Statins Use and Risk of Breast Cancer Recurrence and Death: A Systematic Review and Meta-Analysis of Observational Studies

Marjan Mansourian[1], Shaghayegh Haghjooy-Javanmard[2], Azadeh Eshraghi[3], Golnaz Vaseghi[4]*, Alireza Hayatshahi[5], Jean Thomas[5]

[1]Applied Physiology Research Center and Department of Biostatistics and Epidemiology, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran; [2]Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran; [3]Department of Pharmacology and Toxicology, Faculty of Pharmacy-International Campus, Iran University of Medical Sciences, Tehran, Iran; [4]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; [5]Department of Pharmacy Practice, School of Pharmacy, Loma Linda university, California, USA.

Received, July 27, 2015; Revised, November 1, 2015; Accepted, January 26, 2016; Published, January 30, 2016.

ABSTRACT- Purpose. Statins are widely prescribed drugs for lowering cholesterol. Some studies have suggested that statins can prevent breast cancer recurrence and reduce mortality rate. However they are not conclusive. Present systematic review and meta-analysis of published cohort studies was conducted to determine the effects of statins intake and risk of breast cancer recurrence and mortality rate. **Methods.** Online databases (PubMed, Embase, Scopus, EBSCO and Cochrane Collaboration) were searched through October 2014. Pooled relative risks and 95 % confidence intervals were calculated with random-effects. **Results.** A total of 8 cohort studies (4 for recurrence 2 for mortality and 2 for both) involving 124669 participants with breast cancer were eligible. Our results suggest a significant reduction in recurrence (OR= 0.79. I^2= 38%) and death (OR = 0.84, I^2 = 8.58 %) among statin users. **Conclusion.** Our meta-analysis suggests that breast cancer patients will benefit from statin intake, however from these cohorts we are unable to differentiate between various statins in terms of effectiveness and duration of use. We highly propose conducting randomized clinical trials.

INTRODUCTION

Breast cancer is one of the most invasive cancers and a leading cause of mortality in women (1). Despite the discovery of new adjuvant treatments, breast cancer recurrence is not an uncommon problem in these patients. Therefore, finding new strategies to overcome cancer recurrence seem reasonable (2). Statins are well-known lipid-lowering drugs which can prevent cardiovascular diseases (3). They are well-tolerated and serious side effects are rare (4). Statins also show some promising effects on inhibiting mammary tumor growth and exhibit possible anti-carcinogenic properties (5). Previous studies in triple negative breast cancer cell lines have shown that statins prevent DNA binding of nuclear factor kappa beta at the phosphate and tensin homolog promoter (6). Statins also block the mevalonate pathway and deplete cholesterol precursors such as farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP), which decrease the ability of cells to perform post-translational protein prenylation, resulting in blocking the function of proteins in breast cancer cell lines (7,8). Despite the preclinical results, no prospective randomized control trials (RCTs) have evaluated the effects of statins on reduction of breast cancer risk. However, several studies have investigated the association between statin use and risk of breast cancer. Two meta-analyses have been conducted to evaluate the combined results of heterogeneous populations. The authors in both studies found no association between statin use and the risk of breast cancer, however there were some limitations in these studies especially among high risk populations (9). Subsequently, we propose that exposure to statin 1 year before tumor detection may influence the cancer phenotype and decrease the grade and stage

Corresponding Author: Golnaz Vaseghi; Isfahan Cardiovascular Research Center, Cardiovascular Research Institute,Isfahan university of Medical Sciences, Isfahan, Iran; golnazvaseghi@yahoo.com

of tumors in comparison with the total number of tumors (10). Statins also target histone deacetylase (11). Drugs which inhibit histone deacetylation have been approved for lymphoma and some other cancer treatment except for breast cancer (12). Based on these evidences some other studies have hypothesized that patients with already diagnosed breast cancer may benefit from statin administration. However, these studies have yielded mixed results, some indicate significant reduction in secondary breast cancer recurrence and mortality (2,13,14) while others have found non-meaningful effects (14,15-17). We aimed to conduct a systematic review and meta-analysis of these studies to summarize the evidence between statin use and risk of secondary breast cancer and mortality. We also tried to evaluate whether these associations varied by study design, type of statin use and breast cancer site, which may help resolve inconsistencies among the results from the different studies.

Material and methods

The present study was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for reviews of observational studies (18).

Search strategies

A literature search of database (PubMed, Embase, Scopus, EBSCO and Cochrane Collaboration) was conducted using relevant key word: (Statin OR HMG-CoA reductase inhibitors OR Atorvastatin OR Cerivastatin OR Fluvastatin OR Lovastatin OR Pravastatin OR Rosuvastatin OR Simvastatin) AND (breast) AND (Cancer OR Neoplasm) AND (recurrence OR relapse OR secondary OR mortality OR death). Additionally, the relevant reviews and retrieved articles were searched manually for more eligible studies through October 2014.

The following information was abstracted from each study: study design, country of participants, definition and numbers of cases and control subjects, frequency of recurrence cases, and number of cancer-specific motility. All studies taken into account presented preferably estimated HRs corrected for potential confounders.

