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ORIGINAL REPORT

Use of Statins and Breast Cancer: A Meta-Analysis of Seven Randomized Clinical Trials and Nine Observational Studies

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ABSTRACT

Purpose
A growing body of evidence suggests that statins may have chemopreventive potential against breast cancer. Laboratory studies demonstrate that statins induce apoptosis and reduce cell invasiveness in various cell lines, including breast carcinoma cells. However, the clinical relevance of these data remains unclear. The nonconclusive nature of the epidemiologic data prompted us to conduct a detailed meta-analysis of the studies published on the subject in peer-reviewed literature.

Patients and Methods
A comprehensive search for articles published up until 2005 was performed; reviews of each study were conducted; and data were abstracted. Before meta-analysis, the studies were evaluated for publication bias and heterogeneity. Pooled relative risk (RR) estimates and 95% CIs were calculated using the random and the fixed-effects models. Subgroup and sensitivity analyses were also performed.

Results
Seven large randomized trials and nine observational studies (five case-control and four cohort studies) contributed to the analysis. We found no evidence of publication bias or heterogeneity among the studies. Statin use did not significantly affect breast cancer risk (fixed effects model: RR = 1.03; 95% CI, 0.93 to 1.14; random effects model: RR = 1.02; 95% CI, 0.89 to 1.18). When the analyses were stratified into subgroups, there was no evidence that study design substantially influenced the estimate of effects. Furthermore, the sensitivity analysis confirmed the stability of our results.

Conclusion
Our meta-analysis findings do not support a protective effect of statins against breast cancer. However, this conclusion is limited by the relatively short follow-up times of the studies analyzed. Further studies are required to investigate the potential decrease in breast cancer risk among long-term statin users.

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INTRODUCTION

3-Hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) inhibitors (statins) are a therapeutic class of agents that reduce plasma cholesterol levels by inhibiting hepatic HMG-CoA reductase, the rate-controlling enzyme in cholesterol synthesis.[1] Statins have been linked with several beneficial effects beyond their effect on cardiovascular disease, including reductions in risk of dementia,[2-4] fractures,[5-8] and cancer.[9-11]

A growing body of evidence suggests that statins may have chemopreventive potential against breast cancer. Laboratory studies demonstrate that statins induce apoptosis and reduce cell invasiveness in various cell lines, including breast carcinoma cells.[12-17] However, the clinical relevance of these data remains unclear. The results of

animal and mechanistic studies are difficult to extrapolate to humans, but they cannot be dismissed. At a minimum, they require us to look hard for such effects in human populations.

Several observational epidemiologic studies have examined the relationship between statins and breast cancer. The findings from these studies are inconsistent. Some studies reported that the use of these drugs is inversely related with the risk of breast cancer, whereas other studies found no or positive associations. However, randomized controlled trials (RCTs) of statins for cardiovascular outcomes have limited the ability to examine the relationship between statins and breast cancer because of the relatively small number of women enrolled and the relatively short follow-up periods.

Three meta-analyses of major RCTs demonstrated no association between the use of statins and the risk of fatal and nonfatal cancer.[18-20] However, it is unlikely that exposure to statins affects the incidence of all types of cancer, and increases or decreases in any specific type of cancer are likely to be masked by random variation in the effects of statins on all other cancers. Therefore, the end point of all cancers is not sensitive, and a negative finding does not imply a lack of an effect at a particular site, such as the breast. Thus, the effect of statins on the risk of breast cancer remains to be determined.

Given the widespread and long-term use of statins, more knowledge is needed on the relationship between these medications and breast cancer. To address this issue, we conducted a detailed meta-analysis of the studies published on the subject in peer-reviewed literature.

PATIENTS AND METHODS

Search Strategy

To identify the studies of interest, we conducted a computerized literature search. Sources included the Medline (1966 to March 2005) and Science Citation Index Expanded (1970 to March 2005) databases. Search terms included "HMG-CoA reductase inhibitor(s)" or "statin(s)" combined with "cancer(s)" or "neoplasm(s)" or "malignancy(ies)." The title and abstract of studies identified in the computerized search were scanned to exclude any studies that were clearly irrelevant. The full texts of the remaining articles were read to determine whether they contained information on the topic of interest. The reference lists of articles with information on the topic were reviewed to identify citations to other studies of the same topic. Previous meta-analyses[18-20] were searched for references to additional relevant reports.

