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The association between statin use and non-Hodgkin lymphoma; a systematic review and meta-analysis

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ABSTRACT

Introduction: Statins reduce the cancer risk; however, non-Hodgkin lymphoma (NHL) evidence remains controversial. Therefore, we aimed to evaluate the relationship between statin consumption and NHL risk using a systematic review and meta-analysis.

Materials and Methods: In this systematic review and meta-analysis, international databases, including Scopus, PubMed, Web of Science, Cochrane, and Google Scholar search engines, were searched without a time limit up to September 21, 2023. Data analysis was performed using STATA 14 software, and the significance level was considered $P<0.05$.

Results: The results of combining 13 studies (9 case-control studies and 4 cohort studies) with a total sample size of 1 142 740 subjects showed that statin consumption could reduce NHL risk by 22% (RR: 0.78; 95% CI: 0.69, 0.88). Statin consumption in cohort studies reduced NHL risk by 14% (RR: 0.86; 95% CI: 0.77, 0.95), but in case-control studies, it reduced NHL risk by 26% (RR: 0.74; 95% CI: 0.62, 0.90). Furthermore, statin consumption reduced diffuse large B-cell lymphoma risk by 24% (RR: 0.76; 95% CI: 0.67, 0.87) and marginal zone risk by 26% (RR: 0.74; 95% CI: 0.59, 0.93). However, it did not affect reducing the risk of chronic lymphocytic leukemia/small lymphocytic lymphoma (RR: 0.94; 95% CI: 0.85, 1.05), follicular (RR: 0.96; 95% CI: 0.83, 1.10), plasma cell neoplasms (RR: 0.97; 95% CI: 0.70, 1.33), T cell lymphoma (RR: 0.81; 95% CI: 0.55, 1.19) and B cell lymphoma (RR: 0.94; 95% CI: 0.44, 2.01).

Conclusion: Statin consumption significantly reduced the risk of NHL, diffuse large B-cell lymphoma, and marginal zone but did not affect other NHL types.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023469126) and Research Registry (UIN: reviewregistry1732) website.

Implication for health policy/practice/research/medical education:
In a meta-analysis study on the correlation between statin consumption and NHL, we found that statin consumption significantly reduced the risk of NHL, diffuse large B-cell lymphoma, and marginal zone but did not affect other NHL types. This suggests that statins may have a protective effect specifically on certain subtypes of NHL.

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Meta-analysis

Introduction

Non-Hodgkin lymphoma (NHL) holds the distinction of being the preeminent hematologic malignancy observed in the adult population, and its incidence has increased worldwide (1-3). It is Canada's fifth most frequently identified malignancy is recognized as the sixth primary contributor to cancer-related fatalities (4). NHL represents a variegated assortment of malignancies, involving approximately 81 560 fresh incidences and 20,720 fatalities within the confines of the United States during the year 2021 (5). NHL has different subtypes, including diffuse large B-cell lymphoma, one of the most common invasive subtypes, accounting for 30% to 40% of all lymphomas (6). Several risk factors for NHL have been identified thus far. Said risk factors encompass immune deficiency disorders, organ transplantation, specific infections (such as HIV), as well as certain autoimmune disorders (such as rheumatoid arthritis) (7,8).

Statins are extensively utilized in the realm of medical practice for both the primary and secondary mitigation of cardiovascular ailments and cerebrovascular incidents (9,10). Laboratory and animal investigations have revealed that statins possess the ability to exert antitumor impacts via routes that are either dependent or independent on cholesterol. Moreover, statins have the capacity to generate effects that are antiproliferative, anti-inflammatory, and antiangiogenic (11). On the other hand, various studies have shown that statin consumption prevents cancer growth and metastasis (12-16).

Statins may reduce lymphoma risk as chronic inflammation is a potential risk factor for lymphoma (17). However, in some studies, statin consumption reduced NHL risk (18,19), and conversely, in other studies, statin consumption did not affect NHL risk (20-22). Statin consumption and NHL risk remain controversial and important. Therefore, we decided in this study to combine previous studies and investigate the relationship between statin consumption and NHL risk and its different types using a systematic review and meta-analysis.

Materials and Methods

This investigation was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (23), and its protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) website (CRD42023469126).

