Statin Intake and Gastric Cancer Risk: An Updated Subgroup Meta-analysis Considering Immortal Time Bias

Jong-Myon Bae

Department of Preventive Medicine, Jeju National University College of Medicine, Jeju, Korea

A retrospective record-linkage study (RLS) based on medical records containing drug prescription histories involves immortal time bias (ITB). Thus, it is necessary to control for this bias in the research planning and analysis stages. Furthermore, a summary of a meta-analysis including RLSs that did not control for ITB showed that specific drugs had a preventive effect on the occurrence of the disease. Previous meta-analytic results of three systematic reviews evaluating the association between statin intake and gastric cancer risk showed that the summary hazard ratio (sHR) of the RLSs was lower than 1 and was statistically significant. We should consider the possibility of ITB in the sHR of RLSs and interpret the results carefully.

Key words: Data linkage, Bias, Hydroxymethylglutaryl-CoA reductase inhibitors, Stomach neoplasms, Meta-analysis

Pharmacoepidemiology studies can be categorized by their design as retrospective record-linkage studies (RLSs) based on medical records containing drug prescription histories, and prospective post-hoc analyses of randomized controlled trials (PRTs) [1,2]. However, RLSs applying secondary data involve immortal time bias (ITB); thus, it is necessary to control for this bias in the research planning and analysis stages [3]. A study participant must survive the period between entry into the cohort and the first prescription of the medication being evaluated in order to receive the medicines for incident-free follow-ups [4]. The ITB systematically underestimates the incidence rate in the group exposed to the medication; thus, a RLS might conclude that the drug prevents the outcome analyzed in the study [5]. Furthermore, a summary of a meta-analysis including RLS studies that did not control for ITB showed that specific drugs had a preventive effect on the occurrence of the disease.

While approximately 50% of gastric cancers may be triggered by several risk factors [6], there is increasing interest in chemoprevention against gastric cancer based on the preventive effect of eradicating Helicobacter pylori [7]. Liu et al. [8] reported that simvastatin inhibited gastric cancer cells by suppressing RhoA activity, and den Hoed and Kuipers [9] suggested that statin intake may lead to a modest reduction of gastric cancer risk.

The author searched PubMed for relevant articles published through May 2, 2022. Table 1 summarizes the meta-analytic results of 3 systematic reviews evaluating the association between statin intake and gastric cancer risk [10-12]. The summary hazard ratio (sHR) of the RLSs was lower than 1 and was statistically significant [11,12]. However, the selected PRT articles differed between the 2 studies [10,11], with the sHR showing conflicting results. For a more scientifically rigorous interpretation, an updated subgroup meta-analysis [13,14] of 8 articles [15-22] included in the 3 systematic reviews is presented in Table 1. Although there were 3 papers published using the same cohort (the Korean National Health Insurance Service cohort) through the search date [18,23,24], the study of You et
al. [18], with the longest follow-up period, was selected as a representative. A forest plot illustrated that the sHR of the 4 RLSs [15-18] showed a consistent preventive effect, whereas that of the 4 PRTs [19-22] did not (Figure 1).

Several methods including matching, analysis using time-dependent covariates, and the difference of cumulative incidence, have been suggested to control for ITB [3,25]. Cheung et al. [17] conducted a sensitivity analysis to control for ITB by treating all medications, including statins, as time-varying covariates in a multivariable Cox model. However, any RLS should consider other time-related biases, including protopathic bias, latency time bias, time-window bias, immeasurable time bias, and depletion of susceptibility, in addition to ITB [3]. Therefore, the possibility of ITB in the sHR of RLSs should be considered. It would be more appropriate to deduce that there is no association between statin intake and gastric cancer risk based on PRTs, because PRTs enable a more scientifically valid interpretation of the data than RLSs. Furthermore, Hippisley-Cox and Coupland [20] reported a difference in the hazard ratio between men and women (Figure 1); therefore, the effect of statin intake according to sex should be evaluated in future studies.

Table 1. Summary hazard ratios (sHRs) and their confidence intervals (CIs) of the published systematic reviews

| Study          | Searching  | Selected | sHR (95% CI) | I-squared (%) |
|----------------|------------|----------|--------------|---------------|
| Singh et al. 2013 [10] | Dec 2012   | 3 PRT    | 0.83 (0.66, 1.05) | -             |
| Wu et al. 2013 [11]      | Mar 2013   | 3 PRT    | 0.73 (0.53, 0.93) | 28.5          |
|                          |            | 3 RLS    | 0.87 (0.77, 0.99) | 24.7          |
| Seo et al. 2022 [12]     | 2020       | 5 RLS    | 0.71 (0.59, 0.85) | 68.0          |

PRT, post-hoc analysis of a randomized controlled trial; RLS, record-linkage study.

