William M Gallagher [3]	william.gallagher@ucd.ie
Kathleen Bennett [1]	bennettk@tcd.ie
Thomas I Barron [1, 4]	barront@tcd.ie

INSTITUTIONS

[1] Trinity Centre for Health Sciences, Trinity College, University of Dublin, Dublin, Ireland.

[2] Institute of Health & Society, Newcastle University, Newcastle Upon Tyne, England.

[3] UCD School of Biomolecular and Biomedical Science, UCD Conway Institute, University College Dublin, Dublin, Ireland.

[4] Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

CORRESPONDING AUTHOR

Dr. Thomas I Barron

Department of Pharmacology & Therapeutics,

Trinity Centre for Health Sciences,

St James's Hospital,

Dublin 8,

Ireland.

barront@tcd.ie

RESEARCH SUPPORT

This work was supported by the Irish Cancer Society Collaborative Cancer Research Centre BREAST-PREDICT [CCRC13GAL to WM Gallagher, K Bennett, D O'Connor, TI Barron] and the Health Research Board Ireland [ICE20119 to K Bennett, L Sharp]. L Murphy and A Smith's positions are funded by the Irish Cancer Society Collaborative Cancer Research Centre BREAST-PREDICT [CCRC13GAL]. TI Barron's position was funded by the Health Research Board Ireland [ICE20119]. The Health Research Board Ireland and the Irish Cancer Society had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit for publication.

ABSTRACT

Background: Preclinical and epidemiological evidence suggests a role for statins in the treatment of breast cancer. However, uncertainties over the benefit of initiating statin use in the adjuvant treatment setting remain. This study investigates associations between statin-use initiated after a breast cancer diagnosis, and breast cancer-specific mortality. **Methods**: Women, with stage I-III breast cancer, aged 50-80, and not prescribed a statin prior to diagnosis were identified from the National Cancer Registry of Ireland (N=4,243). Women initiating post-diagnostic statin use were identified from linked national prescription refill data (N=837). Multivariable Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for associations between de-novo post-diagnosis statin use and mortality. **Results**: The median duration of post-diagnostic statin use was 6.7 years and the mean on-treatment exposure intensity was 86.3%. In multivariable analyses no association was found between post-diagnostic statin initiation and breast cancer-specific mortality (HR 0.88, CI 0.66, 1.17). There was no effect modification by statin type (hydrophilic/lipophilic), or ER status. Similarly, in analyses of high-intensity use (≥80% for longer than 12 consecutive months) we found no association with breast cancer-specific mortality for all statins combined (HR 1.03, 95%CI 0.71, 1.50), and separately for hydrophilic/lipophilic statins. **Conclusion:** 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. Future studies should assess whether there are molecular subgroups of patients for whom statin use may be beneficial.

INTRODUCTION

Randomized trials have demonstrated that statins, or 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMGCR) inhibitors, are effective for the reduction of cholesterol and prevention of cardiovascular disease[1]. Statins inhibit the rate-limiting step of the cholesterol biosynthesis pathway, leading to reduced levels of mevalonate and its downstream products[2]. Many of these downstream products play important roles in cellular processes such as membrane integrity, protein synthesis, and cell signalling, and their inhibition by statins may have anticancer effects[3,4]. There is also some epidemiological evidence to suggest that statins could have a role in the management of breast cancer[5–12], with one study reporting a statistically significant reduction in recurrence for users of simvastatin, a lipophilic statin[7]. However, uncertainties over the benefit of statins in the adjuvant breast cancer setting remain, as any possible effect may be limited to reductions in locoregional recurrence[7] and to date no studies of statin use have reported a reduction in breast cancer-specific mortality[8,11,12]. Additionally, most studies have included women who initiated statin use prior to their breast cancer diagnosis, and it is unclear from their results what benefit may be attributable to the post-diagnostic initiation of statin treatment[6–12]. A clearer understanding of the effect of post-diagnostic statin initiation on breast cancer-specific mortality is necessary to inform the undertaking of clinical studies of statins for the adjuvant treatment of breast cancer[13].

