# The Impact of Statin Therapy on the Recurrence of Early-Stage Estrogen Receptor-Positive Breast Cancer: A Meta-Analysis

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## ABSTRACT

**Abstract:** Statins have been recognized for their significant role in mitigating drug resistance to endocrine therapy in breast cancer. A substantial body of research has indicated that statin usage is associated with a marked improvement in both overall survival rates and Breast Cancer-Specific Survival (BCSS) among patients. The objective of this research is to determine whether the use of statins influences the local recurrence in early-stage Estrogen Receptor-Positive (ER+) breast cancer patients. This investigation could provide crucial insights into the potential of statins as an adjunct therapy to reduce the risk of recurrence in this patient population.

**Materials and methods:** Our review encompassed three studies comparing the recurrence rates in stage I-III ER+ breast cancer patients who did and did not use statins. The endpoint focused on recurrence, with the inclusion criterion being studies that reported fully adjusted Hazard Ratios (HRs). Summary Odds Ratios (ORs) were derived using random-effects models. Publication bias and heterogeneity were evaluated through sensitivity analyses, Q statistic tests, and $I^2$ tests.

**Results:** Three population-based studies, comprising a total of 27163 patients with ER+ breast cancer, were included in our analysis: 4101 of whom were on statin therapy, and 23062 were not. The pooled OR revealed a notably significant 52% reduction in the risk of recurrence for patients who used statins compared to those who did not (Summary OR=0.43; 95% CI: 0.27–0.70, P=0.0006). Our analysis of three population-based studies, demonstrates a significant 57% reduction in recurrence risk for early-stage ER+ breast cancer patients treated with statins. However, it is crucial to acknowledge the substantial heterogeneity present among the studies, as indicated by an $I^2$ of 94% and a highly significant *chi-square* test (P <0.00001). Based on the leave-one-out sensitivity analysis plot, all three studies are within the confidence intervals of the overall effect estimate, which can suggest that the meta-analysis results are relatively robust. Regarding publication bias, Egger's test yielded a P-value of 0.1964, indicating no evidence of small-study effects or publication bias in this meta-analysis.

**Conclusion:** The pooled OR for statin use compared to non-use is 0.43 with a 96% CI of (0.27, 0.70). Despite the considerable variation in ORs and high heterogeneity, the conclusions drawn from the three studies are relatively consistent, indicating that the use of statins indeed reduces the recurrence rate in early-stage ER+ breast cancer patients.

**Keywords:** Breast cancer; Statins; Recurrence; Hormone receptor-positive;

Heterogeneity

## INTRODUCTION

Statins, a prevalent class of lipid-lowering medications, have emerged in recent years as potential anti-tumor agents, particularly within the realm of breast cancer therapy. And statins have an important positive effect on reducing drug resistance to endocrine therapy in breast cancer [1]. In recent years, several studies have reported the association between statin use and the survival rate of patients with breast cancer. Especially for triple-negative breast cancer, a more aggressive subtype, the use of statins has significantly improved the overall survival and breast cancer-specific survival rates of patients. Statin use post-diagnosis was associated with a reduced risk of cancer-specific mortality (HR, 0.85; 95% CI, 0.75-0.96). The reduction was more pronounced in women with hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer (HR, 0.71; 95% CI, 0.57-0.88) [2]. The purpose of this study is to determine whether statin lipid-lowering drugs can reduce the recurrence rate in patients with ER+ breast cancer.

## MATERIALS AND METHODS

### Literature search

This review adhered meticulously to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines, aiming to systematically compare the recurrence rates in hormone receptor-positive breast cancer patients between those treated with statins and those untreated. A comprehensive literature search was meticulously conducted by two independent reviewers, XiaoWen Ma and Jia Gao, employing established search strategies across various databases, including PubMed, Medline, Cochrane, and Web of Science. The search criteria were inclusive, spanning from January 1, 2004, to January 1, 2024. The search employed the following medical subject headings (MeSH): ("statin"(All Fields)) AND ("breast neoplasms"(MeSH Terms)) AND ((clinicalconference(Filter) OR clinicalstudy(Filter) OR clinicaltrial(Filter) OR comparativestudy(Filter) OR controlledclinicaltrial(Filter) OR multicenterstudy[Filter] OR observationalstudy(Filter) OR randomizedcontrolledtrial(Filter)) AND (fft(Filter))). All identified citations were independently assessed by the two authors and categorized as relevant or irrelevant. Studies deemed relevant were then selected for full-text review, and their reference lists were meticulously searched for additional significant citations. Ecological studies, case reports, reviews, and editorials were deemed ineligible for inclusion.

