Research Paper

Effect of Lipophilic and Hydrophilic Statins on Breast Cancer Risk in Thai Women: A Cross-sectional Study

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Abstract

Background: Statins are proposed as a chemoprevention agent for breast cancer due to their anti-inflammatory effect. The effects of lipophilic and hydrophilic statins on breast cancer risk might be different due to their different pharmacologic properties. Therefore, this study aimed to assess a casual-effect of lipophilic and hydrophilic statins on breast cancer risk using a counterfactual framework approach.

Methods: A cross-sectional study of 15,718 women who were screened for breast cancer at Mammographic center, Ramathibodi Hospital, Bangkok, Thailand, was conducted during September 2011 to 2012. A counterfactual framework approach was applied to assess causal effects of treatments (i.e., lipophilic and hydrophilic statins) on outcome (i.e. breast cancer). Multi-logit and logistic regression models were used for treatment and outcome models, respectively. An inverse probability weight regression analysis (IPWRA) was then applied to estimate potential outcome mean (POM) and average treatment effect (ATE) by combining the outcome and treatment models.

Results: Breast cancer risks were 0.0072 (95% CI: 0.0055, 0.0089), 0.0051 (95% CI: 0.0008, 0.0095), and 0.0038 (95% CI: 0.002, 0.0056) for non-statin users, hydrophilic, and lipophilic statin users, respectively. The estimated risk differences were -0.0021 (95% CI: -0.0067, 0.0026) and -0.0034 (95% CI: -0.0059, -0.0009) for hydrophilic and lipophilic statins respectively. The number needed to treat for hydrophilic and lipophilic statins were 2.1 (95% CI: -2.6, 6.7) and 3.4 (95% CI: 1.0, 5.9) per 1000 subjected, respectively.

Conclusions: Our results suggested that using lipophilic statin could significantly reduce risk of breast cancer in Thai women.

Key words: breast neoplasms; hydroxymethylglutaryl-CoA Reductase Inhibitors; hydrophilic statin; lipophilic statin; counterfactual approach

Introduction

Breast cancer is the most common cancer in women across the world. The age standardized incidence rate is 89.2 per 100,000 in the USA [1] and 26.4 per 100,000 in Thailand [2]. Primary prevention of breast cancer is thus very important for decreasing disease burden. Recently, 3-hydroxy-3-methylglu-taryl-coenzyme A reductase (HMG-CoAR) inhibitors (statins) have been proposed as a potential class of chemoprevention agents due to their immunomodulatory and anti-inflammatory effects [3, 4]. By blocking HMG-CoAR, statins can inhibit the mevalonate pathway and reduce cholesterol

precursors such as farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP) [5]. Depletion of FPP and GPP arrests cell-cycle progression could induce apoptosis, suppress angiogenesis and inhibit tumor growth and metastasis in breast cancer cells [6, 7].

However, clinical evidence for an effect of statin use on breast cancer risk shows inconsistent results, in which some observational studies reported a higher risk of breast cancer in statin users [8-10], whereas others showed protective effects [11-14]. These inconsistent findings might be explained by inadequate sample sizes, different study designs, or analyses, and particularly adjusting for confounding factors in the previous studies.

A meta-analysis that included seven randomized control trials (RCT) was performed to assess the efficacy of statin use in the prevention of breast cancer [15, 16]. Although their total sample size was very large, they did not detect a treatment effect; this may have been due to high heterogeneity, perhaps explained by pooling studies that used different types of statins (i.e. lipophilic and hydrophilic) together. The effects of lipophilic and hydrophilic statins on breast cancer risk might be different due to their different pharmacologic properties and thus pooling them in one analysis may have obscured a protective effect.

The counterfactual approach has been applied in health science [17-19] and economic [20] research to assess treatment efficacy where RCTs cannot be conducted for ethical reasons or high cost. The approach has become more popular in recent years where electronic records of observational data from routine clinical practice are available. Therefore, this study was conducted to assess the effect of statin types (i.e. lipophilic and hydrophilic) on breast cancer incidence using a counterfactual analysis approach.