In a large cancer registry-based cohort of women with incident breast cancer, this study aimed to measure associations between statin use initiated after a breast cancer diagnosis (de-novo), and breast cancer-specific and all-cause mortality, and to investigate whether associations between statin use and mortality are modified by the solubility characteristics of statins or breast tumour characteristics

METHODS

SETTING & DATA SOURCES

This study was carried out using patient records from the National Cancer Registry Ireland (NCRI), which have been linked to individual-level prescription dispensing data from Ireland's Primary Care Reimbursement Services (PCRS) pharmacy claims database. These data have been described previously[14]. Briefly, the NCRI

records details about all cancers diagnosed in the population normally resident in Ireland. For each tumour diagnosis, hospital-based tumour registration officers (TRO) collect information on patient characteristics, tumour characteristics and treatment received. 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% overall and higher for breast cancer[15]. 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 financial reimbursement of dispensed medication claims made under the General Medical Services (GMS) community drug scheme. The GMS scheme provides subsidized healthcare, including prescription medications at no or minimal cost, to approximately one third of the Irish population. Eligibility for the scheme is assessed by a combination of age and means test. The PCRS pharmacy claims database records details, including quantity and dose, of all prescription drugs dispensed to patients with eligibility for the scheme. Drugs are coded according to WHO–ATC classifications[16].

COHORT & EXPOSURE DEFINITIONS

The study population comprised of women with a diagnosis of stage I-III breast cancer (ICD-10 C50) between 1st January 2001 and 31st December 2011. Women were included in the study population if they were aged between 50-80 years at diagnosis; had GMS eligibility from at least 1 year prior to 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 or treatment[17]. Prescriptions for statins dispensed in the year prior to breast cancer diagnosis were identified from the PCRS database, and women receiving statin therapy during this time were excluded from the study population.

Within the remaining cohort of women we identified de-novo post-diagnostic statin exposure from prescriptions dispensed between breast cancer diagnosis and the end of follow up (death or 31st December 2012, whichever occurred first). For each day of follow-up, we calculated statin dosing intensity based on the number of days' supply of statin received in the prior year. 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 following diagnosis; ii) women were identified as having high-intensity exposure from the first date they had taken a statin at an intensity of ≥80%, for longer than 1 year. Once allocated to an exposure category, women remained in this category to the end of follow-up.

COVARIATES & OUTCOMES

The following patient, tumour and treatment characteristics were obtained from the NCRI database: age (years) at diagnosis, smoking status at diagnosis (never, past, current, unspecified), tumour stage (I, IIa, IIb, IIIa, IIIb-c), histologic tumour grade (low, intermediate, high, unspecified), oestrogen (ER), progesterone (PR) and human epidermal growth factor-2 (HER-2) receptor status (positive, negative, unspecified) and receipt of chemotherapy (yes, no) or radiotherapy (yes, no) in the year after diagnosis. Anti-oestrogen therapy started in the year after breast cancer diagnosis (yes, no) was identified using the PCRS database. The PCRS database was also used to identify other prescribed, and potentially confounding medication use in the year prior to diagnosis (exposed, unexposed); aspirin[18], anti-diabetics,[18] non-steroidal anti-inflammatory drugs[19] and bisphosphonates[20]. The number of drug classes (4th level WHO-ATC classification) dispensed in the year before diagnosis was used as a proxy measure of co-morbidity [21]. Death certificates were used to determine the date and cause of death (all-cause or breast cancer-specific). Breast cancer-specific deaths were identified using SEER definitions for cancer-specific mortality (Table S1)[22].

STATISTICAL ANALYSIS

All analyses were performed using SAS® v9.3 (SAS® Institute Inc, Cary, NC). The proportion of de-novo post-diagnostic statin users was tabulated for each covariate and differences in the rates of post-diagnostic statin initiation across covariates were compared using univariate Poisson regression. Results were regarded as significant at a two-sided α-level of 0.05. The length of time from diagnosis to statin initiation was calculated and Kaplan Meier analysis was used to estimate the median duration of statin use from initiation to last exposure (censored at death or end of follow-up). 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.