Selection Criteria

The studies considered in this meta-analysis were either RCTs or observational epidemiologic studies (case-control or cohort studies) that evaluated exposure to statins and breast cancer risk. Articles were excluded from the analyses if there was insufficient published data for determining an estimate of relative risk (RR) or a CI. In studies with multiple publications from the same population, only data from the most recent publication were included in the meta-analysis, with reference in the text to the older publication.

Randomized clinical trials were considered eligible if they had a minimum duration of 3 years, enrolled at least 500 women, and reported either breast cancer mortality or diagnoses of nonfatal breast cancer occurring during the trial. Trials with more than 500 women were selected to minimize publication bias because publication of breast cancer data of such large studies is unlikely to depend on the magnitude and direction of their results.

We did not assess the methodologic quality of the primary studies (RCTs or observational studies) because quality assessment in meta-analysis is controversial. Scores constructed in an ad hoc fashion may lack demonstrated validity, and results may not be associated with quality.[21-23] Instead, we performed subgroup and sensitivity analyses because they are widely recommended.[23-25]

In this meta-analysis, we included studies reporting different measures of RR (risk ratio, odds ratio, incidence rate ratio, and standardized incidence ratio). In practice, these measures of effect yield similar estimates of RR because breast cancer is a rare occurrence.

Data Extraction

Two reviewers abstracted the data independently to a predefined form. The following data were collected from each study: (1) publication data, first author's last name, year of publication, and country of the population studied; (2) study design; (3) number of patients; (4) RR and 95% CI; (5) case definition for breast cancer; (6) definition of statin exposure; and (7) control for confounding factors by matching or adjustments, if applicable.

Risk ratios and 95% CIs were calculated for each RCT in an intent-to-treat analysis. In observational studies, when more than one estimate of effect (RR) was presented, the most adjusted estimate was chosen (ie, the estimate controlled for the largest number of potential confounders). Differences in data extraction were resolved by consensus, referring back to the original article.

Statistical Analysis

Studies were grouped on the basis of study design, and we conducted two separate meta-analyses (one meta-analysis of large RCTs and a second meta-analysis of observational epidemiologic studies). This was done to examine consistency of results across varying study designs with different potential biases.

We used the following two techniques to calculate the pooled RR estimates: the Mantel-Haenszel method,[26] assuming a fixed-effects model, and the DerSimonian-Laird method,[27] assuming a random-effects model. In the absence of heterogeneity, the fixed-effects and the random-effects models provide similar results. When heterogeneity is found, both models may be biased.[28] Publication bias was evaluated using the funnel graph, the Begg and Mazumdar adjusted rank correlation test,[29] and the Egger regression asymmetry test.[30]

To evaluate whether the results of the studies were homogeneous, we used the Cochran's Q test.[31] We also calculated the quantity I^2 that describes the percent variation across studies that is a result of heterogeneity rather than chance. Negative values of I^2 were put equal to zero, so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.[32] Furthermore, we compared the pooled RR estimates derived from the two separate meta-analyses (meta-analysis of RCTs *v* meta-analysis of observational studies) with a test of interaction.[33]

To evaluate the stability of the results, we also performed a one-way sensitivity analysis. The scope of this analysis was to evaluate the influence of individual studies by estimating the average RR in the absence of each study.[34] All *P* values are two tailed. For all tests, $P < .05$ was considered statistically significant.

This work was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology Group[23] and the Quality of Reporting of Meta-Analyses recommendations for improving the quality of meta-analyses of RCTs.[35] Stata 6 software (STATA Corp, College Station, TX) was used for the statistical analyses.

RESULTS

Search Results

Six hundred eighty-three records were identified by the primary computerized literature search. However, after screening the titles and abstracts, 644 studies were excluded because they were either laboratory studies, review articles, or irrelevant to the current study. We retrieved 39 potentially relevant manuscripts for further review. The full text was read, and the reference lists were checked. Finally, we identified 18 studies examining the association between use of statins and breast cancer risk.[36-53] Two studies were excluded from the meta-analysis because of the rule for multiple publications from the same population.[52,53]

The remaining 16 studies were included in the meta-analysis.[36-51] Seven of 16 studies were RCTs of statins for cardiovascular outcomes,[36-42] five were case-control studies,[44-46,49,50] and the remaining four were cohort studies.[43,47,48,51] The number of breast cancer patients ranged from 12 to 89 in the RCTs, from 65 to 1,132 in the case-control studies, and from three to 3,141 in the cohort studies.

