REVIEW

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Statin Use and Liver Cancer Risk: A Meta-Epidemiological Study of Retrospective Cohort Studies by the Types of Constructed Cohort

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Abstract

Objective: Previous systematic reviews of retrospective cohorts (RSC) indicate that statin use decreases the risk of liver cancer. However, the summary effect size (sES) of the randomized controlled trials was not statistically significant. This study aimed to conduct a subgroup meta-analysis based on the types of constructed cohorts. **Methods:** RSCs were selected from previous systematic reviews. Based on the characteristics of the source database (national vs. hospital) and the selection criteria of the subjects (population vs. patients), RSCs were categorized into three types of study cohorts: a national-based population cohort (NPo), national-based patient cohort (NPa), and hospital-based patient cohort (HPa). The sES and 95% confidence intervals were calculated using a random-effects model. **Result:** The 28 cohorts from 23 RSC were classified into 15 NPa, 7 NPo, and 6 HPa. The sES of 15 NPa decreased the liver cancer risk with statin intake history with statistical significance, but 7 NPo lost statistical significance. **Conclusion:** The lack of statistical significance in NPo supports the argument that the conclusions of existing systematic reviews on RSC have low validity. It is necessary to conduct a subgroup meta-analysis of the NPo, NPa, and HPa proposed in this study when conducting a systematic review of RSCs, which will evaluate various outcomes of a specific drug intake with time-varying exposure.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors- Liver neoplasms- Bias- Data linkage

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Introduction

According to the Global Cancer Statistics 2020 report, primary liver cancer ranks sixth and third in incidence and mortality rates, respectively [1]. The incidence of hepatocellular carcinoma in high-risk countries has been dramatically reduced by introducing vaccination against the Hepatitis B virus [2]. Contrastingly, the incidence rates in formerly low-risk countries have increased, possibly partly because of the increasing prevalence of obesity and diabetes [3, 4]. Accordingly, the possibility of liver cancer chemoprevention using statins with lipid-lowering effects has been suggested [5].

Table 1 summarizes the summary effect sizes (sES) of the 17 systematic reviews conducted to evaluate the association between statin intake history and liver cancer risk by study design [5- 21]. The sES of the observational studies showed a statistically significant protective effects, but that of the randomized controlled trials (RCT) had not statistically significant. In other words, the sES between the RCT and observational studies were different.

All follow-up studies selected by the 17 systematic reviews in Table 1 were retrospective cohort studies (RSC), which are vulnerable to notorious biases in pharmaco-epidemiological studies evaluating the outcomes of a specific drug, especially using electronic health record databases [22, 23]. Confounders by indications or contraindications should be considered because the history of specific drug intake varies depending on the underlying diseases in each cohort participant [24]. Moreover, immortal time bias should also be considered because the intake history of each cohort participant was a time-varying exposure [25]. These biases systematically underestimate the outcome risk in the group prescribed the drug of interest [24, 26, 27]. Yeh et al. (2022) [28] reported that statin use is not associated with the risk of liver cancer in patients with diabetes after controlling for time-dependent confounders. To interpret the conflicting results between RCT and RSC in evaluating the association between statin use and liver cancer risk, a meta-epidemiological study should be conducted according to the types of constructed cohort and methods of controlling potential confounders (MCPC) in RSC.

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Materials and Methods

The selection criterion for the subgroup analysis was 'a retrospective cohort study to evaluate the association between statin intake history and the risk of liver cancer. In addition, some RSCs not selected in the previous systematic reviews were searched using the 'similar articles' tool provided by PubMed on June 30, 2023 [29].

The RSCs secured using the above processes were reviewed for duplicates. It was determined when all the following three points were satisfied: the source database, period of constructing the historical cohort, and criteria for selecting subjects. If a duplication was found, the RSC with the highest number of liver cancer cases was selected.

Based on the characteristics of the source database (national vs. hospital) and the selection criteria of subjects (population vs. patients), the studies were categorized into three types of study cohorts: a national-based population cohort (NPo), national-based patient cohort (NPa), and hospital-based patient cohort (HPa). The MCPC was checked during the process of cohort construction and statistical analysis in each RSC.