For survival analyses, person time was calculated from the date of breast cancer diagnosis to the end of follow-up. Multivariate Cox regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between post-diagnosis de-novo statin use and breast cancer-specific and all-cause mortality. Patients were categorised as statin exposed (yes/no) from the time they received their first statin prescription. These exposures were lagged in 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[23]. The exposure lag time was set at 2 years, the median survival time after a breast cancer recurrence[24], and varied in sensitivity analyses (0, 1, 3, 4 years). The previously described covariates were selected for inclusion in multivariable survival analyses, based on prior knowledge of patient and clinical characteristics associated with breast cancer-specific mortality.

We conducted the following subgroup analyses. Firstly, we stratified analyses by high/low exposure intensity, as described above (time varying, lagged by 2 years). Secondly, analyses were stratified by statin solubility: lipophilic (atorvastatin, fluvastatin, simvastatin), hydrophilic (pravastatin, rosuvastatin), both[25]. Prior studies have suggested that only lipophilic statin use is associated with improved breast cancer outcomes[7]. Thirdly, analyses were stratified by ER status (positive, negative, unspecified) as preclinical studies have reported differential effects of statins on ER positive and negative breast cancer cell lines[26,27]. The presence of effect modification was assessed with the inclusion of an interaction term in the multivariable model.

We conducted sensitivity analyses in which the high intensity statin exposure was defined as ≥80% intensity for longer than two consecutive years; and the time without pre-diagnostic statin exposure was extended from 1 to 3 years. To explore our results in further detail we conducted a post-hoc analysis of lipophilic/hydrophilic statin use stratified by high/low exposure intensity.

RESULTS

COHORT & EXPOSURE CHARACTERISTICS

We identified 4,243 women from the linked PCRS-NCRI database with stage I-III breast cancer, aged between 50 and 80, and not receiving a statin prescription prior to their diagnosis (Figure 1). The median post-diagnostic follow-up for these patients was 4.9 years and their characteristics are described in Table 1. Within this cohort, we identified 837 (19.7%) women who initiated statin use after their breast cancer diagnosis. The overall rate of de-novo statin initiation was 42.8 new users per thousand patient years. Rates of statin initiation were significantly higher in women with a history of diabetes, lower tumour stage at diagnosis and positive oestrogen receptor status. The median length of 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 2,426 and 12,369 years respectively.

DE-NOVO STATIN USE AND MORTALITY

The results from univariate and multivariate analyses of statin-use on breast cancer-specific and all-cause mortality, adjusting for patient and tumour characteristics, co-prescribed medications, and comorbidities, are shown in Table 2. In these we found no association between de-novo statin initiation and breast cancer-specific mortality (HR 0.88, 95%CI 0.66, 1.17). Subgroup analyses in women taking statin at an intensity of ≥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 i) varying the exposure lag time from 0 to 4 years; ii) modifying the definition of high intensity exposure to ≥80% for longer than two consecutive years; and iii) increasing the pre-diagnostic period without statin exposure from one to three years (Table 3).

The results from subgroup analyses stratified by statin solubility characteristics (hydrophilic, lipophilic, or both) are presented in Table 2. We found no statistically significant associations between hydrophilic or lipophilic statin use and breast cancer-specific mortality. There appeared to be a nominal reduction in breast cancer-specific mortality for patients using lipophilic statins and we explored this further in a post-hoc analysis of lipophilic/hydrophilic statin use stratified by high/low exposure intensity. In this analysis, high intensity

lipophilic statin use (median duration of use 5.8 years; mean on-treatment exposure intensity was 88.2%) was not associated with a reduction in breast cancer-specific mortality (HR 1.05, 95%CI 0.67, 1.63; Table 2). There was no evidence of effect modification by ER status ($P_{interaction}$=0.69).