Search strategy

International databases, including Scopus, PubMed, Web of Science, Cochrane, and Google Scholar search engines, were searched without a time limit up to September 21, 2023. Standard keywords and Medical Subject Headings (MeSH) were used for searching: Lymphoma, Non-Hodgkin; Pleomorphic Lymphoma, Undifferentiated Lymphoma; Statin, Hydroxymethylglutaryl-CoA Reductase Inhibitors; HMG-CoA Reductase Inhibitor. Then, the keywords were combined using Boolean operators (AND, OR) to perform advanced searches. Finally, the reference lists of eligible primary studies were reviewed to complete the manual search. An example of the Web of Science search strategy is provided below: Lymphoma, Non-Hodgkin OR Pleomorphic Lymphoma OR Undifferentiated Lymphoma (All Fields) AND Statin OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR HMG-CoA Reductase Inhibitor (All Fields).

PICO component

- Population: Individuals who use statins. For this purpose, we evaluated studies that examined the association between statin consumption and NHL risk.
- Intervention: Statin consumption.
- Comparison: Individuals who never used statins.
- Outcomes: NHL risk and subtypes.

Inclusion criteria

The reviewed studies included cohort and case-control studies that examined the association between statin use and NHL risk.

Exclusion criteria

Inaccessible full text of studies, studies that evaluated the effect of statin and another drug combination on NHL, low-quality studies, abstract-only publications, duplicate studies, descriptive studies, and studies without sufficient data for analysis.

Quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used to evaluate observational studies quality (24). This checklist has 22 questions, and the score ranges from 0 to 44. The cutoff point for this checklist was considered 15 in this investigation. Finally, disagreements about the responses to the checklist questions were reviewed and turned into a specific option by consensus between the two evaluators.

Data extraction

Two independent researchers extracted the data from the studies. The researchers entered the extracted data into a checklist including author name, investigation publication year, study location, study design, age of statin group participants, age of non-statin group participants, total sample size (number of statin users and non-users), study duration, risk ratio between statin consumption and

NHL with its 95% confidence interval, risk ratio between statin consumption and each of the following subtypes: diffuse large B-cell lymphoma, chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), follicular, marginal zone, plasma cell neoplasms, T cell lymphoma, B cell lymphoma with their 95% CIs. The third researcher reviewed the data extracted by the two previous researchers to resolve any potential discrepancies.

Statistical analysis

The risk ratio (RR) index was used to combine study results. For this purpose, the logarithm of RR was calculated in each study. The Cochrane Q test and I^2 index were used to assess heterogeneity. The fixed effects model was used for low heterogeneity, and the random effects model was used for high heterogeneity. Therefore, we used the random effects model in this investigation (I^2=73.5%). The funnel plot was used to show whether bias existed in the literature search phase. Data analysis was performed using STATA 14 software, and the significance level was considered P<0.05.

Results

Study selection

After searching the databases, 122 articles were found. By reviewing the titles, 28 duplicate articles were removed. The abstract of the following 94 articles have been reviewed, and eight were excluded due to full-text inaccessibility. The full text of the remaining 86 articles was reviewed, and 25 articles were excluded due to incomplete information required for data analysis. Sixty-one articles remained, of which 48 more were excluded due to other exclusion criteria, and finally, 13 articles were included in the systematic review and meta-analysis process (Figure 1).

This meta-analysis examined 13 studies with a total sample size of 1,142,740 subjects (42,683 in the statin user group and 1,100,057 in the non-statin user group). Of these 13 studies, 9 were case-control studies, and 4 were cohort studies (Table 1).

According to Figure 2, the use of statins reduced the risk of NHL by up to 22%, with a relative risk of 0.78; 95% CI: 0.69, 0.88). Further analysis based on study design showed that in cohort studies, statin consumption reduced the risk of NHL by 14% (RR: 0.86; 95% CI: 0.77, 0.95). In case-control studies, statin consumption reduced the risk of NHL by 26% (RR: 0.74; 95% CI: 0.62, 0.90). All of these associations were statistically significant, as shown in Figure 3.