STATISTICAL ANALYSIS

Heterogeneity was assessed using the Cochran Q and I^2 statistics. For the Q statistic, a P value<0.10 was considered statistically significant for heterogeneity; for the I^2 statistic, heterogeneity was interpreted as moderate (I^2: 50%–75%), or high (I^2 >75%) (19). The overall analysis including all eligible studies was performed to assess the association between statin use and breast cancer recurrence and mortality rate. Pooled HR estimates and corresponding 95% CIs were calculated using the inverse variance method. In the absence of a statistically significant heterogeneity (I^2: 0%–25%), fixed model was used. To test the robustness of association and characterize possible sources of statistical heterogeneity, sensitivity analysis was carried out by excluding studies one-by-one and by analyzing the homogeneity and effect size for the remaining studies. Publication bias was assessed using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test (20, 21). All P-values were two-tailed. For all tests, a probability level of <0.05 was considered statistically significant. All calculations and graphs were carried out using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

RESULTS

Study selection:

Figure.1 shows the process of study selection for the meta-analysis. Twenty one relevant references were initially identified during our search. After screening titles and abstracts, 8 were selected for full-text review.

Study characteristics

Table 1 summarizes the characteristics of qualified studies in this meta-analysis. The 8 studies, involving 124669 participants with breast cancer, were published up until October 2014. Among the study participants, 25927 were statin users. There were 38071 cases of breast cancer recurrences or death, determined.

Breast Cancer Recurrence rate and the use of statins

On meta-analysis of all studies assessing the risk of recurrence, the use of statins was associated with a statistically significant 21% reduction in recurrence rate (unadjusted OR= 0.792; 95% CI: 0.735–0.853) (Figure.2). There was no considerable heterogeneity observed across studies (Cochran's Q-test, P < 0.061; I^2 = 38%). To assess whether any one study had a dominant effect on the meta-analytic HR, each study

was excluded and its effect on the main summary estimate and Cochran's Q-test P value for heterogeneity was evaluated. No study significantly affected the summary estimate. There was no evidence of significant publication bias, both quantitatively (Egger's regression test, P = 0.084) and on visual inspection of the funnel plot (Figure 3).

Breast cancer-specific mortality and the use of statins

On meta-analysis of all studies assessing breast cancer-specific mortality, the use of statins was associated with a statistically significant 16% reduction in cancer-specific mortality rate (unadjusted OR= 0.849; 95% CI: 0.827–0.870) (Figure.4). There was no considerable heterogeneity observed across studies (Cochran's Q-test, P =0.360; I^2=8.58%). To assess whether any one study had a dominant effect on the meta-analytic HR, each study was excluded and its effect on the main summary estimate and Cochran's Q-test P value for heterogeneity was evaluated. No study significantly affected the summary estimate. There was no evidence of significant publication bias, both quantitatively (Egger's regression test, P = 0.464) and on visual inspection of the funnel plot (Figure 5).

DISCUSSION

Despite some authors' belief that the use of statins may not have any significant protective effects on breast cancer recurrence (17), findings from our systematic review and meta-–analysis propose that statin intake will significantly decrease the risk of recurrence (OR= 0.79) and rate of mortality (OR=0.84). To the best of our knowledge this is the first meta-analysis on statin use and breast cancer recurrence and mortality. We analyzed 6 and 4 cohort studies (2 for both mortality and death) for detection of statins effect on recurrence and mortality rate, respectively.

High doses of fluvastatin as neo-adjuvants significantly decreases breast cancer proliferation (22),(23). As another possible mechanism, it is proposed that simvastatin stimulates production of a variant of the p53 transcription factor and reduces bone metastases (24). Statins inhibit breast cancer cell growth in vitro which may demonstrate the biological plausibility to statins' preventive effect on breast cancer progression (25). A pre-surgical clinical trial reported antiproliferative effect of atorvastatin on invasive breast cancer at 80 mg/day dose for two weeks (26). This effect was shown only in tumors expressing HMGCR (3-Hydroxy-3-Methylglutaryl-CoA Reductase), proposing that statins target this enzyme in breast cancer tissue. They also decreased estrone sulfate level which is another possible mechanism for the anti-cancer action (27).

Mutant p53 up-regulates the mevalonate pathway which induces an invasive phenotype. Adding simvastatin to the culture medium reverses this phenotype to normal morphology, however the malignant phenotype persist when both simvastatin and geranylgeranylpyrophosphate (GGPP) are present in the medium (28).

The initial report of association between post-diagnosis statin use and risk of breast cancer came from a large US cohort. The mean duration of statin use was 1.96, and HR of 0.67, 0.8 and 0.38 were obtained from less than 100 days, between 100 days and two years, and more than 2 years of treatment respectively. In this study the patients mainly used lipophilic statin (16).

A second report was obtained from a cohort study of Danish breast cancer patients. In this study patients were followed up for 6.8 years after diagnosis. Overall HR was 0.83, but 0.7 for simvastatin alone. The authors concluded that while simvastatin had significant effects, hydrophilic statins had no effects(13).

In a cohort of 703 breast cancer patients, it had been showed that use of statins for more than 6 months significantly reduced the risk of cancer recurrence. The study associated usage of statins with a lower recurrence rate (adjusted HR = 0·48) (2).