STATA statistical software (STATA Corp, TX, USA, version 17) was used to calculate sES and 95% confidence intervals (CI) using a random-effects model [30]. Statistical significance was set at 0.05.

Results

Of the 17 systematic reviews listed in Table 1, 25 RSC studies were selected for subgroup meta-analysis. In addition, six RSCs not selected in the systematic reviews were secured using a similar articles option provided by PubMed [28, 31-35]. After excluding eight duplicated articles (Table 2), 23 RCS with 28 cohorts were finally selected for subgroup meta-analysis (Figure 1) [28, 31-52].

Table 3 summarizes the source database, selected subjects, and MCPC for each article. Fourteen RSC were considered, and several MCPC were applied (/26=60.9%). Propensity score (n=10), time-varying model (n=6), matching date (n=3), and inverse probability of treatment weighting (n=3) were applied to the MCPC. The 28 cohorts from the 23 RSC were classified into 15 NPa, 7 NPo, and 6 HPa groups based on the characteristics of the constructed cohort.

Follow-up results for the 28 cohorts were extracted from 23 RSCs (Table 4). The subgroup meta-analysis of 15 NPa decreased the risk of liver cancer in patients with a history of statin intake; however, seven NPo lost statistical significance (Figure 2). These findings did not change in the subgroup meta-analysis when MCPC was

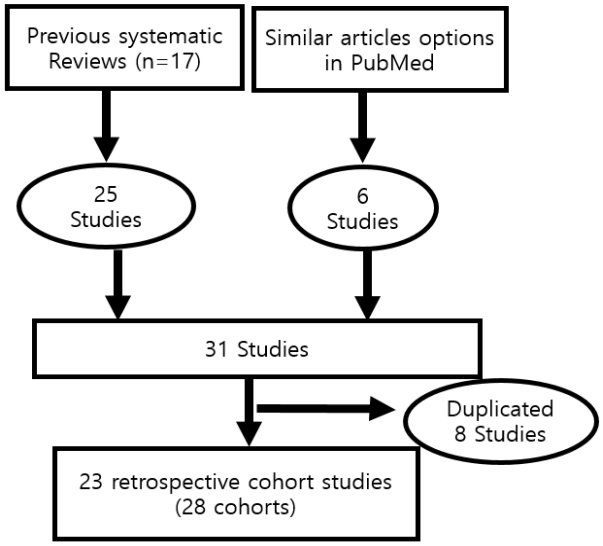

Figure 1. The Flow Chart of the Final Selection for Subgroup Meta-Analysis

Table 1. Summary Repots* of Published Systematic Reviews for Evaluating the Association between Statin Intake History and Liver Cancer Risk

First author (year) [reference]	Searching to	All selected	Randomized Trials	Follow-up Studies	Case-Control studies
Pradelli (2013) [6]	Mar 2012	0.58 (0.46-0.74) [5]	-	[3]	[2]
Singh (2013) [7]	May 2012	0.63 (0.52-0.76) [10]	0.95 (0.62-1.45) [3]	0.58 (0.42-0.81) [4]	0.63 (0.49-0.81) [3]
Shi (2014) [8]	Mar 2014	0.58 (0.51-0.67) [12]	1.06 (0.66-1.71) [1]	0.51 (0.44-0.58) [5]	0.63 (0.54-0.73) [6]
Zhong (2016) [9]	Mar 2016	0.60 (0.53-0.69) [24]	0.96 (0.62-1.49) [3]	0.53 (0.46-0.62) [11]	0.71 (0.60-0.83) [6]
Zheng (2017) [10]	Sep 2016	0.45 (0.36-0.57) [5]	-	-	-
Yi (2017) [11]	Feb 2017	0.46 (0.24-0.68) [6]	-	0.37 (0.18-0.55) [4]	0.64 (0.33-0.94) [2]
Li (2022) [12]	Jan 2019	0.47 (0.38-0.56) [10]	-	0.49 (0.40-0.58) [7]	0.39 (0.13-0.64) [3]
Khazaaleh (2022) [13]	May 2019	0.57 (0.49-0.67)[20]	0.98 (0.63-1.51) [3]	0.63 (0.52-0.75) [7]	0.53 (0.44-0.65) [11]
Gu (2019) [14]	Jun 2019	0.75 (0.64-0.86) [4]	-	-	-
Chang (2020) [15]	Jul 2019	0.54 (0.42-0.66) [18]	-	0.50 (0.38-0.67) [11]	0.57 (0.43-0.75) [8]
Islam (2020) [16]	Sep 2019	0.54 (0.47-0.61) [24]	0.95 (0.61-1.47) [3]	0.49 (0.42-0.57) [10]	0.56 (0.46-0.67) [12]
Li (2020) [17]	Sep 2019	0.54 (0.44-0.66) [13]	-	-	-
Facciourusso (2020) [18]	Dec 2019	-	0.98 (0.76-1.32) [3]	0.52 (0.41-0.73) [16]	
Wong (2021) [19]	Apr 2020	0.57 (0.52-0.62) [13]	-	-	-
Wang (2021) [20]	Oct 2020	0.57 (0.49-0.65) [26]	-	-	-
Wang (2022) [5]	Jan 2021	0.58 (0.51-0.67) [29]	0.95 (0.62-1.45) [3]	0.59 (0.48-0.72) [18]	0.54 (0.42-0.70) [10]
Zeng (2023) [21]	Mar 2022	0.52 (0.37-0.72) [10]	-	-	-