Afterwards, we studied the connection between taking statins and the risk of different types of NHL. Our research showed that statin usage reduced the risk of diffuse large B-cell lymphoma by 24% (RR: 0.76; 95% CI: 0.67, 0.87) and marginal zone lymphoma by 26% (RR: 0.74; 95%

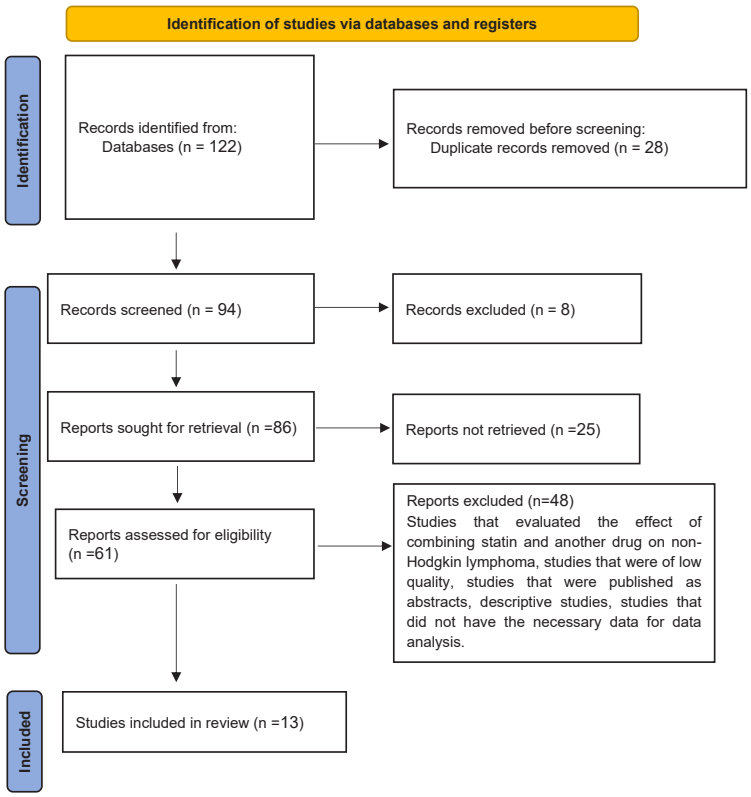

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Information of the articles that entered the systematic review and meta-analysis process

Author, year	Country	Type of Study	Sample size (total)	Sample size in statin group	Age in statin group (year)	Sample size in non-statin group	Age in non-statin group (year)	During the study period
Bedimo RJ, 2021 (20)	USA	Cohort	47940	23970	54	23970	49	From 2002– 2017
Liebow M, 2021 (21)	USA	Case-control	3902	1703	61.8	2199	61.6	Sep 2002 through Dec 2012
Desai P, 2018 (22)	USA	Cohort	161563	712	50-79	160851	NR	Through Sep 2012
Ye X, 2018 (18)	Canada	Case-control	32856	5541	>40	27315	>40	Between 1999 and 2014
Cho SF, 2015 (19)	Taiwan	Case-control	18657	1715	58.99	16942	58.73	Between 2005 and 2008
Fortuny J, 2006 (B-cell) (25)	Czech Republic, France, Germany, Ireland, Italy, and Spain	Case-control	4568	2362	NR	2206	NR	From 1998 to 2004
Iwata H, 2006 (B-cell) (26)	Japan	Case-control	1100	221	46-94	879	44-91	1995 and 2001
Jacobs EJ, 2011 (27)	USA	Cohort	133255	1504	>60	131751	NR	From 1997 to 2007
Chao C, 2011(28)	USA	Case-control	1554	259	43.2	1295	43.1	From 1996 to 2008
Bracci PM, 2007 (From 1988-1993) (29)	USA	Case-control	4106	1591	NR	2515	NR	1988-1993
Bracci PM, 2007 (From 2001-2006) (29)	USA	Case-control	4159	2078	NR	2081	NR	2001-2006
Friedman GD, 2008 (Men) (30)	USA	Cohort	361859	164	>20	361695	NR	August 1994 to Dec 2003
Friedman GD, 2008 (Women) (30)	USA	Cohort	361859	118	>20	361741	NR	Aug 1994 to Dec 2003
Zhang Y, 2004 (B-cell) (31)	USA	Case-control	1318	601	NR	717	NR	Between Jan 1996 and Jun 2000
Coogan PF, 2007(32)	USA	Case-control	4044	144	40-79	3900	40-79	1991 to 2005
Fortuny J, 2006 (T-cell) (25)	Czech Republic, France, Germany, Ireland, Italy, and Spain	Case-control	4568	2362	NR	2206	NR	From 1998 to 2004
Iwata H, 2006 (T-cell) (26)	Japan	Case-control	1100	221	46-94	879	44-91	1995 and 2001
Zhang Y, 2004 (T-cell) (31)	USA	Case-control	1318	601	NR	717	NR	Between Jan 1996 and Jun 2000

NR: Not reported.