Mortality rate was assessed among patients 40 years and older who had used statin, in a cohort of Danish population. Authors evaluated risk with daily doses of statins and found HR of 0.83, 0.87 and 0.87 for 0.01-0.75, 0.75-1.5 and higher than 1.5 daily, respectively (15).

In 2013, one study evaluated the effect of statins on recurrence and mortality in primary inflammatory breast cancer, a rare form of breast cancer. This study also supports the protective role of lipophilic statins on inflammatory breast cancer (29).

Another large study on a prospective cohort of 3,024 non-metastatic breast cancer was conducted recently, which showed non-significant reduction in cancer recurrence with HR of 0.83 for stage I and III and 0.84 for menopausal women, however the authors also found an overall increase in the risk of

cancer mortality rate. The authors in this study did not support the role of statins in the reduction of breast cancer recurrence and mortality rate (17).

In a U.S. prospective cohort study of 4,216 women with breast cancer, use of lipophilic statins decreased the rate of breast cancer recurrence (HR = 0·76), however hydrophilic statins had no effect (HR = 1·01) (14).

The most recent cohort from Finland (31236 participants) showed decreased risk of mortality in patients taking statin post and pre diagnostic (HR=0.46 and HR= 0.54). Authors believed that decrease due to post-diagnostic statin use was likely affected by healthy adherer bias and was not clearly dose-dependent (30).

Although these results propose that statins, especially simvastatin, can reduce cancer recurrence, it should be mentioned that perhaps other patient characteristics and not lipid-lowering medication is responsible for the underlying mechanism for the observed results. Also increased levels of cholesterol might reduce the risk of metastases (31). In a recent meta-analysis, the authors have shown the beneficial effects of statin in prevention of cancer death especially in colon cancer patients. The previous study did not calculate the effect of statin use on breast cancer recurrence risk (32). Well-designed studies considering statins consumption, as well as cholesterol levels, are required in order to clarify the specific role of statins in the chemoprevention of breast cancer recurrence.

In conclusion, our analysis of the available data suggests that statin use results in 21% reduction in breast cancer recurrence and 16% reduction in mortality rate. This provides a justification for launching further randomized clinical trials.

ACKNOWLEDGMENT

The authors would like to thank Hajar Naji for her kindness. **Ethical approval -** For this type of study, formal consent is not required

REFERENCES

1. American Cancer Society. Breast Cancer Facts & Figures. American Cancer Society. Atlanta, USA, 2011-2012
2. Chae YK, Valsecchi ME, Kim J, Bianchi AL, Khemasuwan D, Desai A, Tester W. Reduced risk of breast cancer recurrence in pacients using ACE inhibitors, ARBs andlor statins.Cancer Invest,2011; 29:585-593.
3. Schwabe U, Paffrath D (2010) Arzneiverordnungs-Report 2010: Springer-Verlag, Berlin/Heidelberg/New York.
4. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, Krumholz HM.Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation,2006;114:2788-2797.
5. Campbell MJ, Esserman LJ, Zhou Y, Shoemaker M, Lobo M, Borman E, Baehner F, Kumar AS, Adduci K, Marx C, Petricoin EF, Liotta LA, Winters M, Benz S, Benz CC.Breast cancer growth prevention by statins. Cancer Res,2006;66:8707–8714.
6. Ghosh-Choudhury N, Mandal CC, Ghosh-Choudhury N, Ghosh Choudhury G. Simvastatin induces depression of PTEN expression via NFkappaB to inhibit breast cancer cell growth. Cell Signal,2010;22:749–758.
7. Kang S, Kim ES, Moon A. Simvastatin and lovastatin inhibit breast cell invasion induced by H-Ras. Oncol Rep, 2009;21:1317–1322.
8. Laezza C, Malfitano AM, Proto MC, Esposito I, Gazzerro P, Formisano P, Pisanti S, Santoro A, Caruso MG, Bifulco M.Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme Areductase activity and of Rasfarnesylation mediate antitumor effects of anandamide in human breast cancer cells. EndocrRelat Cancer, 2010;17:495–503.
9. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J ClinOncol,2005;23:8606-8612.
10. Kumar AS, Benz CC, Shim V, Minami CA, Moore DH, Esserman LJ. Estrogen Receptor–Negative Breast Cancer Is Less Likely to Arise among Lipophilic Statin Users. Cancer Epidemiol Biomarkers Prev,2008;17:1028-1033.
11. Lin YC, Lin JH, Chou CW, Chang YF, Yeh SH, Chen CC. Statins increase p21 through inhibition of histone deacetylase activity and release of promoter-associated HDAC1/2. Cancer Res,2008;68:2375-2383.
12. Vaklavas C,Chatzizisis YS, Tsimberidou AM. Common cardiovascular medications in cancer therapeutics. PharmacolTher,2011;130:177-190.
13. Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, Sørensen HT, Lash TL. Statin Prescriptions and Breast Cancer Recurrence Risk: A Danish Nationwide Prospective Cohort Study. J Natl Cancer Inst, 2011;103:1461–1468.
14. Boudreau MD, Yu O, Chubak J, Wirtz HS, Bowles EJ, Fujii M, Buist DS. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. Breast Cancer Res Treat, 2014;144:405-416.

15. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med,2012;367:1792–1802.
16. Kwan ML, Habel LA, Flick ED, Quesenberry CP, Caan B. Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. Breast Cancer Res Treat, 2008;109:573–579.
17. Nickels S, Vrieling A, Seibold P, Heinz J, Obi N, Flesch-Janys D, Chang-Claude J. Mortality and Recurrence Risk in Relation to the Use of Lipid-Lowering Drugs in a Prospective Breast Cancer Patient Cohort. PLoS One,2013; 25:e75088.
18. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB.Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA,2000;283:2008–2012.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ,2003;327:557-60.
20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics,1994;50:1088-1101.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ, 1997;315:629-634.
22. Garwood E, Kumar A, Baehner F, Moore DH, Au A, Hylton N, Flowers CI, Garber J, Lesnikoski BA, Hwang ES, Olopade O, Port ER, Campbell M, Esserman LJ. Fluvastatin reduces proliferation and increases apoptosis in women with high grade breast cancer. Breast Cancer Res Treat,2012;119:137-144.
23. Mandel C, Ghosh-ChoudhuryN, Yoneda T, Ghosh-Choudhury G. Simvastatin prevents skeletal metastasis of breast cancer by an antagonistic interplay between p53 and CD44. J BioChem. 2001: 286:11314-11327.
24. Freed-Paster W, Mizuno h, Zhao X, Langerod A, Moon SH, Rodriguez-Barrueco R, Barsottu A, Chicas A, Li W, Polotskaia A, Bissell MJ, Osborne TF, Tian B, Lowe SW, Silva JM, Børresen-Dale AL, Levine AJ, Bargonetti J, Prives C. Mutant p53 disrupt mammary tissue architecture via mevalonate pathway. Cell.2002;148:244-268.
25. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. Nat Rev Cancer, 2005;5:930–994
26. Bjarnadottir O, Romero Q, Bendahl PO, Jirström K, Rydén L, Loman N, Uhlén M, Johannesson H, Rose C, Grabau D, Borgquist S.Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. Breast Cancer Res Treat, 2013;138:499–508
27. Higgins MJ, Prowell TM, Blackford AL, Byrne C, Khouri NF, Slater SA, Jeter SC, Armstrong DK, Davidson NE, Emens LA, Fetting JH, Powers PP, Wolff AC, Green H, Thibert JN, Rae JM, Folkerd E, Dowsett M, Blumenthal RS, Garber JE, Stearns V. A short-term biomarker modulation study of simvastatin in women at increased risk of a new breast cancer. Breast Cancer Res Treat, 2012;131:915–924
28. Freed-Pastor W, Mizuno H, Zhao X, Langerod A, Langerød A, Moon SH, Rodriguez-Barrueco R, Barsotti A, Chicas A, Li W, Polotskaia A, Bissell MJ, Osborne TF, Tian B, Lowe SW, Silva JM, Børresen-Dale AL, Levine AJ, Bargonetti J, Prives C. Mutant p53 Disrupts Mammary Tissue Architecture via the Mevalonate Pathway. Cell, 2012;148(1–2):244–258.
29. Brewer TM, Masuda H, Liu DD, Shen Y, Liu P, Iwamoto T, Kai K, Barnett CM, Woodward WA, Reuben JM, Yang P, Hortobagyi GN, Ueno NT. Statin use in primary inflammatory breast cancer: a cohort study. Br J Cancer, 2013;109:318-324.
30. Murtola TJ, Visvanathan K, Artama M, Vainio H, Pukkala E, Wright JM. Statin Use and Breast Cancer Survival: A Nationwide Cohort Study from Finland. Plus one,2014; 9:1-8.
31. Ozdemir BH, Akcali Z, Haberal M. Hypercholesterolemia impairs angiogenesis in patients with breast carcinoma and, therefore, lowers the risk of metastases. Am J ClinPathol, 2004;122:696–703.
32. Zhong S, Zhang X, Chen L, Ma T, Tang J, Zhao J. Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies. Cancer Treat Rev, 2015;41:554-567.