Materials and Methods

Study setting and participants

The study design was cross-sectional and included 15,718 women, aiming to develop and validate a breast cancer risk prediction model in Thai adult women [21]. This risk prediction model was intended to prioritize women for receiving an organized breast cancer screening program in Thailand. In brief, breast cancer screening data were retrieved from the mammographic center, Ramathibodi Hospital from September 2011 to September 2012. Women with a previous history of invasive breast cancer and ductal carcinoma in situ (DCIS) were excluded.

Self-reported risk factors for breast cancer (i.e. age, family history of breast and ovarian cancers in the first-degree relative, reproductive data (including age at menarche and at first live birth, breastfeeding, and menopausal status), external hormone usage (i.e. hormonal replacement therapy (HRT), oral contraceptives(OC), and medroxyprogesterone injection), history of breast biopsy, body mass index (BMI) , health risk behavior (i.e. smoking and alcohol intake), and underlying diseases (i.e. diabetes mellitus (DM), hypertension, dyslipidemia, and chronic kidney disease (CKD))) were collected by interview. These underlying diseases were also verified with medical databases that contained the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The ICD-10 were coded by trained hospital staffs.

Details regarding statin usage (i.e. type of statin, and duration of use) were retrieved from the Drug Databases, Medical Statistic Unit, Ramahibodi Hospital. These data were then merged with mammographic screening data. Statins were classified as hydrophilic (i.e., pravastatin and rosuvastatin) or lipophilic (i.e., atorvastatin, simvastatin, pitavastatin, and fluvastatin) [22]. Statin use was defined as using any types of statin for at least 6 months.

The primary outcomes of interest were combined invasive breast cancer and DCIS, which were verified by pathological diagnosis. This study was approved by the Institutional Review Board of Ramathibodi Hospital, Mahidol University and complied with the principles of Declaration of Helsinki. All participants provided written inform consent.

Statistical analysis

Characteristics of subjects were described by lipophilic and hydrophilic statin user and non-user groups using frequency (%) and mean if they were categorical and continuous data, respectively. These characteristics were compared using Chi-square and t-tests, respectively. Treatment effect of statins was determined using a counterfactual analysis [23, 24]. Two equations were simultaneously constructed as follows: First, the treatment model was constructed by fitting treatment variable (i.e., hydrophilic statin vs lipophilic statin vs non-statin using) on covariates (i.e. age, BMI, DM, hypertension, CKD, age at menarche and menopause, smoking, alcohol drinking, OC and HRT use) using multi-logit equation. Probabilities of receiving and not receiving treatments were then estimated. Second, the outcome model was constructed using a logit equation by fitting the breast cancer variable on the covariates (i.e. age, family history of breast and ovarian cancers in the first-degree relative, age at menarche and at first live birth, breastfeeding, menopausal status, HRT, OC), and medroxyprogesterone injection use, history of

breast biopsy, BMI, smoking, alcohol intake, DM, hypertension, dyslipidemia, and CKD).

An inverse probability weight regression analysis (IPWRA) was then applied to estimate potential outcome mean (POM) and average treatment effect (ATE) by combining the outcome and treatment models. An overlap assumption (i.e., each individual woman had a positive probability of receiving each treatment) was assessed using an overlap plot. The plot displayed estimated densities of predicted probability of each treatment level after adjusting for covariates. The overlap assumption is not violated if there is a chance of seeing patients in both treatment and control groups for each combination of covariates. STATA version 14.0 was used for the analyses [25]. P value less than 0.05 was considered as statistically significant.