CI: 0.59, 0.93) as demonstrated in Figures 4-7.

In contrast, statin consumption had no statistically significant effect on reducing the risk of chronic lymphocytic leukemia/ small lymphocytic lymphoma (RR: 0.94; 95% CI: 0.85, 1.05), follicular (RR: 0.96; 95% CI: 0.83, 1.10), plasma cell neoplasms (RR: 0.97; 95% CI: 0.70, 1.33), T cell lymphoma (RR: 0.81; 95% CI: 0.55, 1.19) and B cell lymphoma (RR: 0.94; 95% CI: 0.44, 2.01) (Figures 5, 6, 8, 9, 10).

Figure 11 shows that this investigation had no publication bias. The literature search phase was performed completely without bias because the publication bias funnel plot was not statistically significant ($P = 0.542$).

Discussion

This investigation showed that statin consumption reduced NHL risk by 22%. This rate was 14% for cohort and 26% for case-control studies, and we realized that statin consumption reduced NHL risk twice in case-control studies and was about twice that in cohort studies. In examining the subgroups, we also saw that the risk of diffuse large B-cell lymphoma in statin users was 24% lower than in those who did not use statins. Statin consumption also reduced marginal zone risk by 26%. However, the risk of chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular plasma cell neoplasms, T cell lymphoma, and B cell lymphoma did not differ significantly between statin users and non-users.

In a study by Ye et al, which investigated the association of statin consumption and NHL risk and survival, the results showed that statin consumption was correlated with a diminished risk of NHL (OR = 0.82, 95% CI 0.69–0.99) and the risk of marginal zone lymphoma was lower in statin consumers compared to those without (OR = 0.54, 95% CI 0.31–0.94). Still, no such association exists for other NHL subtypes (33). Based on Ponvilawan et al meta-analysis, which was performed on six studies and assessed the correlation between statin use and diffuse large B-cell lymphoma risk, statin consumption significantly reduced diffuse large B-cell lymphoma risk

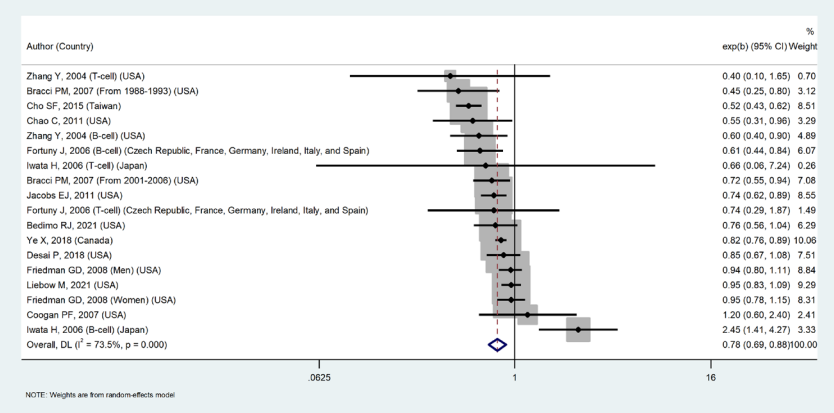

Figure 2. Forest plot of the association between statin and risk of non-Hodgkin lymphoma with its 95% confidence interval.