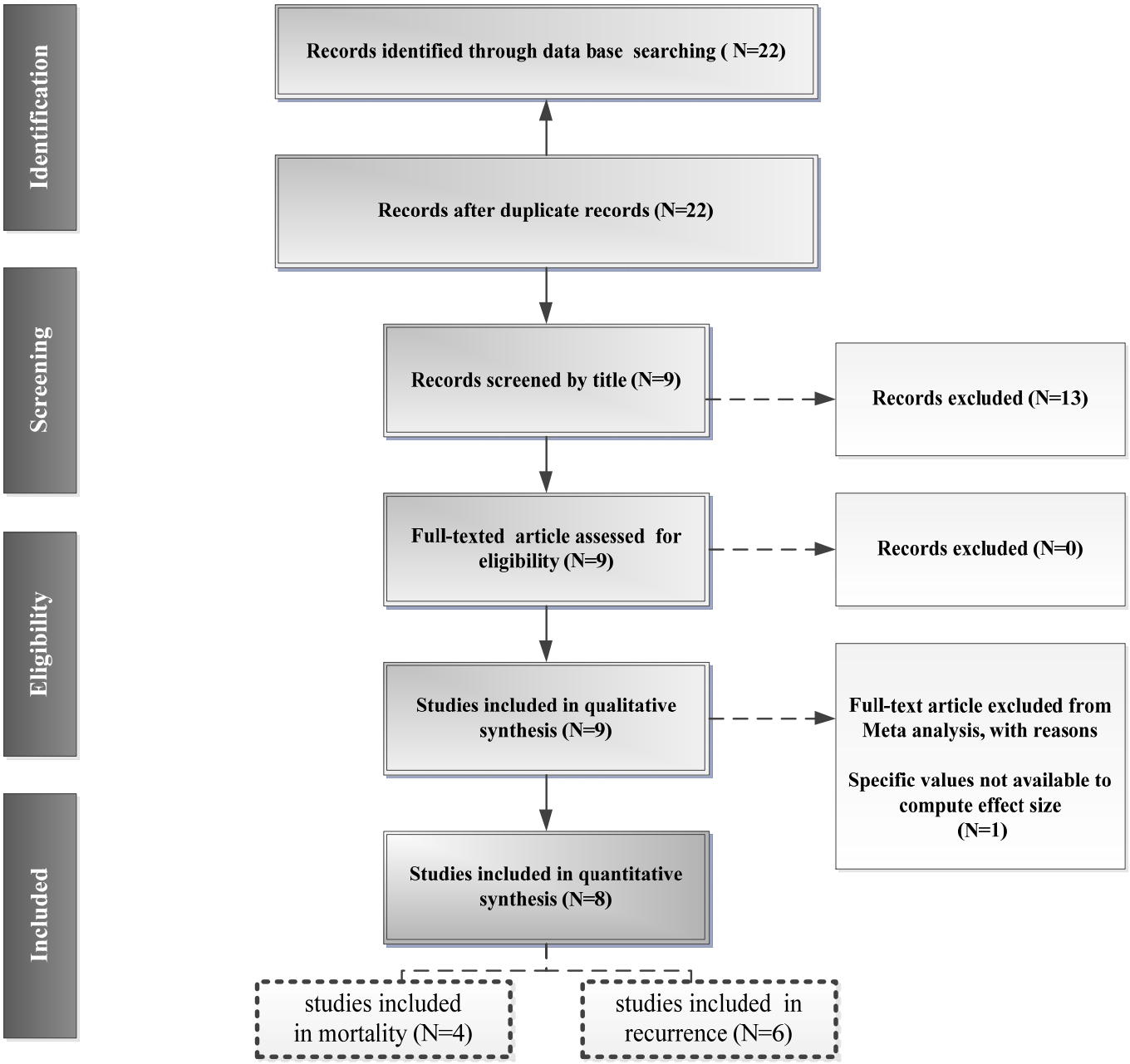

Figure 1. Flowchart representing the selection process ASCO American society of clinical oncology