### Eligibility criteria

**Inclusion criteria:** 1) Studies published comprehensive adjusted risk estimates (at least accounting for age, tumor size, and lymph node status) comparing statin use versus no statin use in patients with ER+ breast cancer, without any prior history of cancer or metastatic disease. 2) They were independent studies that did not duplicate results already published in another article. 3) The studies reported HRs for recurrence rate, along with their corresponding 95% CIs. In this article, "recurrence" refers to local recurrence, regional recurrence, distant recurrence, and contralateral recurrence. The selected recurrence data pertain exclusively to patients who were prescribed statins following a breast cancer diagnosis, encompassing both those who continued statin use after diagnosis and those who initiated statin therapy subsequent to the diagnosis of breast cancer.

**Exclusion criteria:** 1) Studies lacking a comparative group between statin users and non-users. 2) Studies without comprehensive adjusted risk estimates for the specified factors. 3) Studies that did not report HRs with corresponding 95% CIs for recurrence rates.

**Data extraction:** Two reviewers, XiaoWen Ma and Jia Gao, independently and precisely extracted data, ensuring consensus on all outcomes. A standardized data-collection protocol was meticulously applied to compile pertinent data from each article selected for inclusion. For each eligible study, the following details were meticulously documented: 1) Lead author's name. 2) Publication year. 3) Comprehensive set of study characteristics, including research objective, patient recruitment timeframe, geographical context, eligibility criteria, median follow-up period, breast cancer stage, types of statistical adjustments made, median age of the patient cohort, and recurrence rate. Additionally, detailed information for each arm of the treatment groups was recorded, including: 1) Total number of patients in the statin use and no statin use cohorts. 2)

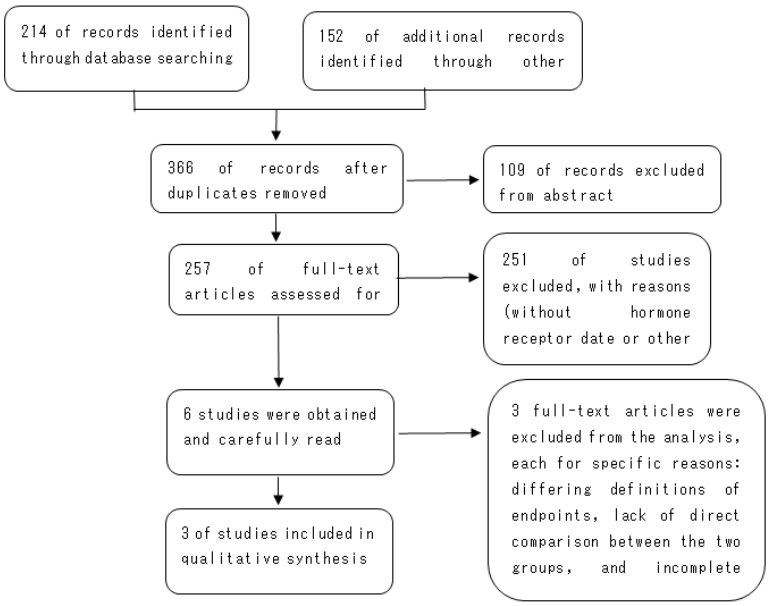
Distribution of patients across various tumor stages (T1, T2, T3 and Tx), nodal stages (N0, N1, N2 or more). 3) Duration and type of statin use. This rigorous approach to data extraction and documentation ensured the integrity and reliability of the information used in our systematic review and meta-analysis.

**Data analysis and statistical methods:** Each HR, meticulously adjusted for a comprehensive set of confounding variables, along with its corresponding confidence interval, was extracted and converted into an OR. The summary OR was calculated by pooling the study-specific estimates using random-effects models. The $I^2$ statistic was used to measure the extent of heterogeneity, representing the proportion of total variation across studies attributable to heterogeneity, with higher $I^2$ values indicating greater heterogeneity. Conventionally, an $I^2$ threshold below 50% is considered to represent an acceptable level of variability. Forest plots were generated, including both the study-specific estimates and the summary OR. Heterogeneity and sensitivity analyses were carefully evaluated, considering all possible factors that could influence the estimates, including adjustments for confounding factors, types of endpoints, and study design characteristics. Publication bias was assessed graphically using Egger's test. All statistical analyses were meticulously conducted using Stata software version 17 and the Cochrane Review Manager (RevMan) version 5.4.