Six of seven RCTs were trials of monotherapy with a statin compared with placebo,[36-41] whereas one RCT was a nonblinded trial comparing statin treatment with a usual care control group.[42] All RCTs reported site-specific cancer outcomes (secondary end points) including breast cancer. So, we were able to conduct a post hoc analysis of these trials and calculate risk ratios for breast cancer in an intent-to-treat analysis. All observational studies[43-51] were controlled for potential confounding factors (at least for age) by matching or adjustments.

The publication dates of the studies included in the meta-analysis ranged between 1993 and 2005. Study designs, along with the estimated RRs and 95% CIs, are listed in Tables 1 and 2 for the RCTs and the observational studies, respectively.

Meta-Analysis of RCTs

Seven large RCTs of statins contributed to the analysis.[36-42] Approximately 17,000 women (among 61,000 participants) were randomly assigned in the seven trials, with an average follow-up of nearly 5 years. The number of women enrolled onto the individual trials ranged from 576 to 5,082 (Table 1).

The two larger trials[40,42] reported a lower risk of breast cancer in the treatment group, whereas the other five trials[36-39,41] reported a higher risk. Only one study[37] reported a statistically significant difference (one patient in the placebo group *v* 12 in the treatment group), raising concerns regarding the safety of statins. However, this specific trial had enrolled the smallest number of women among the seven trials, and three of these 12 cancers occurred in women who previously had breast cancer.

Meta-analysis of all seven trials showed no evidence for an association between statin monotherapy and breast cancer risk. The overall incidence of breast cancer was 1.55% in the treatment group (132 incident cases of breast cancer) and 1.43% in the nontreatment group (122 incident cases). The association of statin use with breast cancer was not statistically significant either assuming a fixed-effects model (RR = 1.04; 95% CI, 0.81 to 1.33) or a random-effects model (RR = 1.19; 95% CI, 0.81 to 1.73; Table 3). Figure 1

Table 1. Randomized Controlled Trials Included in the Meta-Analysis

Study	Agent	Duration of Follow-Up (years)	Total No. of Patients	Women		Incident Breast Cancer					
						Statin Group		Nonstatin Group			
				No.	%	Patients	Total No.	Patients	Total No.	RR	95% CI
Strandberg et al[36]	Simvastatin	Median: 10.4	4,444	827	19	7	407	5	420	1.44	0.46 to 4.52
Sacks et al[37]	Pravastatin	Median: 5.0	4,159	576	14	12	286	1	290	12.17	1.59 to 92.97
LIPID Study Group[38]	Pravastatin	Mean: 6.1	9,014	1,516	17	10	756	8	760	1.26	0.50 to 3.17
Downs et al[39]	Lovastatin	Mean: 5.2	6,605	997	15	13	499	9	498	1.44	0.62 to 3.34
Heart Protection Study Collaborative Group[40]	Simvastatin	Mean: 5.0	20,536	5,082	25	38	2,541	51	2,541	0.75	0.49 to 1.13
Shepherd et al[41]	Pravastatin	Mean: 3.2	5,804	3,000	52	18	1,495	11	1,505	1.65	0.78 to 3.48
ALLHAT-LLT Research Group[42]	Pravastatin	Mean: 4.8	10,355	5,051	49	34	2,511	37	2,540	0.93	0.59 to 1.48

Abbreviations: RR, relative risk (risk ratio); LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

Table 2. Observational Studies Included in the Meta-Analysis

Study	Study Location	Study Design	All Female Patients (No.)	BRCA Patients (No.)	RR	95% CI	Control for Potential Confounders*
Friis et al[43] 2005	Denmark	Cohort	166,621	3,141	1.02	0.76 to 1.36	1-4
Boudreau et al[44] 2004	US	C-C	1,983	975	0.9	0.7 to 1.2	1, 5
Graaf et al[45] 2004	Netherlands	C-C	10,320	467	1.07	0.65 to 1.74	1-3, 6-9, 11-13
Kaye and Jick[46] 2004	UK	C-C	8,978	698	0.9	0.6 to 1.3	1, 14, 15
Beck et al[47] 2003	Canada	Cohort	67,472	879	1.09	0.93 to 1.28	1
Cauley et al[48] 2003	US	Cohort	7,528	244	0.31	0.10 to 0.98	1, 3, 16, 17
Coogan et al[49] 2002	US	C-C	2,463	1,132	1.5	1.0 to 2.3	1, 3, 14, 18-21
Blais et al[50] 2000	Canada	C-C	715	65	0.67	0.33 to 1.38	1, 9, 10, 13, 22
Lovastatin Study Groups[51] 1993	US, Canada, Finland	Cohort	241	3	1.15	0.37 to 3.55	1