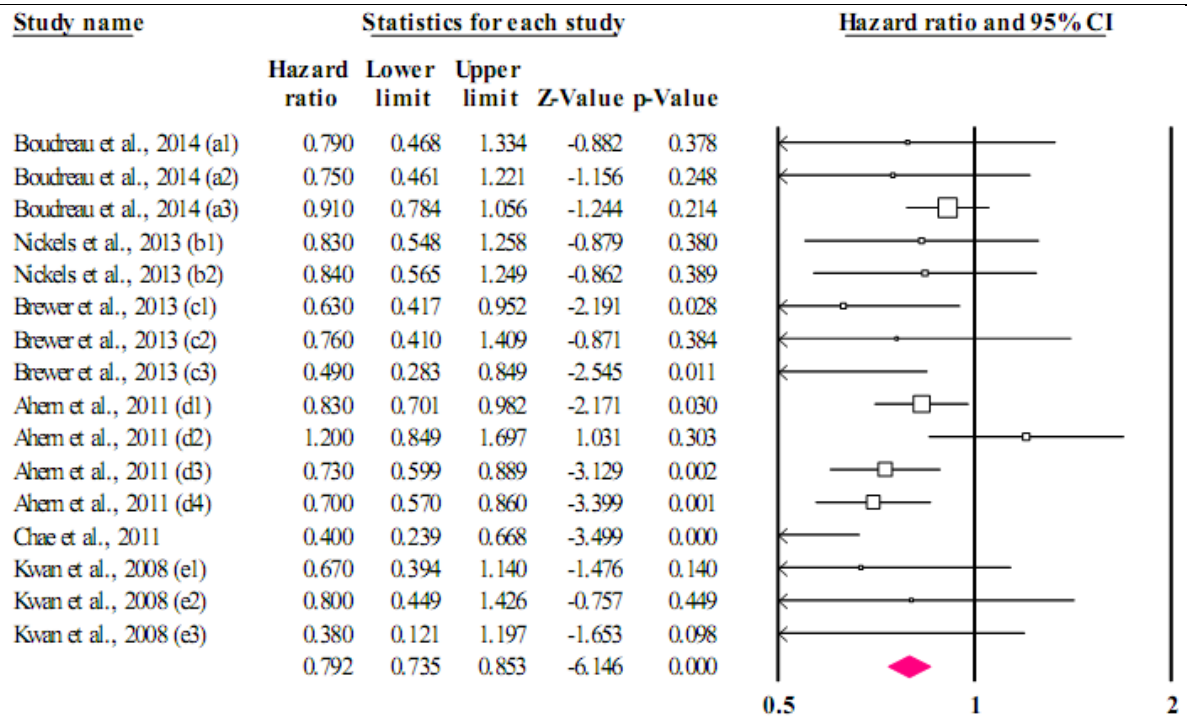

Figure 2. Overall meta-analysis of statin use and Breast Cancer Recurrence (a_1: Statin usage <1 year , a_2:Statin usage 1-2.9 years , a_3: Statin usage more than 3 years; b_1:Patients with stage I-III of breast cancer, b_2:Patients with stage I-III of breast cancer (only postmenopausal); c_1:Any type of statin user, c_2:lipophilic statin user, c_3:Weakly lipophilic and hydrophilic statin users; d_1:Users of any statin, d_2: User of only hydrophilic, d_3: User of only lipophilic, d_4:User of only simvastatin; e_1:Any statin usage >100 days supply, e_2: Any statin use for 101 days – ≤2 years supply, e_3:Any statin use >2 years supply).

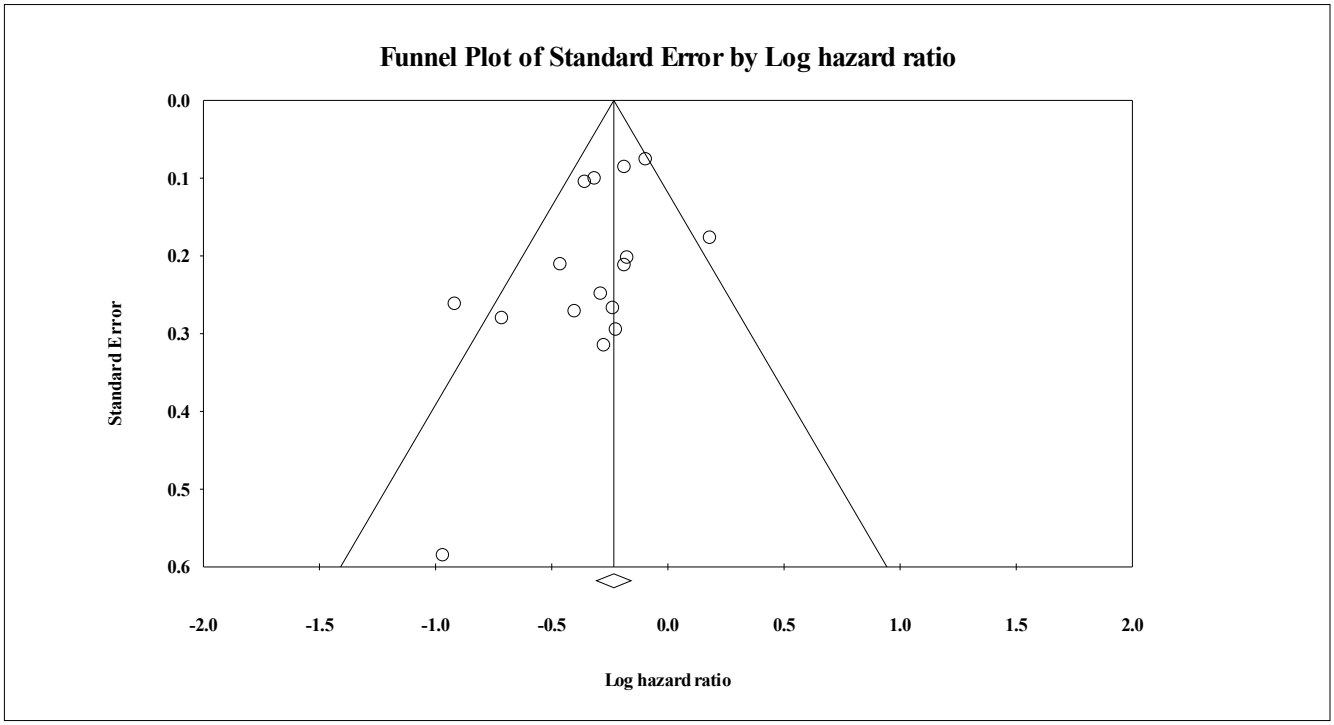

Figure 3. Funnel plot for publication bias in the studies investigating risk for Breast cancer recurrence associated with use of statins.