Table 1. Characteristics between lipophilic, hydrophilic statin users and non-statin users

Characteristics	Statin users		Non-users (%) (n = 9,703)	P-value[a]
	Lipophilic (%) (n = 4,624)	Hydrophilic (%) (n = 1,391)		
Age, years				<0.001
≤ 50	490 (10.60)	140 (7.48)	4,225 (43.54)	
51-60	2,206 (47.71)	755 (54.28)	3,946 (40.67)	
> 60	1,928 (41.70)	532 (38.25)	1,532 (15.79)	
BMI, kg/m²				
< 23	1,624 (35.17)	525 (37.74)	4,994 (51.50)	<0.001
23-26	1,584 (34.30)	508 (36.52)	2,701 (27.85)	
> 26	1,410 (30.53)	358 (25.74)	2,002 (20.65)	
Smoking				
No	4,591(99.35)	1,382 (99.50)	9,625 (99.31)	0.701
Yes	30 (0.65)	7 (0.50)	67 (0.69)	
Alcohol drinking				
No	3,997 (86.44)	1,183 (85.05)	8,186 (84.37)	0.005
Yes	627 (13.56)	208 (14.95)	1,517 (15.63)	
Hypertension				
No	2,292 (49.57)	866 (62.26)	7703 (79.39)	<0.001
Yes	2,332 (50.43)	525 (37.74)	2000 (20.61)	
Diabetes mellitus				
No	3,839 (83.02)	1,249 (89.79)	9252 (95.35)	<0.001
Yes	785 (16.98)	142 (10.21)	451 (4.65)	
Chronic kidney disease				
No	4,479 (96.86)	1,369 (98.42)	9603 (98.97)	<0.001
Yes	145 (3.14)	22 (1.58)	100 (1.03)	
Oral contraceptive use				
Never	3,354 (72.53)	1,010 (72.61)	6971 (71.84)	<0.001
Ex-users	1,252 (27.08)	374 (26.89)	2494 (25.70)	
Current users	18 (0.39)	7 (0.50)	238 (2.45)	
HRT use				
Never	3,518 (76.48)	992 (71.73)	8467 (87.61)	<0.001
Ex-users	898 (19.52)	341 (24.66)	913 (9.45)	
Current users	184 (4.00)	50 (3.62)	284 (2.94)	

[a]From chi-square test
BMI: body mass index; HRT: hormonal replacement therapy

Results

Among 15,718 participants, 107 women were diagnosed with breast cancer with a prevalence of 0.68% (95% CI: 0.56%, 0.82%). A total of 6,015 (38.3%) women were statin users with a mean duration of use of 7.27 (SD = 1.21) years. Among statin users, 4624 (77%) women were prescribed a lipophilic statin,

whereas 1,391(23%) women were prescribed a hydrophilic statin.

Characteristics between lipophilic and hydrophilic statin user and non-user groups are presented in Table 1. The distributions of 8 variables (i.e. age, BMI, alcohol drinking, history of hypertension, DM, and CKD, OC and HRT uses,) were significantly different between lipophilic and hydrophilic statin users and non-statin users (see Table 1). However, results from the multivariate multi-logit model showed only age, BMI, history of hypertension, DM, and CKD, and HRT use were statistically significantly associated with lipophilic and hydrophilic statin uses (see Table 2), and these variables were further considered in the treatment model.