*, summary effect size (95% confidence intervals) [number of selected articles]

Table 2. Results of Evaluating Duplication among Retrospective Cohort Studies Selected for Subgroup Meta-Analysis

Source database	Periods of the constructed cohort	Participants	Selected	Excluded
Taiwan's National Health Insurance Research Database	1997-2012	Hepatitis B viral infection	Lee et al. (2019)	Tsan et al. (2012), Wu et al. (2012), Chen et al. (2015), Fu et al. (2015),
Taiwan's National Health Insurance Research Database	1999-2010	Hepatitis C viral infection	Tsan et al. (2013)	Huang et al. (2015), Chang et al. (2017)
Electronically Retrieved Cohort of HCV Infected Veterans	1996-2009	Hepatitis C viral infection	Simon et al. (2016)	Butt et al. (2015). Mohanty et al. (2016)

administered. The four cohorts without MCPC in the HPa group also showed no statistical significance.

Discussion

A new finding of this subgroup meta-analysis is that the NPo group lost statistical significance, whereas the NPa group showed the same results as the systematic reviews in Table 1. This indicates that the sES of the seven NPo group and of the RCT showed the same position.

This study is the first to conduct a subgroup meta-analysis to stratify the constructed historical cohorts into NPo, NPa, and HPa, based on the nature of the source database and the selection criteria of the subjects. An NPo is representative of a population in a national database, but an NPa loses its merit. Although an NPa could represent specific patients, it would be harder to manage time-varying exposure than an HPa because a national database has a less detailed drug intake history than a hospital database. Thus, the NPa was the most vulnerable to time-varying confounders among the three types of constructed cohorts. As previous systematic reviews most commonly selected NPa studies, the results could be interpreted as being underestimated by uncontrolled hidden confounders.

Additionally, some systematic reviews did not consider the duplication of the constructed cohort among the selected RSCs. Eight RSCs [54-61] were excluded after checking for duplicate sample (Table 2). Thus, the sES in Table 1 can be interpreted as a summary value over-