## Findings

**Results of the search strategy:** A total of 366 articles were identified through the specified MeSH terms. Following an initial screening, 109 records were excluded based on the abstract, resulting in 257 articles selected for full-text review. We retrieved and meticulously examined all 6 eligible studies. Ultimately, 3 articles were excluded from the analysis: 2 for employing an alternative endpoint definition, and 1 for using endocrine therapy as a proxy for the inclusion criterion of hormone receptor positivity (Figure 1).

**Figure 1.** Flowchart of the article selection process.




## Description of studies

The meta-analysis provides a comprehensive description of the included studies, as detailed in Table 1. This table presents a thorough summary, including the total number of cases, publication years, geographical regions, and diagnostic periods, along with study designs, considerations for age and tumor stage, and follow-up durations. The analysis included a total of 27163 patients with ER+ breast cancer from 3 population-based studies: 4101 were on statin therapy, and 23062 were not. The timeframe for diagnosis and treatment across these studies ranged from 1996 to 2015, offering a substantial dataset for analysis. Of these three studies, one was prospective, while the other two were retrospective in nature.

**Table 1.** Characteristics of ER+ patients across the three studies.

| First author | Public year | Country and diagnostic time | Study type | Cases | Controls | BC stage | Median follow-up (months/years) | Outcomes measured |
|---|---|---|---|---|---|---|---|---|
| Ahern TP [3] | 2011 | Denmark 1996-2003 | Prospective cohort | 14200 | NA | I-III | 6.8 y | HR |
| Sim Y [4] | 2022 | Singapore 2005-2015 | Retrospective cohort | 5000 | NA | I-III | 8.67 y | HR |
| Borgquist S [5] | 2017 | Sweden 1998-2003 | Retrospective cohort | 7963 | Early postmenopausal ER+ | I-III | 8y | HR |

## Electrical physiological signals

Table 2 delineates the distribution of T and N stages among patient groups in the studies. The participants, all diagnosed with stages I-III breast cancer, underwent surgical treatment followed by standard postoperative endocrine therapy. Enrollment in the three studies was not subject to age limitations. Nevertheless, comprehensive TNM staging information was constrained, with detailed T and N stage data available for only one of the studies, as illustrated in Table 2.

**Table 2.** T and N stages and adjuvant therapies of the BCT group patients and mastectomy group patients.

| Study | Group | Mean age | Total case | T | | | | N | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | X | 0 | 1 | 2 or more |
| Ahern TP [3] | Statins use | NA | 2613 | NA | NA | NA | NA | NA | NA | NA |
| | No use | NA | 11587 | NA | NA | NA | NA | NA | NA | NA |
| Sim Y [4] | Statins use | NA | 851 | NA | NA | NA | NA | NA | NA | NA |
| | No use | NA | 4149 | NA | NA | NA | NA | NA | NA | NA |
| Borgquist S [5] | Statins use | NA | 637 | 165 | 385 | 138 | 9 | 413 | 208 | 76 |
| | No use | NA | 7326 | 1092 | 2880 | 1146 | 129 | 3095 | 1500 | 652 |

Table 3 presents a comparative analysis of the total patient count, recurrence incidence, recurrence rates, HRs, and P-values between early-stage ER+ breast cancer patients who were on statin therapy and those who were not, across the three studies. In each of these studies, the adjusted HRs are accompanied by confidence intervals that exclude the value of 1, with HRs less than 1. This suggests a consistent trend indicating that the recurrence rate among ER+ breast cancer patients who utilized statins is significantly lower compared to those who did not, highlighting the potential benefits of statin use in this patient population.