DISCUSSION

In this cancer registry-based cohort of newly diagnosed breast cancer patients with stage I-III disease, we did not observe an association between de-novo post-diagnostic statin use and a reduction in breast cancer-specific mortality. Our study population consisted of 4,243 women not taking a statin prior to their breast cancer diagnosis, of whom 837 initiated de-novo statin use. Within statin initiators we observed long durations of treatment, and high levels of use while on treatment, which suggests that our results are unlikely to be due to inadequate statin exposure. Additionally, in stratified analyses of high-intensity statin use (median duration >8yrs, mean treatment intensity >89%) we found consistent null or close to null estimates for all statins combined, and separately for hydrophilic or lipophilic statins. A statistically significant association with reduced 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 six months and, as noted above, high-intensity lipophilic statin use was not associated with a reduction in breast cancer-specific mortality.

Overall, our results are consistent with those from the small number of prior studies that have specifically examined de-novo post-diagnostic statin use and breast cancer-specific mortality[5,11]. In these studies, statin use initiated after diagnosis was not associated with a statistically significant improvement in breast cancer outcomes. Studies of de-novo statin use address the clinically relevant question of whether there is a benefit associated with initiating statin treatment after a breast cancer diagnosis, and their results may inform the design and conduct of clinical studies in the adjuvant setting. Several studies have also examined post-diagnostic statin use in women who initiated statin treatment prior to their breast cancer diagnosis,[6–12] with some reporting large statistically significant reductions in breast cancer recurrence and mortality[7,9], in particular for users of lipophilic statins[7]. However, it is unclear from their results what benefit may be attributable to the post-diagnostic initiation of statin treatment.

The results from observational studies of statin use and breast cancer outcomes must be interpreted with care as 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[28–31]. This has been shown to cause appreciable residual confounding if unaccounted for in analyses, and a tendency to overestimate any beneficial effect of statins[32,33]. Observational studies have frequently attributed a variety of non-cardiovascular health benefits to statin use[30,34,35] including protection from cancer incidence and mortality[36,37]. However, secondary analyses of randomized trial data have not confirmed these associations[35,38], and many of the findings from observational studies have subsequently been attributed to the preferential prescribing of statins to healthier patients[28,35]. There is some evidence to indicate that statins are also selectively prescribed for women with better prognosis breast cancer. In studies by Snyder et al, women with later stage breast cancer were considerably less likely to be screened for hypercholesterolemia after their diagnosis[39,40], and in our study women with later stage disease had a significantly lower rate of post-diagnostic statin initiation (Table 1). Patients with poor prognosis cancer are also more likely to discontinue statin use after their diagnosis[41]. Fully accounting for the selective prescribing of statins in analyses of breast cancer outcomes is challenging. For example, in the only study reporting a significant association between statin use and breast cancer recurrence[7], the observed benefit was solely attributable to reductions in locoregional (ipsilateral, lymph node) and contralateral recurrences, with no reduction in distant recurrence. While standard baseline prognostic information (e.g. stage, grade, receptor status) was adjusted for, there are additional strong clinical predictors of locoregional recurrence (such as the presence of residual disease after neo-adjuvant therapy, sub-optimal lymph node evaluation at surgery, and the presence of positive tumour margins after surgery[42–45]), which may influence the prescribing and use of statins. Additionally, locoregional recurrences are strongly influenced by patients' healthcare choices, in particular decisions to forego additional surgery to re-excise positive tumour margins[45] and non-compliance with adjuvant radiation[46,47], chemotherapy or hormonal therapy[48]. The presence of residual confounding must therefore be carefully considered in studies reporting beneficial effects of statins on breast cancer outcomes. Finally it should also be borne in mind that locoregional and contralateral recurrences are associated with considerably lower mortality than distant metastatic recurrences[46,49,50]. Therefore, the reductions in locoregional and contralateral recurrence observed in some studies of statins may not translate in to similar reductions in breast cancer-specific mortality. This

may also explain differences between the mortality results we report here and those from previous studies examining breast cancer recurrence[7].