Table 2. Factors associated with statin use: A multivariate multi-logit model

Factors	Coefficient	Standard error	P-value	Odds ratio (95% CI)
Lipophilic statin				
Age, years				
≤50	-	-	-	1
51-60	1.37	0.057	<0.001	3.93 (3.52, 4.39)
> 60	1.95	0.063	<0.001	7.04 (6.22, 7.97)
BMI, kg/m²				
< 23	-	-	-	1
23-26	0.35	0.047	<0.001	1.42 (1.29, 1.55)
> 26	0.38	0.051	<0.001	1.46 (1.32, 1.62)
Hypertension				
No	-	-	-	1
Yes	0.77	0.044	<0.001	2.15 (1.97, 2.34)
Diabetes mellitus				
No	-	-	-	1
Yes	0.81	0.069	<0.001	2.26 (1.97, 2.59)
Chronic kidney disease				
No	-	-	-	1
Yes	0.99	0.150	<0.001	2.70 (2.01, 3.62)
HRT use				
Never	-	-	-	1
Ex-users	0.35	0.056	<0.001	1.42 (1.27, 1.59)
Current users	0.53	0.106	<0.001	1.70 (1.38, 2.09)
Hydrophilic statin				
Age, years				
≤50	-	-	-	1
51-60	1.89	0.109	<0.001	6.64 (5.37, 8.22)
> 60	2.33	0.116	<0.001	10.27 (8.17, 12.89)
BMI, kg/m²				
< 23	-	-	-	1
23-26	0.40	0.070	<0.001	1.49 (1.30, 1.71)
> 26	0.32	0.079	<0.001	1.38 (1.18 , 1.61)
Hypertension				
No	-	-	-	1
Yes	0.32	0.067	<0.001	1.37 (1.20, 1.56)
Diabetes mellitus				
No	-	-	-	1
Yes	0.42	0.107	<0.001	1.52 (1.23, 1.88)
Chronic kidney disease				
No	-	-	-	1
Yes	0.43	0.252	0.090	1.53 (0.94, 2.52)
HRT use				
Never	-	-	-	1
Ex-users	0.63	0.075	<0.001	1.88 (1.62, 2.18)
Current users	0.42	0.162	0.010	1.52 (1.10, 2.09)

BMI: body mass index; CI: confidence interval; HRT: hormonal replacement therapy

Table 3. Characteristics between breast cancer and non-breast cancer women

Characteristics	Breast cancers n= 107 (%)	Non-breast cancers n = 15,611 (%)	P-value
Demographic data			
Age, year			
≤ 60	76 (71.03)	11,650 (74.63)	0.395
> 60	31 (28.97)	3,961 (25.37)	
BMI, kg/m²			
≤ 23	36 (33.64)	7,110 (45.54)	0.020
24-26	35 (32.71)	4,764 (30.52)	
≥27	36 (33.64)	3,737 (23.94)	
History of smoking			
Never	106 (99.07)	15,508 (99.34)	0.730
Ever	1 (0.93)	103 (0.66)	
History of alcohol drinking			
Never	94 (87.85)	13,272 (85.11)	
Ever	13 (12.15)	2,322 (14.89)	0.428
Family history of cancer in 1st degree relative			
Breast cancer			
No	103 (96.26)	14,249 (91.40)	0.083
Yes	4 (3.74)	1,341 (8.6)	
Ovarian cancer			
No	104 (99.05)	15,442 (99.16)	0.915
Yes	1 (0.95)	131 (0.84)	
Underlying diseases			
Diabetes mellitus			
Yes	15 (14.02)	1,363 (8.73)	0.06
No	92 (85.98)	14,248 (91.27)	
Chronic kidney disease			
Yes	4 (3.74)	233 (1.49)	0.067
No	103 (96.26)	15,378 (98.51)	
Dyslipidemia			
Yes	14 (13.08)	2,896 (18.59)	0.048
No	67 (62.62)	8,269 (52.97)	
Reproductive history			
Age at menarche, year			
≤ 13	39 (36.45)	6,492 (41.59)	0.325
>13	68 (63.55)	9,119 (58.41)	
Age at first live birth, year			
Nulliparity	31 (28.97)	5,394 (34.55)	0.477
≤ 29	51(47.66)	6,772 (43.38)	
>29	25(23.36)	3,445 (22.07)	
Duration of Breastfeeding, month			
Never	41 (38.32)	7,198 (46.11)	0.119
1- 6	31 (28.97)	4,645 (29.75)	
≥ 6	35 (32.71)	3,768 (24.14)	
Menopausal status			
postmenopausal	62 (57.94)	10,893 (69.78)	0.009
premenopausal	45 (42.06)	4,718 (30.22)	
History of breast biopsy			
Yes	14 (13.08)	2,896 (18.59)	0.147
No	93 (86.92)	12,686 (81.41)	
History of HRT use			
Never	100 (93.46)	12,934 (82.85)	0.028
Past user	6 (5.61)	2,156 (13.81)	
Current user	1 (0.93)	521 (3.34)	
History of OC use			
Never	68 (63.55)	11267 (72.17)	<0.001
Past user	30 (28.04)	4,090 (26.20)	
Current user	9 (8.41)	254 (1.63)	
History of medroxyprogesterone injection use			
Never	98 (91.59)	14,632 (93.73)	0.366
Ever use	9 (8.41)	979 (6.27)	