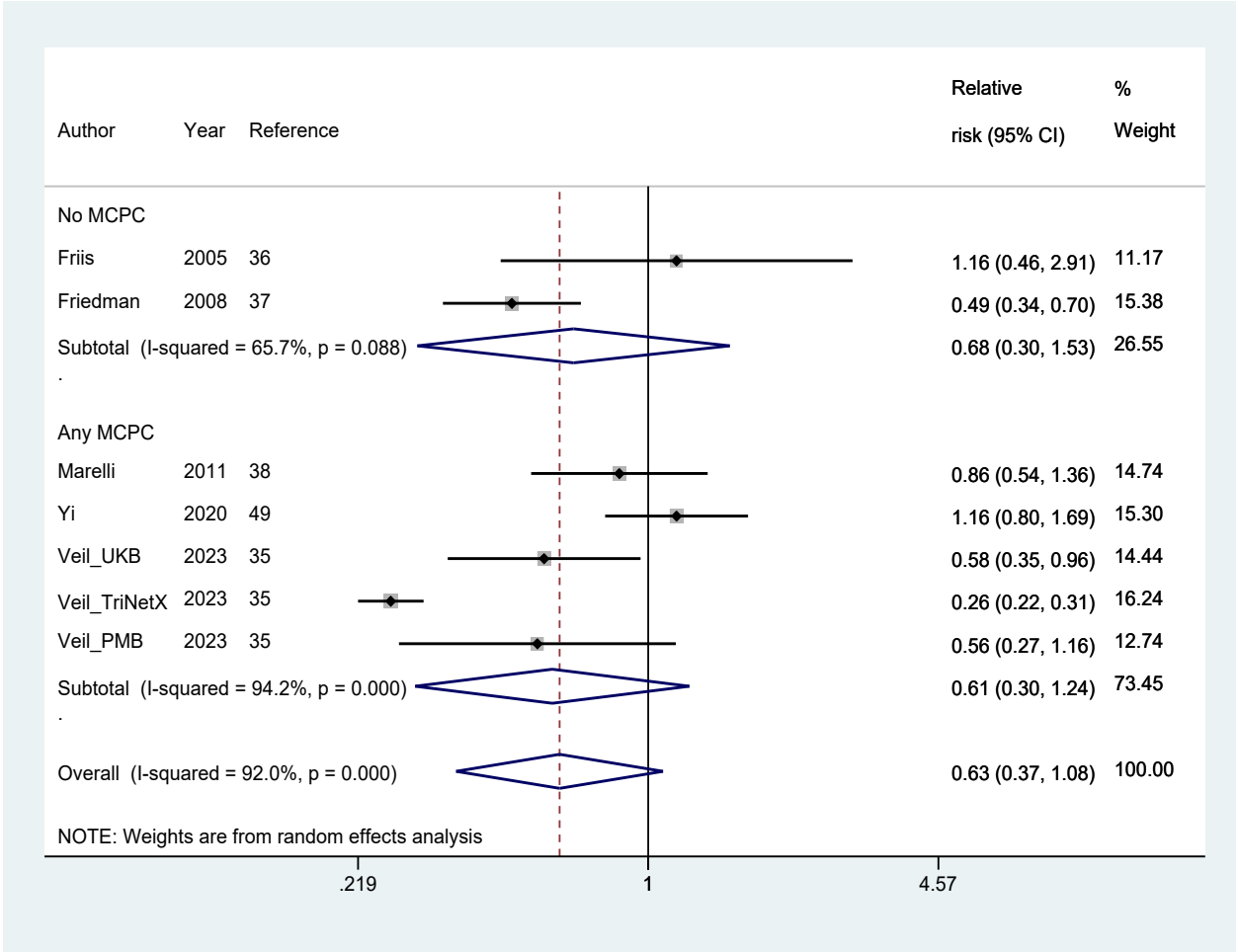

Figure 2. The Forest Plot of Subgroup Meta-Analysis by Methods of Controlling Potential Confounders (MCPC) in National based Population Cohorts

Table 3. Evaluation of Applying Methods of Controlling Potential Confounders in the 23 Retrospective Cohort Studies

First author (year)	Databases	Subjects*	Controlling confounders†
Friis (2005)	Nationwide	Population	none
Friedman (2008)	Nationwide	Population	none
Marelli (2011)	Nationwide	Population	PS
Tsan (2013)	Nationwide	HCVI	none
Galli (2014)	Hospital	HIV	none
Kumar (2014)	Hospital	LC	none
Hsiang (2015)	Hospital	HBVI	PS/TVM
Simon (2016)	Nationwide	HCVI	none
Lee (2017)	Nationwide	NAFLD	TVM
Tsai (2017)	Hospital	HBV/LC	none
Lee (2019)	Nationwide	HBVI	MD/PS
Simon (2019)	Nationwide	HBCI	PS/TVM
Goh (2020)	Hospital	HCVI	TVM
Yi (2020)	Nationwide	Population	none
Chiu (2021)	Nationwide	AUD	MD/PS
Pinyopornpanish (2021)	Hospital	LC	none
Kim (2022)	Nationwide	CRF	PS
Sung (2022)	Nationwide	CRF	PS/TVM
Yeh (2022)	Nationwide	DM	TVM/MSM-IPTW
Kraglund (2023)	Nationwide	ALC	MD
Lu (2023)	Nationwide	HF	PS
Veil (2023)	Nationwide	Population	PS/IPTW
Zou (2023)	Nationwide	NAFLD	MD/PS/IPTW

