Statins and Breast Cancer in Postmenopausal Women without Hormone Therapy

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Abstract. *Background: Epidemiological data on the association between statin use and risk of breast cancer among overweight or obese postmenopausal women who have never used hormone therapy (HT) is limited. Patients and Methods: A hospital-based case-control study was conducted in Fargo, ND, USA. Cases were overweight or obese, postmenopausal White women without a history of HT use who were newly diagnosed with breast cancer. Controls were White women without clinical cancer who were seen at the same hospital for an annual physical examination. Results: From a patient population aged 55 to 81 years old, data were obtained on 95 cases and 94 controls. Overall, there was no association between the use of statins and breast cancer risk odds ratio (OR)=1.3 (95% confidence interval (CI) 0.7-2.5). However, risk varied by hormone receptor status. Compared to non-users, obese women who used hydrophobic statins had an elevated risk of progesterone receptor-negative (PR^-) breast cancer OR=4.0 (95% CI 1.2-13.8), but not of tumors with other hormone receptor profiles. The risk for breast cancer was also significantly increased among overweight women who used hydrophobic statins for less than or equal to 4 years OR=4.1 (95% CI 1.2-14.4). Conclusion: This observational study found an increased risk of breast cancer related to duration of statins use and PR^- among postmenopausal women.*

Breast cancer is the most commonly diagnosed cancer among women in the United States with an estimated 192,569 new cases being diagnosed in 2009. Mortality from breast cancer ranks second only to lung cancer, with 40,470 breast cancer deaths predicted in 2009 (1). Risk for breast cancer increases with age, with 78% of all breast carcinomas occurring in women of more than 50 years of age and 86% of breast cancer deaths occurring in this age group (2).

Although the etiology of most cases of breast cancer remains unknown, excess weight has been reported to increase the risk of breast cancer among postmenopausal women that do not use hormonal replacement therapy (HRT) (3, 4). Morimoto *et al*. (3) found that among non-users of HRT, heavier women (body mass index (BMI)>31.1 kg/m^2) had a significantly increased risk of postmenopausal breast cancer (relative risk (RR)=2.52; 95% confidence interval (CI): 1.62-3.93), compared to slimmer women (baseline BMI≤22.6). Similarly, Huang *et al*. (5) reported a significant positive RR for breast cancer (RR=1.59; 95% CI: 1.09-2.32) when comparing women with a BMI>31 kg/m^2 to those with a BMI<20 kg/m^2 among non-users of HRT.

A recent study (4) on the tumor-specific expression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoAR) in breast cancer has revealed that HMG-CoAR is expressed in various proportions and intensities in the cytoplasm of the tumor cells, sometimes with a membranous pattern. Obesity was significantly associated with a high HMG-CoAR expression assessed both as a high (>50%) fraction of positive cells (RR=2.06; 95% CI: 1.20-3.51), and a strong staining intensity (RR=2.33; 95% CI: 1.08-5.02). The importance of HMG-CoAR in cancer development has been indicated from studies on statins. Statins act as reversible HMG-CoAR inhibitors (6).

Most previous studies have reported no association for statins use and breast cancer risk (7-16). However, the majority of women in these studies used HRT and included women of normal weight. Furthermore, the studies were also subject to significant methodological shortcomings such as ascertainment of cases and lack of adjustment for confounders. Finally, these published studies have not reported on the hormonal phenotype estrogen receptor (ER)/

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Key Words: Breast cancer, postmenopausal women, overweight, obese, Statins, epidemiology.