BMI: body mass index; HRT: hormonal replacement therapy; OC: oral contraceptive

Characteristics of subjects between breast cancer and non-breast cancer groups are summarized in Table 3. A simple logistic regression suggested 11 variables (i.e. age, BMI, family history of breast cancer, CKD, DM, DLP, duration of breastfeeding, menopausal status, history of breast biopsy, OC and HRT usages) that were considered in multiple logistic regression model. However, only 4 variables (i.e. age, BMI, OC, and menopausal status) were significantly associated with breast cancer and then were kept in the outcome model (see Table 4).

Table 4. Factors associated with breast cancer and the scoring scheme from multivariate logistic regression analysis

Factors	Coefficient	SE	P value	OR (95% CI)
Age, year				
> 60	0.54	0.25	0.035	1.71 (1.04, 2.81)
≤ 60				1
Oral contraceptive use				
Current user	1.52	0.38	<0.001	4.58 (2.16, 9.71)
Past user	0.16	0.22	0.473	1.17 (0.76, 1.80)
Never user				1
BMI, kg/m²				
≥ 27	0.70	0.24	0.003	2.02 (1.26, 3.24)
24-26	0.44	0.24	0.070	1.55 (0.97, 2.49)
≤ 23				1
Menopausal status				
Premenopause	0.64	0.24	0.008	1.91 (1.18, 3.08)
Postmenopause				1

BMI: body mass index; CI: confidence interval; OR: odds ratio; SE: standard error

Risk of breast cancer and statin use

The POMs (i.e., breast cancer risks) estimated using the IPWRA method were 0.0072 (95% CI: 0.0055, 0.0089), 0.0051 (95% CI: 0.0008, 0.0095), and 0.0038 (95% CI: 0.002, 0.0056) for non-statin users, hydrophilic, and lipophilic statin users, respectively, see Table 5. The estimated ATEs (i.e., risk differences) were -0.0021 (95% CI: -0.0067, 0.0026) and -0.0034 (95% CI: -0.0059, -0.0009) for hydrophilic and lipophilic statins, respectively. The number needed to treat for these corresponding statins were 2.1 (95% CI: -2.6, 6.7) and 3.4 (95% CI: 1.0, 5.9) per 1000 subjects, i.e., we could prevent breast cancer in about 2 and 3 subjects for every 1000 subjects treated with hydrophilic and lipophilic statins respectively, although only the lipophilic statin is statistically significant.

Table 5. Statin-treatment effect model on breast cancer risk

Model	Factors	Risk difference	SE	P-value	95% CI
ATE	Lipophilic statin users vs non-users	-0.0034	0.001	0.008	-0.006, -0.001
	Hydrophilic statin users vs non-users	-0.0021	0.002	0.381	-0.007, 0.003
POM	**Factors**	**Risk**	**SE**	**P-value**	**95% CI**
	Non-statin users	0.0072	0.001	<0.001	0.006, 0.009
	Lipophilic statin users	0.0038	0.001	<0.001	0.002, 0.006
	Hydrophilic statin users	0.0051	0.002	0.019	0.001, 0.010

ATE: average treatment effect; CI: confidence interval; POM: potential outcome mean; SE: standard error

The overlap assumption for applying the treatment effect model was checked by plotting estimated densities of predicted probability (i.e., that non-statin users were non-statin users, and predicted probabilities that statin-users were non-statin users) against propensity score, see Figure S1. The overlap assumption is violated if there is evidence that the estimated density has too much mass around 0 and 1. The plot indicated that the predicted probability that non-statin users were actually not assigned to statin (either lipophilic- or hydrophilic-statin) and predicted probability that statin-users were non-statin users mostly overlapped, although the predicted probability that non-statin users would not be assigned to treatment (either lipophilic- or hydrophilic-statin) had some of its mass around 0.8 to 0.9. Thus, the overlap assumption was largely observed.