**Table 3.** The observed values and statistical results of each study.

| First author | Statins use | | | No use | | | Adjusted HR/OR and CI | P |
|---|---|---|---|---|---|---|---|---|
| | Total case (n) | Recurrence case | Recurrence rate (%) | Total case (n) | Recurrence case | Recurrence rate (%) | | |
| Ahern TP [3] | 2613 | 198 | 7.58 | 11587 | 2174 | 18.75 | 0.69 (0.55 to 0.88) | NA |
| Sim Y [4] | 851 | 59 | 6.93 | 4149 | 773 | 18.63 | 0.57 (0.43-0.76) | <0.001 |
| Borgquist S [5] | 637 | 124 | 19.47 | 7326 | 1881 | 25.68 | 0.84 (0.68-0.99) | 0.04 |

Table 4 presents the Newcastle-Ottawa Scale (NOS) scores for the three studies, each earning a score of 8 points, which is indicative of their high methodological quality.

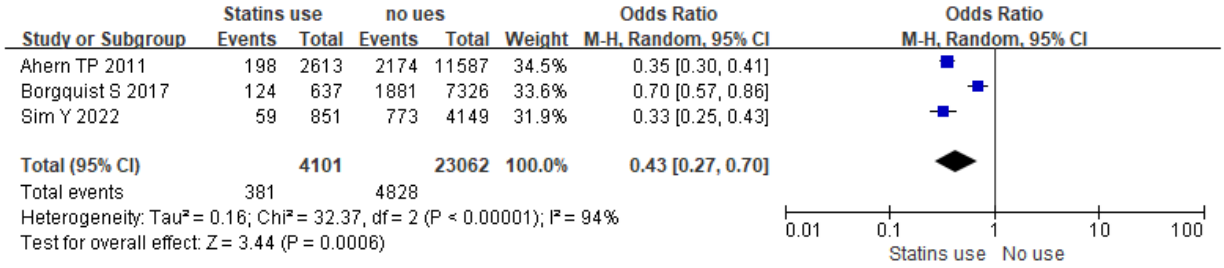
**Table 4.** Newcastle–Ottawa Scale (NOS).

| Study | Selection | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Quality score |
| Ahern TP [3] | ★ | | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Sim Y [4] | ★ | | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Sakellakis M [5] | ★ | | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |

## Meta-analysis findings

**Impact of statin use on recurrence risk in ER+ breast cancer:** Our meta-analysis, synthesizing data from three studies as depicted in Figure 2, compiled a total of three risk estimates. The aggregated OR reveals a notably significant 52% reduction in recurrence risk for patients on statin therapy compared to those not on statins (Summary OR=0.43; 95% CI: 0.2–0.70, P=0.0006), demonstrates a significant 57% reduction in recurrence risk for those treated with statins, as illustrated in Figure 2. This finding suggests that ER+ breast cancer patients who receive statins exhibit a substantial decrease in recurrence rates. However, it is crucial to acknowledge the substantial heterogeneity observed among the studies, with an $I^2$ statistic of 94% and a *chi-square* test P<0.00001. This high degree of heterogeneity suggests considerable variability in the study outcomes, which could potentially influence the overall interpretation of the results.

**Figure 2.** The forest plot compares the effects of statin use versus no use on the risk of recurrence in estrogen receptor-positive breast cancer.

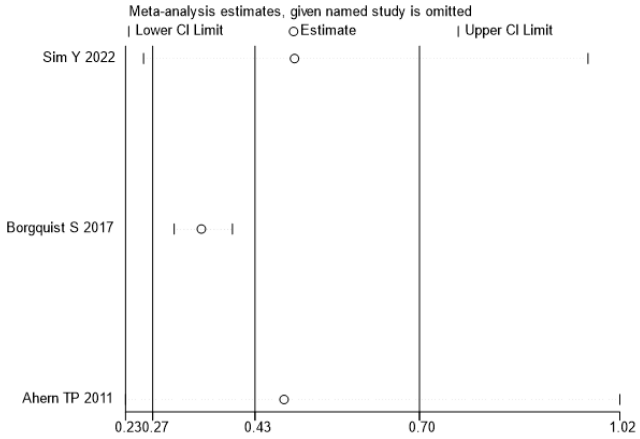



## Sensitivity analysis overview

Based on the leave-one-out sensitivity analysis plot (Figure 3), all three studies ("Sim Y 2022," "Borgquist S 2017," and "Ahern TP 2011") are within the confidence intervals of the overall effect estimate, which can suggest that the meta-analysis results are relatively robust. When each study is excluded in turn, the recalculated overall effect estimates (shown as circles) do not show significant deviation. The confidence intervals (horizontal lines) remain overlapping with the overall pooled estimate's confidence interval, indicating consistency.