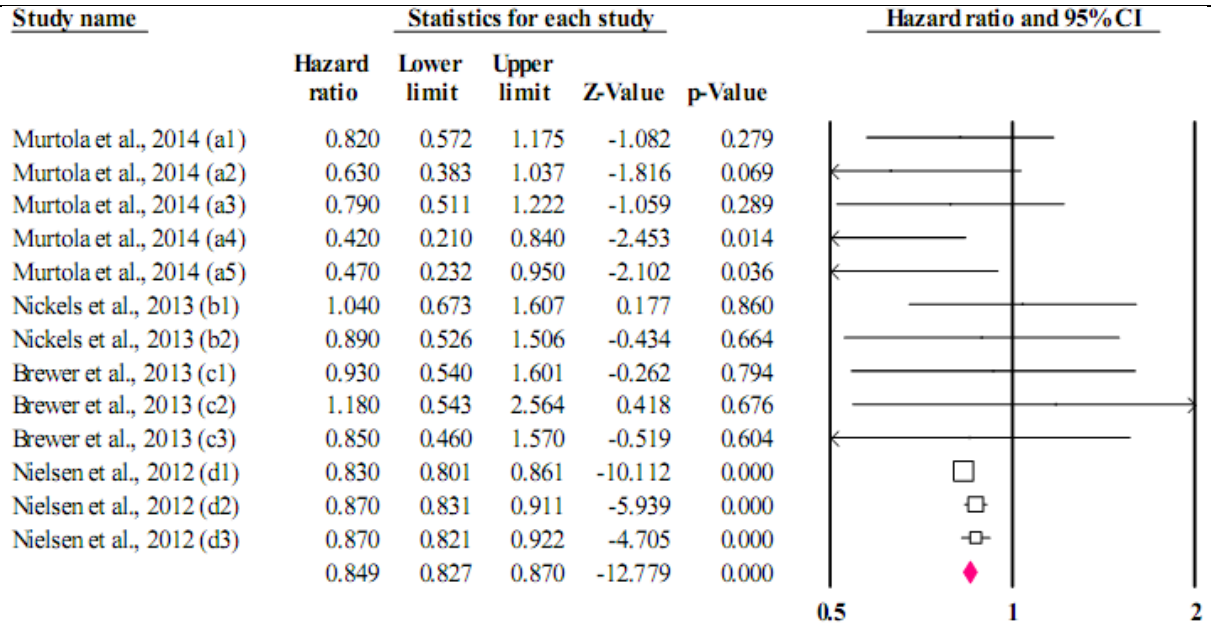

Figure 4. Overall meta-analysis of statin use and Breast Cancer mortality(a1: pre-diagnostic statin use (Intensity of statin use(195 DDDs/year or less)), a2: pre-diagnostic statin use (Intensity of statin use (Over 196 DDDs/years)), a3: post-diagnostic statin use (Intensity of statin use(14–183 DDDs/year)), a4: post-diagnostic statin use (Intensity of statin use (184–300 DDDs/year)), a5: post-diagnostic statin use (Intensity of statin use(301 DDDs/year or more)); b1: Patients with stage I–IV, a2: Patients with stage I–III, b3: stage I–III (only postmenopausal); c1: lipophilic statin user, c2: Weakly lipophilic and hydrophilic statin users, d1: For 0.01 to 0.75 defined daily statin dose per day, d2: For0.76 to 1.50 defined daily statin dose per day, d3:For higher than 1.50 defined daily statin dose per day).