* ALC, alcohol-related cirrhosis; AUD, alcohol user disorder; CRF, chronic renal failure; DM, diabetes mellitus; HBVI, hepatitis B viral infection; HCVI, hepatitis C viral infection; HF, heart failure; HIV, human immunodeficiency virus; LC, liver cirrhosis; NAFLD, non-alcoholic fatty liver disease; † MD, matching date; PS, propensity score; IPW, inverse probability of treatment weighting; MSM, marginal structural models; TVM, time-varying model

Table 4. Subgroup Analysis Stratified by Kinds of Constructed Cohorts and Methods of Controlling Potential Confounders (MCPC)

Constructed cohorts	MCPC	sRR (95% CI) {cohorts}
All		0.57 (0.48-0.67) {28}
	No	0.57 (0.45-0.73) {8}
	Yes	0.56 (0.45-0.69) {20}
Nationwide, patient-based		0.55 (0.45-0.67) {15}
	No	0.53 (0.49-0.57) {2}
	Yes	0.55 (0.43-0.70) {13}
Nationwide, population-based		0.63 (0.37-1.08) {7}
	No	0.68 (0.30-1.53) {2}
	Yes	0.61 (0.30-1.24) {5}
Hospital, patient-based		0.59 (0.38-0.92) {6}
	No	0.65 (0.32-1.29) {4}
	Yes	0.52 (0.28-0.97) {2}

CI, confidence intervals; sRR, summary relative risk

weighted by specific source databases.

This study secured six additional RSCs that were not selected in the 17 reviews in Table 1 using the 'similar articles' tool provided by PubMed. As the most recent search date in Table 1 was March 10, 2022 [16], five RSCs, except Lu et al. (2023) [34], should be considered in previous systematic reviews. As they were categorized into four NPa, one HPo, and one HPa, adding these RSCs did not affect the sES for any of the RSCs. However, these findings support the usefulness of using citation discovery tools provided by PubMed in a meta-epidemiological study that evaluates the reason for contradictory results from several systematic reviews under the same hypothesis [29, 53].

Interpreting the two findings of the subgroup meta-analysis was challenging. First, the effect of four HPa without MCPC was not statistically significant. It can be concluded that HPa is a more appropriate cohort than NPa for a pharmaco-epidemiological study evaluating the outcomes of a drug of interest in specific patients because a hospital database could provide more detailed information on exposure history than a national database. Second, the sES of NPo and NPa were not sensitive to the application of MCPC. The fact that sES in NPa treated with MCPC still showed a protective effect could be inferred that the applied MCPC was incomplete in controlling time-varying confounders. The finding that sES in the NPo without applying MCPC showed no statistical significance suggests that constructing a historical cohort would be more helpful than applying MCPC in managing hidden confounders.

The main limitation of this study was that the gold standard for interpreting the subgroup meta-analysis results was not based on the consistent results of 17 systematic reviews but on the sES of three RCTs. This is because RCTs are the preferred study design for MCPC [24]. Because the sES of NPo cohorts has the same meaning as that of RCTs, NPo rather than NPa is recommended when conducting an RSC with a national database.

In conclusion, the lack of statistical significance in the sES of NPo supports the argument that the conclusions of existing systematic reviews on RSC have low validity. As an RSC examining various outcomes of a specific drug intake as time-varying exposure has the possibility of systematic errors, constructing a cohort and define criteria for participants in the design stage, and applying various MCPCs in the analysis stage is critical. Furthermore, it is necessary to conduct a subgroup meta-analysis using NPo, NPa, and HPa proposed in this study when conducting a systematic review of these RSCs.

Author Contribution Statement

None.

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