"Sim Y 2022," "Borgquist S 2017," and "Ahern TP 2011" do not individually exert undue influence on the overall effect. The estimates remain reasonably stable, reinforcing the conclusion that the combined results of the meta-analysis are not unduly dependent on any single study.

**Figure 3.** The leave-one-out sensitivity analysis assesses the impact of statin use on recurrence risk in estrogen receptor-positive breast cancer.




## Egger's test for publication bias

The Egger's regression test is used to detect potential publication bias or small-study effects in a meta-analysis. The null hypothesis ($H_0$) is that there is no small-study effect, meaning the intercept (beta1) equals zero. Beta1=9.76: This is the estimated intercept from the Egger's test regression model. A significant deviation from zero could suggest the presence of small-study effects or publication bias. SE of Beta1=7.557: The standard error of the estimated intercept. Z=1.29: This is the test statistic for Egger's test. P-value=0.1964: The P-value indicates the probability that the observed value of the test statistic would occur if the null hypothesis were true. The P-value is greater than the conventional significance level of 0.05. This suggests that there is no evidence of small-study effects or publication bias in this meta-analysis based on Egger's test (Figure 4).

**Figure 4.** Public bias analysis for statins use *vs.* no use for ER+ breast cancer recurrence risk.

```
. meta bias, egger random(reml)

  Effect-size label: Log odds-ratio
        Effect size: _meta_es
          Std. err.: _meta_se

Regression-based Egger test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
            beta1 =      9.76
      SE of beta1 =     7.557
                z =      1.29
      Prob > |z| =    0.1964
```

## RESULTS AND DISCUSSION

A study [6] published in the journal Cancer pointed out that the overall survival rate of breast cancer patients taking statins could be relatively increased by 30%, while the BCSS rate could be relatively increased by 58%. This finding provides new insights into the treatment of breast cancer. There may be differences in the effects of different statins on improving the prognosis of patients with breast cancer. Hydrophobic statins (such as simvastatin, atorvastatin, etc.) have a statistically significant relationship with the improvement of patients' overall survival. And research on the recurrence rate of breast cancer, statin users displayed longer mean relapse-free survival (16.6 *vs.* 10.2 years, P=0.028). After data had been

adjusted for patient and disease characteristics, statin users maintained a lower risk of recurrence [4,7,8].
In this meta-analysis the combined OR for statin use versus no use is 0.43 with a 94% CI of (0.27,0.70). This result indicates that statin use is associated with a statistically significant reduction in the recurrence risk (OR<1) compared to no use, with a P-value of 0.0006, suggesting that the overall effect is statistically significant. Heterogeneity Statistics: $Chi^2$ (Q)=32.37, P <0.00001, $I^2$=94%, The *Chi-squared* test for heterogeneity shows a highly significant P-value, confirming the presence of significant heterogeneity among the included studies. This statistic quantifies the proportion of total variation in study estimates due to heterogeneity rather than chance. And there is considerable variation in effect sizes across the three studies. Ahern TP [3] and Sim Y [4] shows a much stronger effect than Borgquist S [5] which could suggest differences in study populations, methods, or definitions of outcomes.

## Discuss the sources of heterogeneity:

**Study-specific odds ratios and confidence intervals:** Ahern TP [3]: OR=0.35 (0.30, 0.41), with a weight of 34.5%. This study shows a strong association between statin use and risk reduction, contributing significantly to the overall pooled effect. However, it also has the smallest confidence interval, indicating high precision, likely due to its large sample size. Borgquist S [5]: OR=0.70 (0.57,0.86), with a weight of 33.6%. This study shows a moderate effect size that is smaller than Ahern TP [3] but still statistically significant. Its result is less extreme than Ahern TP [3] and has a wider confidence interval. Sim Y [4]: OR=0.33 (0.25, 0.43), with a weight of 31.9%, is similar to the result of Ahern TP [3]. Despite the considerable variation in ORs, the conclusions drawn from the three studies are relatively consistent, indicating that the use of statins indeed reduces the recurrence rate in early-stage ER+ breast cancer patients.

