Letters

RESEARCH LETTER

Association Between Aspirin and Cholangiocarcinoma in a Large Asian Cohort

A few observational studies have investigated aspirin as a potential chemopreventive agent for cholangiocarcinomas (CCAs), but the evidence is still limited.[1-4] Petrick et al[1] analyzed US-based cohorts, but medication information was based on self-report. Choi et al[2] and Altaii et al[3] analyzed US hospital-based case-control data, but duration and dose information was limited. A meta-analysis reported a pooled odds ratio of 0.56 (95% CI, 0.32-0.96), but the interpretability is limited because of the significant heterogeneity (I^2, 98%).[4] As prevention trials may not be feasible because of the low incidence of CCA, we sought to address the question using a well-designed observational study.

Methods | We analyzed a sample cohort from the Korean National Health Insurance Services of health examination recipients 40 years or older (N = 514 866) using a validated study design and operational definitions.[5] The institutional review board of Seoul National University Hospital approved the study protocol, and the ethics committee waived the consent requirements because the database was anonymously managed at all stages. A CCA case was defined as a patient with a new diagnosis with the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnosis code C24 or C22.1 from January 1, 2007 (index date), to December 31, 2013. Controls were matched, with a 1:5 ratio, using incidence density sampling stratified by age, sex, income decile, and disability registry status. The participants were censored with all-cause mortality or other cancer diagnoses. The exposure of interest was cumulative aspirin use from January 1, 2002, to December 31, 2006. The data on CCAs were analyzed from December 2019 to May 2020. Heath examination records included height, weight, smoking status, alcohol consumption, and physical activity. Pre-existing hepatolithiasis, chronic viral hepatitis, *Clonorchis sinensis*, or *Opisthorchis viverrini* infection was ascertained using *ICD-10* codes. Statistical analyses were conducted using R, version 3.5.3 (R Foundation).

Results | We identified 922 patients with incident CCA (562 men [61%] and 360 women [39%]; 3305 person-years) and 4610 controls. The median time to event from the index date was 3.6 years (interquartile range, 1.9-5.3 years). The **Table** shows the factors associated with incident CCA. The estimated risk ratio was 0.95 (95% CI, 0.87-1.04) per 1 defined daily dose-year of aspirin use.

Discussion | In this observational study, the association between aspirin and CCA was not significant. This study complements the existing literature by adopting a validated study design.[5] We adopted a case-control design nested in a closed cohort based on a single-payer health system with the death registry. We used incidence density sampling to address survival bias or immortal time bias. The sampling frame of health examination recipients reduces healthy user bias while guaranteeing data completeness. Medication exposures were reliably assessed from the prescription database using anatomical therapeutic chemical–defined daily dose system before the outcome ascertainment period to address time lags between the exposure and carcinogenesis. We adjusted for potential

Table. Factors Associated With Incident Cholangiocarcinoma

Factor	Risk ratio (95% CI)[a]
Aspirin (per 1 DDD-y)	0.95 (0.87-1.04)
NSAID (per 1 DDD-y)	1.15 (0.94-1.41)
Age (per 1 y)	1.08 (1.05-1.11)
Charlson comorbidity index (per 1 score)[b]	1.07 (1.01-1.12)
Current cigarette smoker	1.12 (0.92-1.35)
Alcohol consumption (≥3 per wk)	1.02 (0.82-1.27)
Exercise (≥3 per wk)	0.86 (0.72-1.04)
BMI	
<23	1 [Reference]
23-24.9	0.87 (0.72-1.05)
25-29.9	0.97 (0.81-1.17)
≥30	1.31 (0.86-2.00)
Blood pressure, mm Hg	
<120/80	1 [Reference]
120/80-140/90	1.13 (0.93-1.39)
>140/90	1.09 (0.88-1.35)
Diabetes	1.24 (0.97-1.59)
Hyperlipidemia	0.91 (0.79-1.06)
Metformin use	1.06 (0.76-1.47)
Statin use	0.89 (0.71-1.13)
Hepatolithiasis	3.96 (2.77-5.65)
Chronic viral hepatitis	1.03 (0.70-1.51)
Clonorchis sinensis or *Opisthorchis viverrini* infection	1.02 (0.40-2.61)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DDD, defined daily dose; NSAID, nonsteroidal anti-inflammatory drug.