Abbreviations: BRCA, breast cancer; RR, relative risk; C-C, case control; US, United States; UK, United Kingdom.
*Confounding factors: 1, age; 2, use of nonsteroidal anti-inflammatory drugs; 3, use of hormones; 4, use of cardiovascular drugs; 5, use of antihypertensive drugs; 6, use of diuretics; 7, use of angiotensin-converting enzyme inhibitors; 8, use of calcium channel blockers; 9, use of other lipid-lowering therapy; 10, use of fibric acids; 11, diabetes mellitus; 12, prior hospitalization; 13, comorbidity score; 14, body mass index; 15, smoking; 16, body weight; 17, family history of breast cancer; 18, education; 19, religion; 20, race; 21, alcohol consumption; and 22, previous neoplasms.

graphs the RRs and 95% CIs from the individual trials and the pooled results. The Cochran's Q test resulted in a $P = .10$ ($Q = 10.71$ on 6 *df*), and the corresponding quantity I^2 was 44%, both indicating that the heterogeneity among the studies was moderate (Table 3).

The funnel plot did not have the expected funnel shape. The left corner of the pyramidal part of the funnel, which should contain smaller trials reporting negative or null results, was missing (Fig 2). The *P* values for the Begg and Mazumdar test and Egger test were $P = .13$ and $P = .01$, respectively, suggesting the existence of publication bias, a phenomenon in which statistically significant results are more likely to be published compared with nonsignificant and null results.

Meta-Analysis of Observational Studies

Five case-control studies[44-46,49,50] and four cohort studies[43,47,48,51] evaluated exposure to statins and breast cancer risk. This time, the funnel plot had the expected funnel shape (Fig 2). The *P* values for the Begg and Mazumdar test and the Egger test were $P = .47$ and $P = .26$, respectively, both suggesting a low probability of publication bias. The Cochran's Q test resulted in a $P = .22$ ($Q = 10.75$ on 8 *df*), and the quantity I^2 was 26%, indicating that the results of the studies were homogeneous (Table 3). Statin use did not significantly affect the risk of breast cancer (fixed effects: RR = 1.03; 95% CI, 0.92 to 1.15; random effects: RR = 1.01; 95% CI, 0.88 to 1.17; Table 3).

After stratifying the data into subgroups on the basis of study design, we found no association between statin use and breast cancer either among case-control studies (RR = 1.00; 95% CI, 0.80 to 1.25, random effects) or among cohort studies (RR = 1.01; 95% CI, 0.79 to 1.29, random effects; Table 3). Figure 1 graphs the RRs and 95% CIs from the individual studies and the pooled results.

Overall Analysis

We compared the pooled RR estimates derived from the two separate analyses with a test of interaction.[33] Neither the difference between estimates obtained with fixed-effects models ($Z = 0.07$, $P = .94$) nor the difference between estimates obtained with random-effects models ($Z = 0.79$, $P = .43$) was statistically significant.

In addition, we performed a combined analysis of RCTs and observational studies. The *P* values for the Begg and Mazumdar test and Egger test were $P = .44$ and $P = .66$,

Table 3. Meta-Analysis Results

Study Type	No. of Studies	Fixed-Effects Model		Random-Effects Model		Tests of Homogeneity				Tests of Publication Bias	
		RR	95% CI	RR	95% CI	Q Value	*df*	*P*	I^2 (%)	Begg's *P*	Egger's *P*
All studies	16	1.03	0.93 to 1.14	1.02	0.89 to 1.18	21.46	15	.12	30	.44	.66
RCTs	7	1.04	0.81 to 1.33	1.19	0.81 to 1.73	10.71	6	.10	44	.13	.01
Observational studies	9	1.03	0.92 to 1.15	1.01	0.88 to 1.17	10.75	8	.22	26	.47	.26
Case-control studies	5	0.99	0.83 to 1.18	1.00	0.80 to 1.25	5.78	4	.22	31	.99	.99
Cohort studies	4	1.06	0.92 to 1.21	1.01	0.79 to 1.29	4.66	3	.20	36	.31	.33

Abbreviations: RR, relative risk; RCT, randomized controlled trial.