Table 2. Forest plot by study design. RLS, record-linkage study; PRT, post-hoc analysis of a randomized trial; ES, effect size; CI, confidence interval.

| Year of publication | Gender | ES (95% CI) | Weight |
|---------------------|--------|-------------|--------|
| Friedman 2008       | Men    | 0.86 (0.69, 1.07) | 10.07  |
| Friedman 2008       | Women  | 1.13 (0.83, 1.53) | 9.48   |
| Haukka 2010         | Both   | 0.84 (0.76, 0.92) | 10.64  |
| Cheung 2020         | Both   | 0.44 (0.28, 0.69) | 8.36   |
| You 2020            | Men    | 0.53 (0.40, 0.69) | 9.70   |
| You 2020            | Women  | 0.37 (0.26, 0.53) | 8.99   |
| Subtotal (I-squared = 87.1%, p = 0.000) | | 0.66 (0.50, 0.87) | 57.23  |

| Year of publication | Gender | ES (95% CI) | Weight |
|---------------------|--------|-------------|--------|
| Sato 2006           | Both   | 1.69 (0.44, 6.45) | 2.96   |
| Hippisley-Cox 2010  | Men    | 0.80 (0.72, 0.88) | 10.63  |
| Hippisley-Cox 2010  | Women  | 1.58 (1.47, 1.70) | 10.70  |
| Matsushita 2010     | Both   | 0.66 (0.44, 0.99) | 8.68   |
| CTT 2012            | Both   | 0.95 (0.73, 1.23) | 9.80   |
| Subtotal (I-squared = 96.9%, p = 0.000) | | 1.00 (0.65, 1.55) | 42.77  |
| Overall (I-squared = 96.0%, p = 0.000) | | 0.78 (0.60, 1.03) | 100.00 |

NOTE: Weights are from random effects analysis.
Ethics Statement
This study was waived by an ethics review board because the study subjects were published articles.

CONFLICT OF INTEREST
The author has no conflicts of interest associated with the material presented in this paper.

FUNDING
This work was supported by the 2022 education, research, and student guidance grant funded by Jeju National University.

ACKNOWLEDGEMENTS
None.

AUTHOR CONTRIBUTIONS
All work was done by JMB.

ORCID
Jong-Myon Bae https://orcid.org/0000-0003-3080-7852

REFERENCES
1. Park BJ, Cho YK, Kim SA. Construction of the Korea Elderly Pharmacopeidemiologic Cohort: drug utilization review of cephalosporins in geriatric inpatients. Pharmacoepidemiol Drug Saf 2001;10(6):487-492.
2. Jones JK. Pharmacogenetics and pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2001;10(5):457-461.
3. Suissa S, Dell’Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2020;29(9):1101-1110.
4. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf 2007;16(3):241-249.
5. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;167(4):492-499.
6. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric cancer: epidemiology, risk factors, classification, genomic characteristics and treatment strategies. Int J Mol Sci 2020;21(11):4012.
7. Shah SC, Peek RM Jr. Chemoprevention against gastric cancer. Gastrointest Endosc Clin N Am 2021;31(3):519-542.
8. Liu Q, Xia H, Zhou S, Tang Q, Zhou J, Ren M, et al. Simvastatin inhibits the malignant behaviors of gastric cancer cells by simultaneously suppressing YAP and β-catenin signaling. Onco Targets Ther 2020;13:2057-2066.
9. den Hoed CM, Kuipers EJ. Gastric cancer: how can we reduce the incidence of this disease? Curr Gastroenterol Rep 2016;18(7):34.
10. Singh PP, Singh S. Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. Ann Oncol 2013;24(7):1721-1730.
11. Wu XD, Zeng K, Xue FQ, Chen JH, Chen YQ. Statins are associated with reduced risk of gastric cancer: a meta-analysis. Eur J Clin Pharmacol 2013;69(10):1855-1860.
12. See SI, Park CH, Kim TJ, Bang CS, Kim JY, Lee KJ, et al. Aspirin, metformin, and statin use on the risk of gastric cancer: a nationwide population-based cohort study in Korea with systematic review and meta-analysis. Cancer Med 2022;11(4):1217-1231.
13. Harris RJ, Deeks JJ, Altman DG, Bradburn MJ, Harbord RM, Sterne JA. Metan: fixed-and random-effects meta-analysis. Stata J 2008;8(1):3-28.
14. Bae JM. Meta-epidemiology. Epidemiol Health 2014;36:e2014019.
15. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf 2008;17(1):27-36.
16. Haukka J, Sankila R, Klaukka T, Lonqqvist J, Niskanen L, Tanskanen A, et al. Incidence of cancer and statin usage—record linkage study. Int J Cancer 2010;126(1):279-284.
17. Cheung KS, Chan EW, Wong AY, Chen L, Seto WK, Wong IC, et al. Statins were associated with a reduced gastric cancer risk in patients with eradicated helicobacter pylori infection: a territory-wide propensity score matched study. Cancer Epidemiol Biomarkers Prev 2020;29(2):493-499.
18. You HS, You N, Lee JW, Lim HJ, Kim J, Kang HT. Inverse association between statin use and stomach cancer incidence in individuals with hypercholesterolemia, from the 2002-2015 NHIS-HEALS data. Int J Environ Res Public Health 2020;17(3):1054.
19. Sato S, Ajiki W, Kobayashi T, Awata N; PCS Study Group. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary scle-
20. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010;340: c2197.

21. Matsushita Y, Sugihara M, Kaburagi J, Ozawa M, Iwashita M, Yoshida S, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoepidemiol Drug Saf 2010;19(2): 196-202.

22. Cholesterol Treatment Trialists’ (CTT) Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One 2012;7(1):e29849.

23. Oh TK, Song IA. Drug-specific and dosage effects of statins and the risk of cancer: a population-based cohort study in South Korea. Eur J Cancer Prev 2021;30(2):188-194.

24. Cho MH, Yoo TG, Jeong SM, Shin DW. Association of aspirin, metformin, and statin use with gastric cancer incidence and mortality: a nationwide cohort study. Cancer Prev Res (Phila) 2021;14(1):95-104.

25. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. J Am Soc Nephrol 2008; 19(5):841-843.