Table I. *Distribution of 95 cases of newly diagnosed breast cancer and 94 controls according to demographic and clinical characteristics.*

Variables	Cases		Controls		*p*-Value
	n	%	n	%	
Age at diagnosis (years)					0.0020
55-64	43	45	61	65	
65-81	52	55	33	35	
Median (range)	65 (55-79)		61 (55-81)		
Body mass index (kg/m^2)					0.0900
Overweight	33	35	47	50	
Obese	62	65	47	50	
Median (range)	32 (25-54)		30 (25-54)		
Smoking status					0.2200
Never	56	59	65	69	
Past	27	28	23	24	
Current	12	13	6	7	
Alcohol use					0.2200
No	55	58	46	49	
Yes	40	42	48	51	
Age at Menarche (years)					0.7100
9-11	19	20	8	8	
12-13	42	44	19	20	
14-18	31	33	10	11	
Missing	3	3	57	61	
Median (range)	13 (9-17)		13 (10-18)		
Age at menopause (years)					0.3200
<47	24	25	22	23	
47-51	27	28	29	31	
52-55	30	32	35	37	
≥56	7	7	8	9	
Missing	7	7	-	-	
Median (range)	50 (34-60)		51 (29-60)		
Parity					0.1100
Nulliparous	14	15	7	7	
Ever parous	81	85	87	93	
History of hysterectomy					0.5500
No	79	83	75	80	
Yes	16	17	19	20	
Family history of breast cancer					0.0004
No	53	56	75	80	
Yes	42	44	19	20	
Type of statin use (n=71)	(n=40)		(n=31)		0.2200
Hydrophobic (n=67)	39	41	28	30	
Atorvastatin (Lipitor)	32	34	11	12	
Simvastatin (Zocor)	6	6	16	17	
Lovastatin (Mevacor)	-	-	1	1	
Fluvastatin (Lescol)	1	1	-	-	
Hydrophilic (n=4)	1	1	3	3	
Pravastatin (Pravacol)	1	1	2	2	
Rosuvastatin (Crestor)	-	-	1	1	
None (n=118)	55	58	63	67	
Duration of statin use (years)+	3 (1-6)		4 (1-7)		0.7100
History of type 2 diabetes					0.0800
No	73	77	82	87	
Yes	21	22	12	13	
Missing	1	1	-	-	
Multivitamin use					0.9300
No	36	38	35	37	
Yes	59	62	59	63	
Mammogram within last 2 years					0.0001
No	34	36	10	11	
Yes	52	55	84	89	
Missing	9	9	-	-	

+Based on cases (n=38) and controls (n=30).

Table II. *Distribution of 95 cases of newly diagnosed breast cancer according tumor characteristics.*

Variables	Cases	
	n	%
Stage of breast cancer at diagnosis		
I	59	62
II	25	27
III	3	3
IV	3	3
Missing	5	5
Tumor size (cm)		
≤2	75	79
>2	11	12
Missing	9	9
Hormonal receptor status of tumor		
Estrogen receptor		
Positive	82	86
Negative	10	11
Missing	3	3
Progesterone receptor		
Positive	64	67
Negative	28	30
Missing	3	3
Her2neu receptor status		
Positive	18	19
Negative	63	66
Missing	14	15
Tumor grade		
Well-differentiated	23	24
Moderately-differentiated	48	51
Poorly-differentiated	23	24
Missing	1	1
Type of breast cancer		
Invasive ductal	56	59
Ductal carcinoma *in situ*	15	16
Invasive lobular	10	11
Invasive mammary	5	5
Invasive mucinous	3	3
Other	6	6

progesterone receptor (PR), of tumors arising during statin use. The aim of this study was to examine the association between statin use and risk of breast cancer among overweight or obese postmenopausal women who had never used HRT.

Patients and Methods

A retrospective analysis of medical charts of patients newly diagnosed with breast cancer between January 2005 and December 2008 was performed. Cases were identified from the cancer registry of Meritcare Hospital, North Dakota, USA, serving the Fargo Metropolitan Area. Controls were identified from the primary care database of the same hospital. The population base of this area, according to the 2006 estimate (17), is approximately 240,000. The majority (95%) of the population served in this area is White. The North Dakota Cancer Registry releases annual cancer statistics when the registry's data is estimated to be 95% complete for any given cancer-reporting year. The study was approved by the Institutional Review Boards of Meritcare Hospital and the University of North Dakota.