While we observed no overall association between de-novo statin use and breast cancer-specific mortality in an unselected population, there may be specific molecular subgroups of patients for whom statin treatment could be beneficial. In a window-of-opportunity trial by Bjarnadottir et al., in which women were given high dose atorvastatin (80mg/day) for two weeks between diagnosis and surgical resection of their breast tumour, statin treatment was associated with a statistically significant reduction in Ki67 proliferation index among the subgroup of women with tumours expressing HMGCR.[51] However, while the mean absolute reduction in Ki67 observed in this subgroup (4.6%) was statistically significant, it is less than that obtained with established adjuvant treatments for breast cancer, such as hormonal therapy (63.9%), and the clinical relevance of this observation is unclear[52]. Nevertheless, it would be worthwhile to evaluate tumour expression of HMGCR as a predictor of response to statin treatment in future observational studies.

Some,[7,12] but not all,[9,10] studies have suggested that associations between statin use and breast cancer outcomes may also be modified by the solubility characteristics of individual statins. However, in our analyses we did not observe a difference in effect between hydrophilic and lipophilic statins, overall or with high intensity use. The reasons for this between-study heterogeneity are unclear, although differences in the timing of cohort enrolment should be considered. The availability and indications for use of hydrophilic and lipophilic statins have varied considerably over time and this may result in differences between cohorts in the prescribing patterns of hydrophilic versus lipophilic statins[53,54].

Our study has a number of strengths, including the use of prospectively collected breast cancer outcome and prescription refill exposure data. However, there are also some potential limitations. We could not verify whether women took the medication they received and non-compliance may have resulted in misclassification of exposure. However, we expect that women are unlikely to continue filling prescriptions for a medication they are no longer taking. We did not have information on lifestyle factors that may influence disease progression, such as obesity, and the potential for residual confounding in our analyses should be considered. Finally, when generalising our results, it must be remembered that our study population was a subset of breast cancer cases defined by age and socioeconomic eligibility for the GMS scheme.

In conclusion, 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. We also observed no evidence of effect modification by statin solubility or hormone receptor characteristics.

ACKNOWLEDGEMENTS

We would like to thank the National Cancer Registry Ireland and the Irish Health Services Executive Primary Care Reimbursements Services for providing access to the data upon which this study was based. In particular, we are grateful to the Data Team at the National Cancer Registry Ireland for linking the datasets and Dr. Sandra Deady and Mr Christopher Brown for preparing these for analysis. The interpretation and reporting of these data are the responsibility of the authors and should in no way be seen as the official policy or interpretation of the National Cancer Registry Ireland or the Irish Health Services Executive Primary Care Reimbursements Services.

Study Covariate / Outcome	Definition
Drug Exposures	**WHO ATC Drug Codes**
Aspirin	B01AC06, M01BA03, N02BA01, N02BA51, N02BA71
Anti-diabetic	A10
Bisphosphonate	M05BA, M05BB
Hydrophilic Statin	C10AA03, C10AA07, C10BX02,
Lipophilic Statin	C10AA01, C10AA02, C10AA04, C10AA06, C10BA, C10BX01, C10AA05, C10BX03
Other NSAID	M01A
Hormonal Therapy	L02BA01, L02BA02, L02BA03, L02BG03, L02BG04, L02BG06
Tumor Receptor Status	**NCRI Coding Definition**
ER, PR	Estrogen and progesterone receptor activity was defined as positive if recorded by the NCRI database as unclear/possibly, some receptor activity or positive/strong.
HER2	HER2 receptor activity was defined as positive by immunohistochemistry if recorded by the NCRI database as score 2+, weak/strong positive or weak/strong complete membrane staining in >10% of tumor cells. HER2 receptor activity was defined as positive by fluorescence in-situ hybridization if recorded by the NCRI database as weak/strong positive or some/strong amplification. Where IHC & FISH results were recorded, FISH results were used.
Breast Cancer-Specific Mortality	**ICD10 Codes**
From Howlader *et al.* [55]	B201-B219; C50, D05, D24, D486 C445, D225, D485 C000–C444, C446–C499, C510–D049, D060–D224, D226–D239, D250–D484, D487–D489 N610–N649