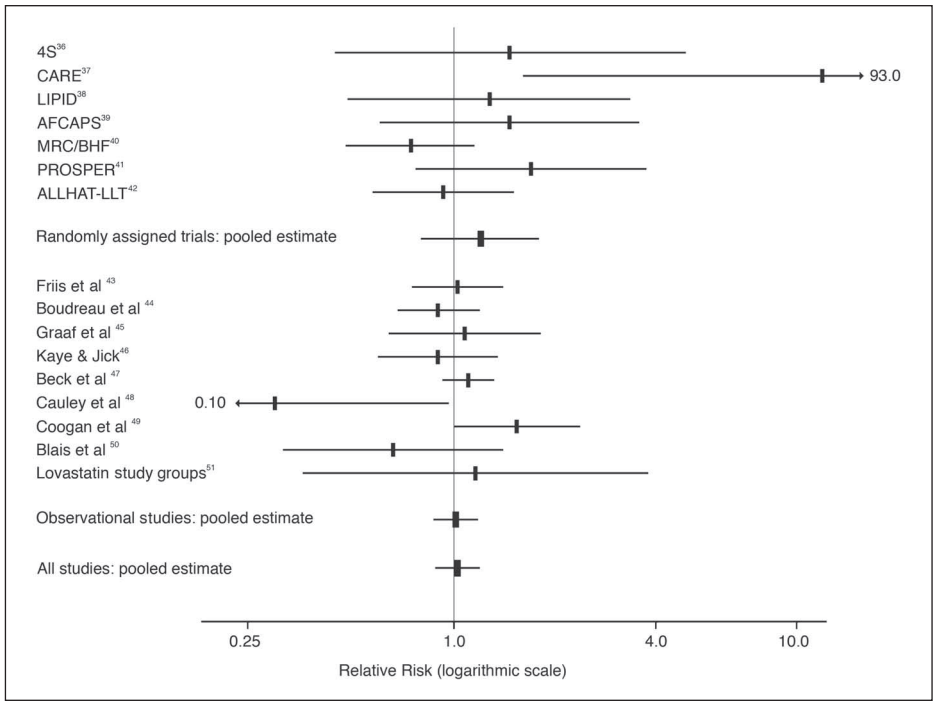

Fig 1. Results from individual studies[36-51] and meta-analyses. The relative risk and 95% CIs for each study are displayed on a logarithmic scale. Pooled estimates are from a random-effects model. 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; MRC, Medical Research Council; BHF, British Heart Foundation; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

respectively, suggesting a low probability of publication bias. Similarly, the Cochran's Q test resulted in a $P = .12$ ($Q = 21.46$ on 15 *df*), and the corresponding quantity I^2 was 30%, both indicating the absence of heterogeneity. Statin use did not significantly affect breast cancer risk (fixed effects: RR = 1.03; 95% CI, 0.93 to 1.14; random effects: RR = 1.02; 95% CI, 0.89 to 1.18; Table 3).

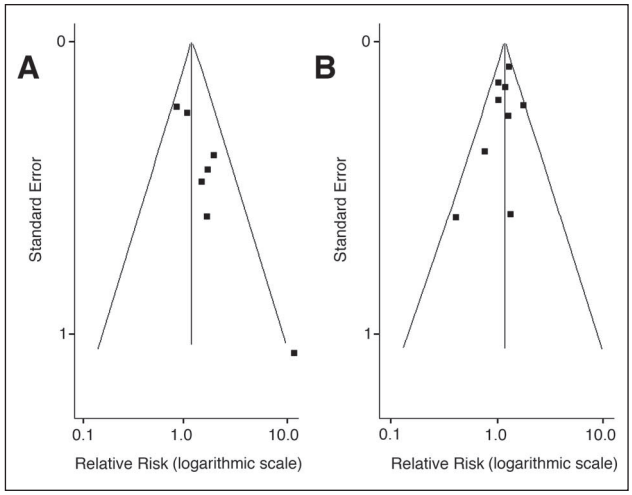

Fig 2. Funnel plots of the relative risk of developing breast cancer, by the SE, for all studies (■) included in the meta-analyses. Relative risks are displayed on a logarithmic scale. (A) For the randomized trials, $P = .13$ for the Begg and Mazumdar test, and $P = .01$ for the Egger test. (B) For the observational studies, $P = .47$ for the Begg and Mazumdar test, and $P = .26$ for the Egger test.

To evaluate the stability of the results, we also performed a one-way sensitivity analysis. In this analysis, the overall effect size was calculated, removing one study at a time. This analysis confirmed the stability of our results (Fig 3).