Study design. Data on age at diagnosis, height, weight, age at menarche, parity, age at menopause, family history of breast cancer, history of hysterectomy, alcohol use, smoking status, type 2 diabetes, type of breast cancer, stage of breast cancer at diagnosis (TNM), tumor grade and size, hormonal receptor status, Her-2/neu receptor status, type of statin use, duration of use, multivitamin use, and mammography within the last two years were collected. Information was obtained for the period within one year prior to diagnosis for the cases and prior to the physical examination for the controls.

The inclusion criteria for the cases were females with histologically confirmed breast cancer as a primary site with the cancer diagnosed between January 2005 and October 2008 using a pathology report from the medical records, age between 55 and 81, postmenopausal and a BMI of 25.0 kg/m^2 or greater. Age 55 years and older was used to approximate menopausal status. The exclusion criteria included diagnosis of any cancer other than primary breast cancer, any history of HRT use and diagnosis outside the study period.

The inclusion criteria for the controls were females who had an annual physical examination between January 2005 and October 2008 at the same hospital as the cases, age between 55 and 81, postmenopausal, a BMI of 25.0 kg/m^2 or greater and without any cancer. The exclusion criteria included diagnosis of any cancer, any history of HRT use and diagnosis outside the study period. Because of the small number of patients who were not White, the study was restricted to Whites.

Statin use was further classified as hydrophobic-only (lovastatin, simvastatin, fluvastatin, or atorvastatin) or hydrophilic-only (pravastatin or rosuvastatin) users (18). It was not possible to evaluate dose because the majority of the patients received the standard dosage for statin. It was not possible to use other lipid-lowering medication (bile acid sequestrants, niacin, or fibric acid derivatives) users as a second comparison group because of the small number of users. Statin users were defined as women who had used a statin for at least a month. In order to assess the effect of duration of use, for each category of statins the risks associated with use for less than or equal to 4 years and greater than 4 years were evaluated. Women who used statins for less than a month were excluded from all the analyses since short-term use of statins is unlikely to have an effect on breast cancer risk.

Statistical analysis. Unadjusted mean or median values were calculated for all the continuous variables and frequency distributions were calculated for all the categorical variables. The comparisons of cases and controls on demographics, reproductive and menopause variables were performed using Wilcoxon signed-rank test or *t*-test for the continuous variables and with Chi-square test for the categorical variables. Odds ratios (OR) and 95% CI were estimated using unconditional logistic regression to compare the risk of breast cancer for women by statins use status. The multivariable logistic regression included terms for age at diagnosis, age at menopause, family history of breast cancer, parity and statins use. All the *p*-values are two-sided. An interaction between yes/no use of statins and age 65 years and older/younger than 65 years was tested using

the likelihood ratio (LR) statistic by comparing the maximum log likelihood of the model with and without the interaction term. Statistics were performed using SAS (SAS Institute, Cary, NC, USA; Version 9.1.3 Users Guide). All the statistical tests were two-tailed with $p<0.05$ considered to be significant.

Results

This study included 95 postmenopausal women with newly diagnosed breast cancer and 94 controls. The median age (range) was 65 (55-79) years for the women with breast cancer and 61 (55-81) years for the controls. The breast cancer patients had a significantly higher prevalence of family history of breast cancer (44% *vs*. 20%, respectively; $p=0.0004$) (Table I). The majority (65%) of the patients were obese. The controls had significantly more mammogram screening within the last two years than the cases ($p=0.0001$). Breast cancer risk associated with the use of statins compared with no use was similar among the women 65 years of age and older compared with the women younger than 65 years of age (*p*-value for interaction, 0.08).

The majority of breast cancer cases were diagnosed at American Joint Committee on Cancer stage I (62%) or stage II (27%); most of the tumors were ER^+ (86%); and histology was primarily ductal (59%). Most of the breast tumors were less than 2 cm and 75% were well to moderately-differentiated (Table II).