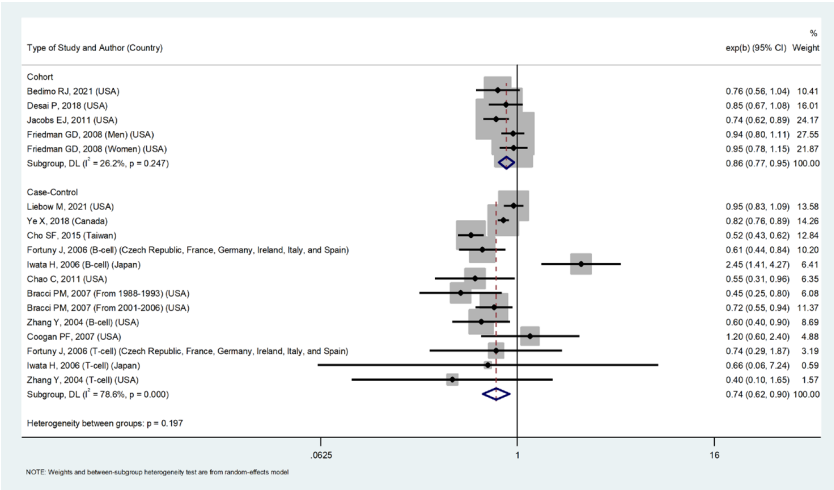

Figure 3. Forest plot of the association between statin and risk of non-Hodgkin lymphoma by type of studies with its 95% confidence interval.

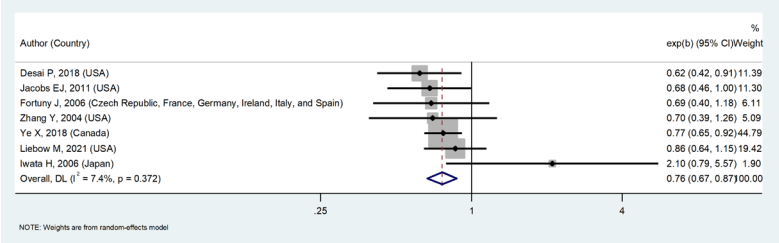

Figure 4. Forest plot of the association between statin and risk of diffuse large B-cell lymphoma with its 95% confidence interval.

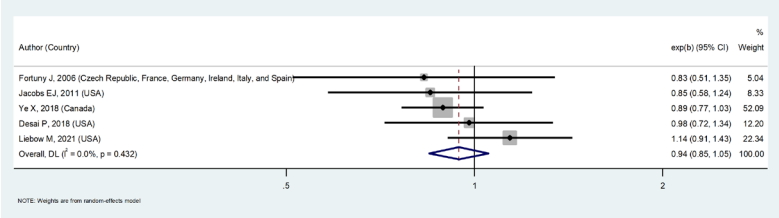

Figure 5. Forest plot of the association between statin and risk of chronic lymphocytic leukemia/small lymphocytic lymphoma with its 95% confidence interval.

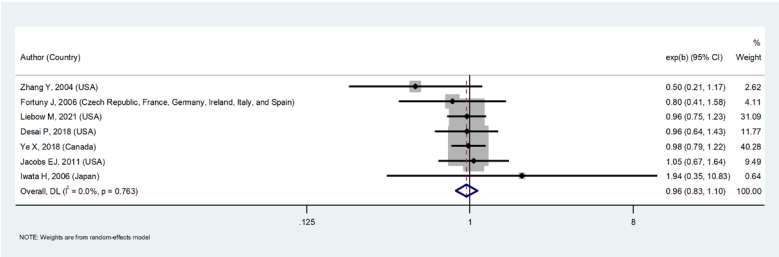

Figure 6. Forest plot of the association between statin and risk of follicular with its 95% confidence interval.

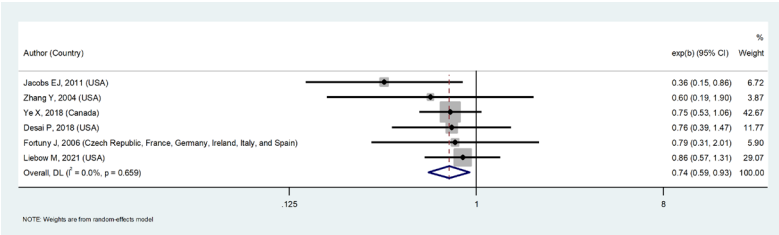

Figure 7. Forest plot of the association between statin and risk of marginal zone with its 95% confidence interval.