TABLE S1: STUDY COVARIATE / OUTCOME DEFINITIONS

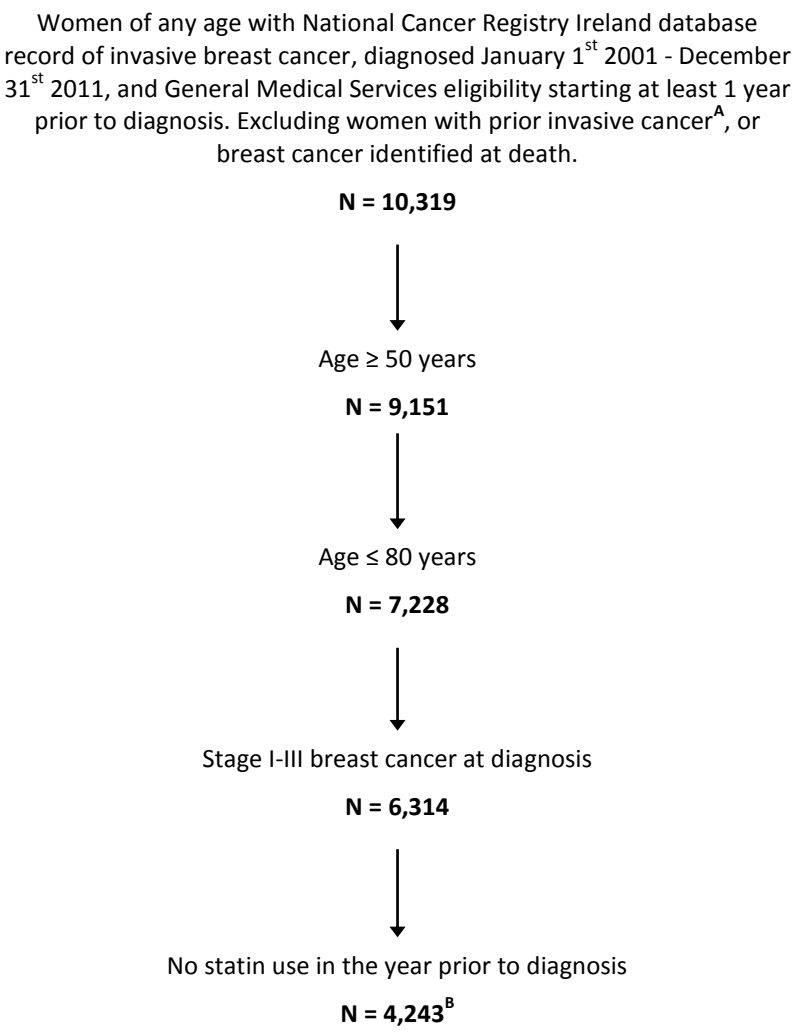

Figure 1. Study inclusion/exclusion criteria.

A) With the exception of non-melanoma skin cancer.

B) Patients with an event prior to the completion of a 2 year exposure lag were excluded from the main analyses.

TABLE 1: CHARACTERISTICS OF WOMEN INCLUDED IN THE STUDY COHORT, BY POST-DIAGNOSIS STATIN EXPSOURE, WITH STATIN INITIATION RATE