Overall, the multivariable model showed no association between the use of statins and breast cancer risk OR=1.3 (95% CI 0.7-2.5). When evaluated separately, hydrophobic statin use was not associated with breast cancer risk. However, the risk for breast cancer was significantly increased among overweight women who used hydrophobic statins for less than or equal to 4 years OR=4.1 (95% CI 1.2-14.4) (Table III). Nulliparous women who had a BMI≥29 kg/m^2 had a significantly increased risk for breast cancer than ever parous women OR=6.9 (95% CI 1.4-34.8).

Finally, the risk varied by hormone receptor status. Compared to non-users, the obese women who used hydrophobic statins had an elevated risk of PR negative breast cancer OR=4.0 (95% CI 1.2-13.8) (Table IV), but not of tumors with other hormone receptor profiles, tumor size, grade, or type of breast cancer (data not shown).

Table III. *Odds ratios (OR) and 95% confidence interval (95% CI) multivariable logistic regression of newly diagnosed breast cancer patients and controls by body mass index.*

	Body mass index (kg/m^2)		
	≥25	≥29	≥33*
Number (cases, controls)	(88, 94)	(67, 60)	(40, 28)
Family history of breast cancer			
No	Ref	Ref	Ref
Yes	2.6 (1.3-5.1)	1.7 (0.8-3.9)	1.4 (0.5-4.1)
Parity			
Ever parous	Ref	Ref	Ref
Nulliparous	2.5 (0.9-7.3)	6.9 (1.4-34.8)	5.6 (0.6-56.5)
Any statin use			
No	Ref	Ref	Ref
Yes	1.3 (0.7-2.5)	1.6 (0.7-3.5)	2.4 (0.7-7.6)
Type of statin use			
None	Ref	Ref	Ref
Hydrophobic	1.4 (0.7-2.8)	1.8 (0.8-4.1)	2.4 (0.7-7.6)
Duration of any statin use			
>4 years	Ref	Ref	Ref
≤4 years	3.6 (1.1-12.5)	2.6 (0.6-12.4)	-†
Duration of hydrophobic statin use			
>4 years	Ref	Ref	Ref
≤4 years	4.1 (1.2-14.4)	3.1 (0.6-15.0)	-†

Age at diagnosis and age at menopause were included in the multivariable logistic regression as a continuous variable. *Cut-off points represent tertiles. †Sample size was too small to compute an OR and 95% CI.

Discussion

Overall, this case-control study did not suggest an association between statin use and breast cancer risk. However, this is the first report to suggest a significantly increased risk of breast cancer among overweight statin users of 4 years or less, and a significantly increased risk of progesterone PR^- tumors among obese women who used hydrophobic statin compared to non-users. However, these findings were limited by the small number of exposed cases.

Most previous studies were consistent with the present finding of no association of statins use and breast cancer risk (7-16). The majority of studies showed no trend in breast cancer risk related to increasing duration of statin use (7, 9, 10, 12, 14). A significantly increased risk of breast cancer among overweight women who used statins for 4 years or less was found in the present study, in accordance with at least two observational studies that reported a reduced risk with statin use for longer than 4 years and longer than 5 years, respectively (8, 11).

Researchers have hypothesized hydrophobic statins to have antiproliferative effects on breast cancer cells (19-21). For example, lovastatin has been shown to stabilize the cell cycle kinase inhibitors p21 and p27 and to arrest breast cancer cell lines in the G_1 phase of the cell cycle (22). Cauley *et al*. (7, 23) reported that hydrophobic statin (*i.e*. simvastatin, lovastatin, and fluvastatin) use was associated with an 18% lower breast cancer incidence hazard ratio (HR)=0.82 (95% CI 0.70-0.97, $p=0.02$) and HR=0.28 (95% CI 0.09-0.86, $p<0.03$) respectively. In the present study,

Table IV. *Association between statin use and risk of breast cancer among obese postmenopausal women by ER, PR and Her2neu status.*