DISCUSSION

There is a long-standing debate concerning the association between use of statins and cancer. In a review of rodent carcinogenicity tests, Newman and Hulley[54] reported that lipid-lowering drugs, including statins, initiate or promote

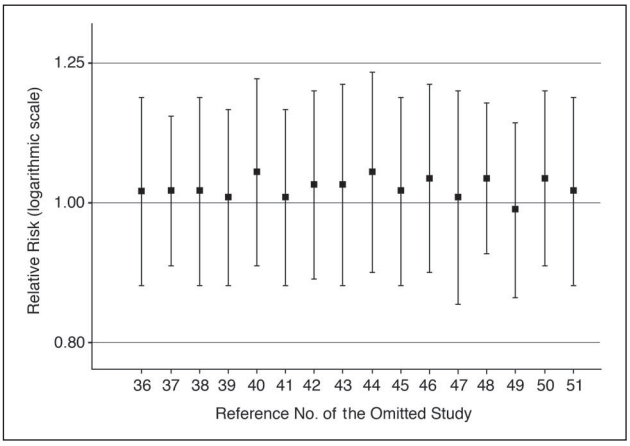

Fig 3. One-way sensitivity analysis. Pooled relative risk and 95% CIs omitting each study.

cancer in rats and mice. However, in most of the reviewed studies, the doses used were substantially higher than the recommended maximum doses for humans, and the employed bioassays were criticized for being inadequate to predict carcinogenicity in humans.[55]

In contrast, several recent laboratory studies indicated that statins may have chemopreventive potential against cancer at various sites including breast. However, the inhibitory effect of statins on breast cancer cells has thus far been tested only in vitro; statins may behave differently in vivo. Specifically, statins are selectively localized to the liver, and less than 5% of a given dose reaches the systemic circulation. Thus, the usefulness of statins as chemopreventive agents for breast cancer is doubted given their selective hepatic uptake and low systemic availability.[56,57]

Meta-analysis serves as a valuable tool for studying rare and unintended effects of a treatment. It extends prior randomized and nonrandomized studies by permitting synthesis of data and providing more stable estimates of effect. To the best of our knowledge, this is the first meta-analysis of published studies to evaluate specifically the association between statin use and breast cancer risk. It provides evidence that statin use is not associated with a substantially decreased or increased risk of breast cancer. Neither a chemopreventive nor a carcinogenic effect of statins on breast is supported by the data.

When meta-analysis of published literature is performed, consideration of study bias is critical. Existence of a bias in favor of publication of statistically significant results is well documented in the literature.[58-60] However, the likelihood of important selection or publication bias in our results is small. We did not exclude any article during the identification and selection process, and the Begg and Mazumdar test and the Egger's test revealed no relation between the estimate of RR and study size. So, we are confident that important publication bias as a result of preferential publication of large studies with significant findings is unlikely to have occurred. Similarly, the tests of heterogeneity indicated little variability between studies that cannot be explained by chance.

Nevertheless, our meta-analysis had several limitations. The first meta-analysis included a group of trials of statins for cardiovascular outcomes, which assessed the incidence of breast cancer as a secondary end point. The examined populations varied, and the risk of breast cancer was approximately three in 1,000 per year, which could make it difficult to detect any effects, either beneficial or harmful. Treatment and follow-up times only lasted for an average of 5 years, which could be thought to be too short a period (compared with the length of time needed for cancer to develop) to draw definite conclusions. In contrast, the second meta-analysis included observational studies that lacked the experimental random allocation of the intervention necessary to optimally test exposure-outcome hypotheses. These studies were also different in terms of study design and definitions of drug exposure.

Systematic reviews have found that randomized and nonrandomized studies often give different results and that the difference is in all directions.[61] In our case, it is noteworthy that the findings were similar in both meta-analyses of RCTs and observational studies, although the primary studies had varying study designs with different potential biases. This fact strengthened our confidence in the validity of our results.

However, the main issue remaining beyond our control in the present study is cancer latency. Because the exposure and follow-up periods of the cohort and the randomized studies included in our analyses were relatively short, estimates of cancer risk resulting from longer exposure to statins are not possible. Given the high and growing prevalence of statin use, it is important to continue monitoring their long-term safety profiles. Until then, physicians need to be vigilant in ensuring that use of statins remains restricted to the approved indications and that women are educated on other changes they can make to their lifestyle that are more likely to reduce their risk of developing breast cancer.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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