Characteristic		De-novo statin use post breast cancer diagnosis [A, B]		
		Non-user *N* = 2,759	User *N* = 837	Initiation rate (per 1000 person years)
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
	Past	306 (11.1)	106 (12.7)	47.5
	Never	1,324 (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
	No	2327 (84.3)	684 (81.7)	41.6
NSAID – (%) [C]	Yes	1,178 (42.7)	384 (45.9)	44.8
	No	1581 (57.3)	453 (54.1)	41.2
Anti-diabetic – (%) [C] *	Yes	60 (2.2)	38 (4.5)	74.7
	No	2699 (97.8)	799 (95.5)	41.9
Bisphosphonate – (%) [C]	Yes	198 (7.2)	46 (5.5)	39.4
	No	2561 (92.8)	791 (94.5)	43.0
Tumour stage – (%) [D] *	I	917 (33.2)	297 (35.5)	44.1
	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
	Intermediate	1,357 (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 – (%) *	Negative	471 (17.1)	110 (13.1)	35.3
	Positive	2,028 (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
	Positive	1,393 (50.5)	415 (49.6)	44.7
	Unspecified	649 (23.5)	243 (29.0)	42.7
HER2 – (%)	Negative	1,679 (60.9)	419 (50.1)	40.8
	Positive	339 (12.3)	99 (11.8)	44.7
	Unspecified	741 (26.9)	319 (38.1)	45.1
Chemotherapy – (%) [E]	Yes	1,123 (40.7)	344 (41.1)	43.2
	No	1636 (59.3)	493 (58.9)	42.5
Anti-Oestrogen – (%) [E]	Yes	2,065 (74.9)	642 (76.7)	43.8
	No	694 (25.1)	195 (23.3)	39.9

***Difference in statin initiation rate *P*<0.05 (Poisson regression)**

IQR: Inter-Quartile Range. **ER**: Oestrogen Receptor. **PR**: Progesterone Receptor. **HER2**: Human Epidermal Growth Factor Receptor 2. **NSAID**: Non-Steroidal Anti-Inflammatory Drug.

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, 31st 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) AJCC Cancer Staging Manual 6th Edition. Springer, 2002.

E) 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 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]**
Statin exposure – yes/no [C]											
Non-user	2,759	-	-	-	12,369	692 (55.9)	Ref -	Ref -	398 (32.2)	Ref -	Ref -
Statin user	837	2.1	6.7	86.3	2,426	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	2,759	-	-	-	12,369	692 (55.9)	Ref -	Ref -	398 (32.2)	Ref -	Ref -
Statin user - low intensity	346	2.4	0.7	82.1	1,165	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	1,261	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	2,759	-	-	-	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)	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	1,579	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	2,759	-	-	-	12,369	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)**	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)**	9 (11.2)	0.37 (0.19, 0.72)	**0.39 (0.20, 0.76)**
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)

Ref: Referent Group, **HR**: Hazard Ratio, **CI**: Confidence Interval.

A) Deaths / 1,000 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-oestrogen therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID & anti-diabetic medication use (yes, no).

C) Statin exposure lagged by 2 years 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

E) Analysis conducted post-hoc.

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 & 4 years											
Statin exposure – yes/no (lag 0 years)											
Non-user	3,038	-	-	-	18,339	909 (49.6)	Ref -	Ref -	562 (30.7)	Ref -	Ref -
Statin user	1,205	2.5	5.7	85.6	4,496	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	3,058	-	-	-	15,291	804 (52.6)	Ref -	Ref -	482 (31.5)	Ref -	Ref -
Statin user	1,033	2.3	6.7	86.0	3,354	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	2,425	-	-	-	9,776	564 (57.7)	Ref -	Ref -	308 (31.5)	Ref -	Ref -
Statin user	640	1.9	6.1	85.9	1,686	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	2,046	-	-	-	7,540	427 (56.6)	Ref -	Ref -	221 (29.3)	Ref -	Ref -
Statin user	492	1.7	6.1	85.7	1,117	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	2,759	-	-	-	12,369	692 (55.9)	Ref -	Ref -	398 (32.2)	Ref -	Ref -
Statin user – low intensity	480	2.5	1.6	82.8	1,613	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	2,670	-	-	-	12,096	677 (56.0)	Ref -	Ref -	392 (32.4)	Ref -	Ref -
Statin user	796	2.2	6.7	86.1	2,307	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)

Ref: Referent Group, **HR**: Hazard Ratio, **CI**: Confidence Interval.
A) Deaths / 1,000 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-oestrogen therapy in year post diagnosis (yes, no); aspirin, bisphosphonate, NSAID & anti-diabetic medication use (yes, no).
C) Statin exposure lagged by 2 years in analysis.