## Possible sources of heterogeneity

**The differences in the study populations are as follows:** Borgquist S [5] study population consists of postmenopausal early-stage breast cancer patients, which may lead to a lower recurrence risk compared to the other two studies that include patients of all ages. Sim Y [4] excluded patients who used statins before surgery, statin use was defined as use after surgery, while the other two studies included breast cancer patients who used lipid-lowering drugs before diagnosis and after diagnosis. Patients using lipid-lowering drugs may be older than those who have not used such drugs, which could lead to a younger study population in Sim Y [4] with a higher baseline recurrence risk.
**Sample size differences:** Ahern TP [3] has a much larger total sample size compared to the other two studies, which could lead to its greater weight and influence on the pooled effect size. The larger sample size may provide more precise estimates, but it can also introduce variability if the study population is significantly different from the others.
And the age baseline of the populations included in the three studies is inconsistent, but due to insufficient detailed data, statistical analysis is not possible, and only descriptive analysis can be conducted: In Ahern TP [3], the age distribution of the statin use group is 50–59 years old (33.7%) and 60–69 years old (40.9%), while for the nonuser group, it is 50–59 years old (33.2%) and 60–69 years old (27.4%). In Borgquist S [5], the statin user group represents 6% of those under 65 years old and 11% of those 65 and older. In Sim Y [4], the statin user group is predominantly aged 50-59 (35.0%) and 60-69 (35.8%), while the nonusers group is mainly 40-49 years old (33.9%) and 50-59 years old (33.2%).
**Differences in research methods:** Ahern TP [3] utilizes a nationwide population-based prospective cohort study, registered through the Danish Breast Cancer Cooperative Group (DBCG), employing the Cox proportional hazards model to estimate the association between statin use and breast cancer recurrence. Borgquist S [5] conducts a retrospective study, employing marginal structural Cox proportional hazards models to address potential biases due to cholesterol levels, specified endocrine treatments, patient-specific risk factors, practice variations, and enrollment locations, comparing patient use of CLM and breast cancer outcomes under different treatment allocations. Sim Y [4] is a retrospective study focusing on patients who used statins post-diagnosis, adjusting for variables such as cardiac events and diabetes through statistical models to eliminate the impact of confounding factors on the results.
The three studies include populations of different ethnicities, and the confounding factors excluded to interfere with the trials are not consistent, which may contribute to heterogeneity among the studies. Ahern TP [3], being a prospective cohort study, can better establish causal relationships compared to the other two retrospective cohort studies, reducing selection and recall biases and providing better control over the data collection process, thus making the results more persuasive.

## Specific differences in outcome evaluation

Ahern TP [3] conducted subgroup analyses that established a correlation between the use of lipophilic statins, such as simvastatin, and a reduced risk of breast cancer recurrence, while hydrophilic statins showed no significant association.

Borgquist S [5] observed significant improvements in Disease-Free Survival (DFS), Breast Cancer-Free Interval (BCFI), and Distant Recurrence-Free Interval (DRFI) for patients using lipid-lowering drugs at the initiation of endocrine therapy; however, these benefits were primarily limited to those undergoing letrozole treatment, with no subgroup analysis conducted on the types of lipid-lowering drugs. Sim Y [4] did not perform subgroup analyses regarding drug types or endocrine therapy. Affects the following:

**Increased heterogeneity:** The studies by Ahern TP [3] and Borgquist S [5] performed different levels of subgroup analyses on the use of lipid-lowering drugs and lipophilic statins, while Sim Y [4] did not perform subgroup analyses based on drug types or endocrine therapy. This inconsistency in analysis methods may lead to increased heterogeneity in the meta-analysis, meaning greater variability between study results, which could affect the overall effect estimate.

**Influence of confounding factors:** Studies that do not perform subgroup analyses based on drug types or endocrine therapy (such as Sim Y) may overlook potential confounding factors. For example, different types of statins (lipophilic *vs.* hydrophilic) or different endocrine therapies (e.g., letrozole *vs.* other drugs) may have varying impacts on the risk of breast cancer recurrence. Failing to distinguish these differences may lead to biased effect estimates.

By considering these factors, the findings suggest that while there is evidence of a beneficial effect of statin use, the differences between studies are substantial and should be explored further to understand the true magnitude and applicability of the observed effects.