Type of statin use	Controls (n=94)		ER^+ (n=82)				ER^- (n=10)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Never use	34	72	28	54	1.0	Ref	5	71	1.0	Ref
Hydrophobic[a]	12	26	24	46	2.1	0.8-5.0	2	29	1.0	0.2-6.0
Type of statin use	Controls (n=94)		PR^+ (n=64)				PR^- (n=28)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Never use	34	72	27	61	1.0	Ref	6	40	1.0	Ref
Hydrophobic	12	26	17	39	1.4	0.5-3.6	9	60	4.0	1.2-13.8
Type of statin use	Controls (n=94)		$Her2neu^+$ (n=11)				$Her2neu^-$ (n=41)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Never use	34	72	5	45	1.0	Ref	26	63	1.0	Ref
Hydrophobic	12	26	6	55	2.6	0.6-10.9	15	37	1.5	0.6-3.8

OR, Odds ratio; 95% CI, 95% confidence interval. All ORs adjusted for age as a continuous variable. [a]Atorvastatin, fluvastatin, lovastatin or simvastatin.

short-term (≤4 years) use of hydrophobic statins among overweight women increased the risk for breast cancer. The inconsistency with the present results may reflect differences in the study populations and the misclassification of atorvastatin (which was not included in the hydrophobic class (7)). Most importantly, the present study did not include any postmenopausal women who used HRT, while 45% of women were HRT users in one study (7) and 57% in the other study (23).

A significantly increased risk of PR^- tumors was found among the obese women who used hydrophobic statins compared to the non-users. We are unaware of any biological mechanisms to support an increased risk of PR^- tumors with hydrophobic statins use. A recent *in vitro* and *in vivo* preclinical study has now shown that different human breast cancer phenotypes are differentially responsive to statins (24), with ER/PR-negative breast carcinomas being most responsive to the anticancer effects of hydrophobic statins. Kumar *et al*. (25) found that statin users were less likely to have breast carcinomas not expressing ER and PR (11% of statin users had carcinomas that were ER^-/PR^- *versus* 19% of non-users, $p=0.02$). However, this was a case-only study and was therefore subject to effects on numerators, effects on denominators or effects on both. Interestingly, Suzuki *et al*. (26, 27) reported a positive association between obesity and the development of ER^+/PR^+ tumors that was confined to never-users of postmenopausal hormones. The possibility that statins might be capable of throwing an invisible switch to induce the expression of hormone receptors in breast carcinomas before their clinical diagnosis is plausible and is worth exploring in the future.

Some limitations in the present study are acknowledged. It is possible that this study was not powered to evaluate the association between statins use and breast cancer risk stratified by overweight or obesity and, therefore, the findings may be due to chance. Study limitations also include the relatively low prevalence of statin use and the limited power to examine long-term (>5 years) effects. Exposure misclassification cannot be ruled out, those who had statins reported in their medical charts but did not subsequently take the medication might have been misclassified as users. This would produce a bias toward the null. Residual confounding is always possible in observational studies. Indeed, a recent comparison of observational study and randomized clinical trial results, with respect to findings regarding postmenopausal hormone use and coronary heart disease, showed that the discrepancy in findings could be substantially explained by confounding (28). Finally, the results may be biased if the prevalence of statin use among the controls was not the same as that of the population from which the cases arose.

As has been previously reported, no significant difference in breast cancer risk by statins use compared to non-use was found. However, a significantly increased risk of breast cancer among overweight statin users of 4 years or less, and a significantly increased risk of PR^- tumors among obese statin users compared to non-users was found. Future studies of statins and breast cancer should assess associations with individual statins or statin categories among non-HRT users and hormonal phenotype of the tumor because class differences may exist.

Acknowledgements

The authors wish to thank the Meritcare Staff in the Department of Quality Improvement for their help with the electronic medical records.

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Received July 11, 2009
Revised October 9, 2009
Accepted October 15, 2009