(OR: 0.70, 95% CI, 0.56-0.88; I2=70%) (34). In a meta-analysis, Pradelli et al examined 10 case-control and four cohort studies. The results showed that statin consumption compared to non-use was correlated with diminished risk of all hematological malignancies (RR: 0.86; 95% CI: 0.77–0.96), leukemia (RR: 0.83; 95% CI; 0.74–0.92) and NHL (RR: 0.81; 95% CI: 0.68 to 0.96) but not with multiple myeloma (RR: 0.89; 95% CI: 0.53–1.51) (35). In the meta-analysis by Xi et al which investigated the association of statin use with hematological malignancy risk, the results demonstrated that statin consumption was correlated with a 19% diminish in hematological malignancies (RR = 0.81, 95% CI: 0.70, 0.92) and a 28% diminish in NHL risk (RR = 0.72, 95% CI: 0.59, 0.87) (36). Additionally, the meta-analysis by Zhang et al which assessed correlation between statin use and

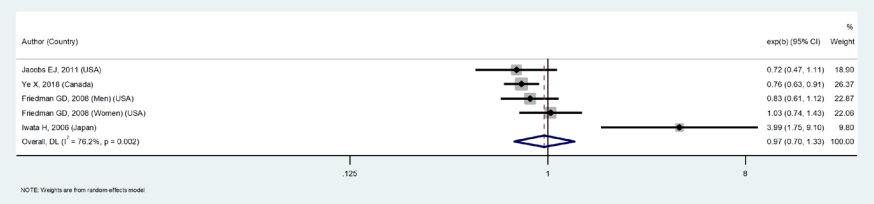

Figure 8. Forest plot of the association between statin and risk of plasma cell neoplasms with its 95% confidence interval.

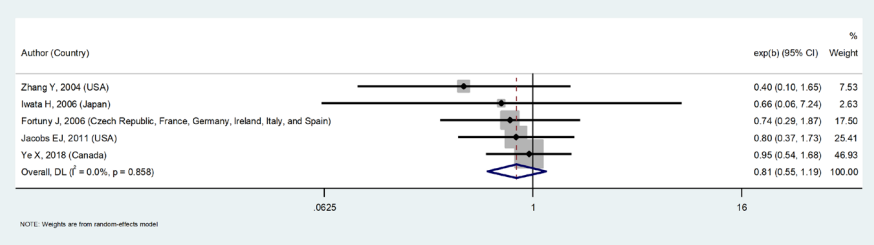

Figure 9. Forest plot of the association between statin and risk of T cell lymphoma with its 95% confidence interval.

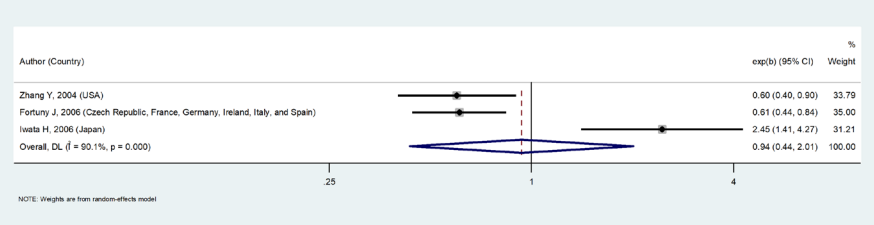

Figure 10. Forest plot of the association between statin and risk of B cell lymphoma with its 95% confidence interval.

multiple myeloma risk, the risk of multiple myeloma was significantly lower in statin users (RR = 0.77, 95% CI 0.63 to 0.95) (37). The above studies' results were consistent with our meta-analysis's results. All studies indicated that statins reduce the risk of hematological malignancies, including NHL. Since inflammation is one of the factors involved in NHL and statins are anti-inflammatory, it is obvious that the risk of NHL is lower in statin users than non-users.

Another meta-analysis by Karbowska et al conducted on 2,797,186 patients, and investigated the correlation of statin therapy with pancreatic cancer risk, the incidence of pancreatic cancer was lower in the statin consumer group compared to non-users (OR = 0.83; 95% CI: 0.72–0.96) (38). Based on the meta-analysis by Su et al on 11,870,553 patients, statin consumption significantly reduced gastric cancer risk (RR: 0.72; 95% CI: 0.64–0.81) (39). Likewise, Islam et al, in a meta-analysis of 59 073 patients with hepatocellular carcinoma, found that statin consumption could reduce the risk of liver cancer (RR: 0.54, 95% CI: 0.47–0.61) (40). As you can see in the results of the mentioned studies, in addition to hematological malignancies, statin consumption has also been effective in reducing the risk of gastric, liver, and pancreatic cancers, consistent with our study's overall conclusion.