### Mechanisms by which statins improve prognosis in breast cancer

ER+ breast cancer patients taking endocrine therapy may experience elevated blood lipid levels due to the reduction of estrogen levels. Statins, which lower blood lipid levels, could potentially improve the postoperative incidence of cardiovascular and cerebrovascular diseases in ER+ patients. On the other hand, statins primarily reduce cholesterol levels by inhibiting HMG-CoA reductase [9-11]. This action helps to diminish the lipid-rich environment required by breast cancer cells, thereby inhibiting tumor growth and spread.

The specific mechanisms include:

**Inhibition of tumor cell proliferation and migration:** Statins are capable of inhibiting the proliferation and migration of breast cancer cells, reducing the invasiveness of these cells [12]. This may be related to statins' ability to regulate the cell cycle, induce apoptosis, and inhibit tumor angiogenesis.

**Enhancement of the immune system's anti-tumor effects:** Statins may also improve the prognosis of breast cancer patients by enhancing the immune system's anti-tumor effects [14]. For example, statins can promote the maturation and activation of dendritic cells, enhancing the body's ability to recognize and eliminate tumor cells [15-20].

## CONCLUSION

In summary, statins have demonstrated significant potential in improving the prognosis of breast cancer patients. However, current research has some limitations, such as insufficient sample sizes and short follow-up durations. Therefore, future studies require large-scale, long-term clinical trials to further validate the efficacy and safety of statins in the treatment of early-stage ER+ breast cancer. Additionally, it is essential to delve into the specific mechanisms by which statins improve the prognosis of breast cancer, providing a scientific basis for personalized treatment of the disease.

## LIMITATIONS OF THIS STUDY

**The meta-analysis data:** Data were not sufficiently detailed to conduct a thorough subgroup analysis based on endocrine therapy medications or lipid-lowering drugs. Additionally, it did not allow for classification based on tumor size, presence of axillary lymph node metastasis, or other immunohistochemical results (such as Her-2 expression). Some laboratory and epidemiological studies have suggested that statins, a class of drugs commonly used to lower cholesterol levels, may have a positive impact on patients with triple-negative breast cancer. Due to the lack of consistent subgroup analysis, the conclusions of the meta-analysis may be limited and unable to clarify the specific relationships between certain drug types or therapy types and disease prognosis. This could result in more generalized findings, making it difficult to provide specific and targeted recommendations for clinical decision-making.

**Study design and generalizability:** The study relied on retrospective data, which is more susceptible to biases such as

selection bias and recall bias compared to prospective studies. And due to the limited number of studies and the specific patient populations they represent, the findings may not be generalizable to all ER+ breast cancer patients.

**Lack of long-term data:** The study did not include long-term follow-up data, which is essential for understanding the long-term effects of statin use on recurrence rates and overall survival.

**Dosage and duration:** Information regarding the dosage and duration of statin use was not detailed, which are important factors that could influence the effects of statins on breast cancer outcomes.

### Future perspectives and research directions

**Large-scale prospective studies:** Conducting large-scale, multicenter, prospective cohort studies to confirm the effects of statins on breast cancer recurrence rates, especially among ER+ patients. These studies should aim to collect more detailed data on statin usage, including type, dosage, and duration.

**Sub-group analysis:** Future studies should aim to perform subgroup analyses based on various factors such as the type of endocrine therapy, specific statin medications, tumor characteristics (size, grade, and molecular subtypes), and patient demographics to better understand the nuances of statin effects.

**Mechanistic studies:** Further laboratory and clinical research is needed to elucidate the mechanisms by which statins may influence breast cancer outcomes. This includes exploring the impact of statins on tumor cell proliferation, migration, angiogenesis, and immune response.

**Genetic and pharmacogenomic studies:** Investigating genetic factors that may influence individual responses to statin therapy could identify patients who are more likely to benefit from statin treatment.

**Randomized controlled trials:** While observational studies provide preliminary evidence, randomized controlled trials are needed to establish a causal relationship between statin use and breast cancer outcomes.

**Combination therapy:** Exploring the potential synergistic effects of statins in combination with other breast cancer treatments, such as chemotherapy, endocrine therapy, or targeted therapies.

**Disease surveillance:** Developing and validating predictive models that incorporate statin use along with other clinical variables to improve risk stratification and personalized treatment strategies for breast cancer patients.

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