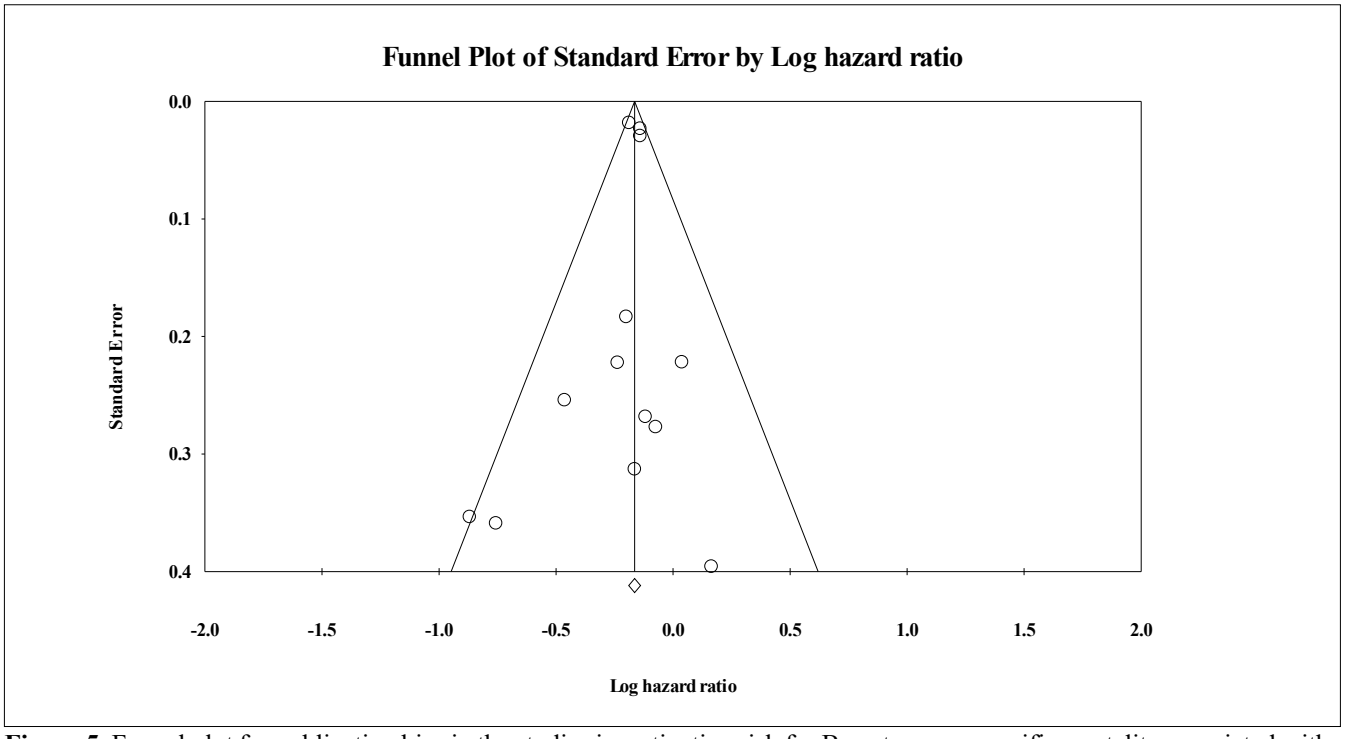

Figure 5. Funnel plot for publication bias in the studies investigating risk for Breast cancer-specific mortality associated with use of statins.

Table 1. Cohort Studies of Statins Use and risk of breast cancer recurrence and mortality rate in the systematic reviews and meta-analyses.

Country (Reference)	Follow up duration	Number of patients			HR (95% CI) for recurrence and/or [mortality] (users *vs* non-users of statin)	Controlled variables
		Total	Statin users	Recurrence and/or mortality		
Denmark (13)	1996-2003	18769	3282	3419	Users of any statin, 0.83 (0.70, 0.98) User of only hydrophilic 1.2 (0.79, 1.7) User of only lipophilic 0.73 (0.60, 0.89) User of only simvastatin 0.70 (0.57, 0.86)	Age, menopausal status at diagnosis, histological grade, ER status and receipt of adjuvant ET, type of primary surgery received, pre-diagnosis exposure to combination hormone replacement therapy, and co-prescriptions of special drugs
USA (2)	1999 - 2005	703	156	149	0.40 (0.24, 0.67)	Age, race, menopausal status at diagnosis, family history of disease, smoking history, diabetes, hormonal receptor status, and hormonal therapy status.
USA (14)	1990-2008	4226	1210	371	Statin usage <1 year, 0.79 (0.47, 1.33) Statin usage 1-2.9 years, 0.75 (0.46, 1.22) Statin usage more than 3 years, 0.91 (0.78, 1.05)	Age, diagnosis year, AJCC stage, hormone receptor status, primary treatment for initial breast cancer, endocrine therapy for the incident breast cancer status, body mass index at diagnosis, smoking status, menopausal status at diagnosis, Charlson co-morbidity score, diabetes status, prescription non-steroidal anti-inflammatories
USA (16)	1997 -2000	1811	367	344	Any statin usage >100 days supply, 0.67 (0.39, 1.14) Any statin use for 101 days – ≤2 years supply, 0.80 (0.45, 1.43) Any statin use >2 years supply, 0.38 (0.12, 1.19)	Age, race, body mass index, stage of breast cancer, and tamoxifen treatment,

Germany (17)	2001 -2005	6213	592	387	Patients with stage I-III of breast cancer, 0.83 (0.53. 1.26) Patients with stage I-III of breast cancer (only postmenopausal), 0.84 (0.56, 1.25) / Patients with stage I–IV, 1.04 (0.67, 1.61) Patients with stage I–III: 0.89 (0.53, 1.51) stage I–III (only postmenopausal), 0.93 (0.54, 1.60)	Age, the traditional prognostic factors tumor size, nodal status, and smoking. Mortality analyses are additionally adjusted for cardiovascular disease, diabetes mellitus, and body-mass index.
USA (26)	1995-2011	723	73	There was no suitable information on the recurrence data / 338	Any type of statin user: 0.63 (0.42, 0.95) lipophilic statin user, 0.76 (0.41, 1.41), [1.18 (0.54, 2.56)] Weakly lipophilic and hydrophilic statin users, 0.49 (0.28, 0.85), [0.85 (0.46, 1.57)]	Radiation therapy, hormonal receptor status, lymphatic/vascular invasion for PFS and lymphatic/vascular invasion, nuclear grade and surgery
Denmark (15)	1995 - 2009	60988	15247	Studying on the recurrence event was not the aim of this study / 29577	For 0.01 to 0.75 defined daily statin dose per day, 0.83 (0.80, 0.86) For 0.76 to 1.50 defined daily statin dose per day, 0.87 (0.83, 0.91) For higher than 1.50 defined daily statin dose per day), 0.87 (0.82, 0.92)	Age, cancer Stage, spread to the lymphatic system, distant metastasis, status with regard to chemotherapy, radiotherapy, diagnosis of cardiovascular disease before cancer, and diagnosis of diabetes mellitus before cancer; year of birth, sex, race, ethnic descent, education; and size of residential area.
Finland (26)	1995-2003	31236	4151	Studying on the recurrence event was not the aim of this study / 3486	Statin intensity*, 14–183: 0.79 (0.51–1.22) Statin intensity*, 84–300: 0.42 (0.21–0.84) Statin intensity*, 301or more): 0.47 (0.23–0.94) Statin intensity*, 195 or less: 0.82 (0.57–1.17) Statin intensity*, 196 or more: 0.63 (0.38–1.03)	Age, tumor stage and morphology, and treatment selection

- Measured as post-diagnostic statin density of HMG-CoA reductase.