However, Xu et al, in a meta-analysis aimed at investigating the correlation of statin consumption with prostate cancer risk, indicated that statin consumption was not significantly associated with prostate cancer risk (RR = 0.94, 95% CI: 0.82–1.08) (41). This investigation was inconsistent with our results. Because in our investigation, statin consumption reduced NHL risk, nevertheless in the study by Xu et al, statin consumption did not reduce prostate cancer risk. Of course, the differences between these two meta-analyses should also be considered. For example, our study population is men and women, while the investigation by Xu et al was performed only on men. In addition, the sample size, patients' age, and disease type examined in these two studies are completely different. This can lead to differences in the final results of the studies.

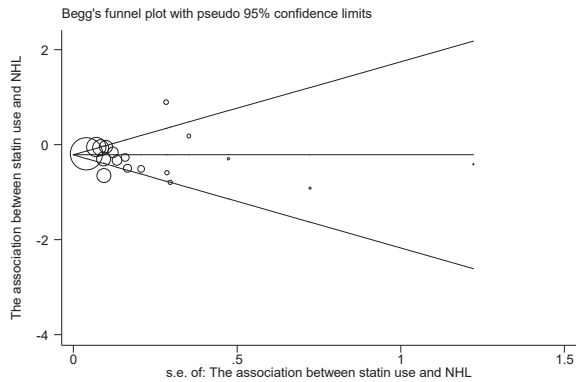

Figure 11. Publication bias funnel plot.

Conclusion

Our findings indicate that statin consumption reduces NHL risk. This association was statistically significant and confirmed in both cohort and case-control studies. Statin consumption was correlated with reduced risk of some non-Hodgkin's lymphomas (diffuse large B-cell lymphoma and marginal zone). Still, it did not affect other non-Hodgkin's lymphomas (CLL/SLL, follicular plasma cell neoplasms, T cell lymphoma, and B cell lymphoma). This suggests that statins may be a safe and harmless treatment for non-Hodgkin's lymphomas. Since, no evidence was found in this investigation indicating statins as a risk factor for non-Hodgkin's lymphomas. Statin administration does not harm NHL patients but can also be beneficial.

Limitations of the study

Limitations for this study are included the following items; the investigation had an uneven distribution of studies across different geographical regions. Most reviewed studies were conducted in the USA. In some countries, no studies were conducted in this field. The type of statin was not specified in the reviewed studies. We could not compare the effect of different statin types on NHL risk, such as atorvastatin or rosuvastatin. The statin dosage was not determined and examined in different studies; therefore, we could not compare the effect of low and high statin doses on NHL risk. The duration of statin consumption by participants in the reviewed studies was not specified, subsequently it was impossible to compare the effect of short-term and long-term statin consumption on NHL risk. Gender is an important factor in many diseases, and since most of the mentioned studies did not report the results of statin consumption on NHL risk by patient gender, we could not compare the effect of statin consumption on NHL risk in women and men. Another important and influential variable is patients' age. Since most of the studies examined in this investigation did not report the mean age of patients, it was impossible to compare statin effects on NHL risk in young and elderly individuals.

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Authors' contribution

Conceptualization: Anna Ghorbani Doshantapeh.
Data curation: Nasim Zaman Samghabadi and Seyede Sara Pakdaman Kolour.
Formal analysis: Atieh Nouralishahi.
Investigation: Navid Asgari and Anna Ghorbani Doshantapeh.
Methodology: Atieh Nouralishahi and Mostafa Assarroudi.
Validation: Razieh Bagheri Shahzadeh Aliakbari.
Project management: Seyede Sara Pakdaman Kolour.
Resources: Anahid Cheraghalian, Elahe Zaremoghadam.
Supervision: Anna Ghorbani Doshantapeh.
Visualization: Navid Asgari.
Writing–original draft: Atieh Nouralishahi, Mostafa Assarroudi, Anahid Cheraghalian, Navid Asgari, and Anna Ghorbani Doshantapeh.
Writing–reviewing and editing: Razieh Bagheri Shahzadeh Aliakbari, Nasim Zaman Samghabadi, Elahe Zaremoghadam, and Seyede Sara Pakdaman Kolour.

Conflicts of interest

There are no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42023469126) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1732). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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