Discussion

We assessed the effect of statin use on lowering breast cancer risk using a counterfactual analysis approach. Our results showed that using lipophilic statins but not hydrophilic statins could significantly reduce risk of breast cancer in Thai women. For every 1000 women treated with a lipophilic statin, 3 women would avoid breast cancer.

Our findings correspond with some previous studies that reported a significantly decreased risk of breast cancer in statin users. Cauley et al. found that among women aged 65 years or older, statin use significantly reduced risk of breast cancer with a hazard ratio of 0.28 (95% CI: 0.09, 0.86) [11]. Moreover, results from a retrospective cohort study showed a reduced breast cancer risk in women who had used statins for longer than 4 years (odds ratio = 0.26, 95% CI: 0.12, 0.55) [8]. The protective effect of statins on breast cancer risk can potentially be explained through the statins' inhibition of the mevalonate pathway. This inhibition disrupts cancer cell growth, and leads to apoptotic cell death [5-7]. In addition, statins impede the activation of the proteasome pathway, and prevent the breakdown of p21 and p27. These molecules can accelerate growth-inhibitory effects and retard cancer cell mitosis [26, 27].

Lipophilic statins can penetrate the cell plasma membrane, whilst hydrophilic statins cannot [28]. Cellular penetration of lipophilic statins may be associated with their inhibition of cell growth. This hypothesis is supported by the findings from a cell culture study in which lipophilic statins but not hydrophilic statins had anticancer action [29]. These observations are consistent with the results from our study that using lipophilic statins significantly reduced the risk of breast cancer by around 48%, whereas hydrophilic statins were not significantly associated with breast cancer risk, although the point estimate suggests a smaller risk reduction of 29%. Moreover, results from the Women's Health Initiative Study showed that lipophilic statin use was associated with an 18% lower breast cancer risk (HR = 0.82, 95% CI = 0.70, 0.97) [30]., although the updated results failed to confirm this association [31]. This conflicting result may be due to misclassification of types of statins in the updated findings, in which atorvastatin was classified as hydrophilic instead of lipophilic.

However, our results contrast with the findings from two meta-analyses that did not find any protective effects of statin use on breast cancer risk. The meta-analysis of observational studies showed no association (pooled RR = 0.99, 95 % CI = 0.94, 1.04) [16], whereas a meta-analysis of RCT suggested a risk effect of statin use (pooled RR = 1.19; 95% CI, 0.81 to 1.73) [15]. The meta-analysis of observational studies included studies with different study designs, types and durations of statin use. Pooling statin effects was mainly based on crude effects, thus the pooled effect is prone for confounding bias. The meta-analysis of RCTs included studies that were primarily designed to assess the effect of statins on other disease conditions, not breast cancer, and so, risk factors for cancer and cancer endpoints were not systematically collected. Therefore, surveillance bias may be a problem.

Our study had some strengths. We made use of routinely available clinical data combine with survey data that we had collected in the mammography clinic. Thus, all possible risk factors for breast cancer were collected and considered in the counterfactual analysis. All women were screened with mammography and breast cancer cases were verified with pathological diagnosis. Thus, surveillance and detection bias were less likely to occur in our study. We estimated the statin treatment effects using counterfactual analysis, which allowed us to estimate what the incidence would be if non-statin users received treatment or vice versa. On the other hand, our data on statin use were retrieved from a drug database, with no objective measure of actual drug compliance; however this would probably have biased us towards the null (people over-report compliance) rather than away from the null.

In conclusion, use of lipophilic statin might reduce the risk of breast cancer in Thai women.

Supplementary Material

Figure S1. http://www.jcancer.org/v07p1163s1.pdf

Competing Interests

The authors have declared that no competing interest exists.

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