[a] Estimated from a multivariable conditional logistic regression model that was conditional on the matching factors and controlling for additional potential confounders (eg, Charlson comorbidity index, cigarette use, alcohol consumption, exercise, blood pressure, diabetes, hyperlipidemia, metformin use, statin use, hepatolithiasis, chronic viral hepatitis, *Clonorchis sinensis*, or *Opisthorchis viverrini* infection). Note that cases and the matched control participants have the same insurance coverage, race, ethnicity, age decade, sex, income decile, and disability registry status.

[b] Calculated from acute myocardial infarction, cerebral vascular accident, congestive heart failure, connective tissue disorder, dementia, diabetes, diabetes complications, HIV, liver disease, paraplegia, peptic ulcer, peripheral vascular disease, pulmonary disease, kidney disease, and severe liver disease based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes of hospital visits.

confounding factors, including preexisting risk factors, behavioral factors, and concurrent medications.[6]

We acknowledge several limitations. First, the people who used aspirin in our study were prevalent users rather than new initiators, and residual confounding is possible. However, unmeasured imbalances between users and nonusers can bias against the null, resulting in a falsely positive association. Second, prescription records may not reflect the actual intake when patients' adherence is low. However, the adherence level would be what could usually be achieved in a real-world clinical setting. Third, we did not distinguish per-tablet doses of aspirin according to anatomical therapeutic chemical-defined daily dose. We also did not distinguish anatomic or pathological subtypes of CCA. Future studies would need a sufficient sample size and statistical power to distinguish different aspirin dosages and CCA subtypes. Finally, this study is based on Asian individuals, and future studies are needed to explore racial or genetic heterogeneity.

Despite these limitations, this study contributes to the literature on aspirin and CCA with a validated study design and detailed health examination data. Further research is needed to investigate the minimum necessary exposure and effect modifications in certain subgroups, if any, for the association between aspirin and the risk of CCA.

Min-Hyung Kim, MD
Sang Min Park, PhD
Jooyoung Chang, MD
In Cheol Hwang, PhD

Author Affiliations: Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea (Kim, Park, Chang); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Kim); Department of Family Medicine, Seoul National University College of Medicine, Seoul, Korea (Chang); Gil Medical Center, Department of Family Medicine, Gachon University College of Medicine, Incheon, Republic of Korea (Hwang).

Accepted for Publication: August 6, 2020.

Published Online: October 29, 2020. doi:10.1001/jamaoncol.2020.5018

Corresponding Author: In Cheol Hwang, PhD, Gil Medical Center, Department of Family Medicine, Gachon University School of Medicine, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, Korea (spfe0211@gmail.com).

Author Contributions: Dr Hwang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kim, Park, Hwang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kim, Hwang.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kim, Chang.
Administrative, technical, or material support: Park.
Supervision: Park, Hwang.

Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the staff of the Korean National Health Insurance Corporation for their cooperation. They were not compensated for their contributions.

1. Petrick JL, Sahasrabuddhe VV, Chan AT, et al. NSAID use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. *Cancer Prev Res (Phila)*. 2015;8(12):1156-1162. doi:10.1158/1940-6207.CAPR-15-0126

2. Choi J, Ghoz HM, Peeraphatdit T, et al. Aspirin use and the risk of cholangiocarcinoma. *Hepatology*. 2016;64(3):785-796. doi:10.1002/hep.28529

3. Altaii H, Al-Kindi SG, Oliveira GH, Yaqoob Z, Romero-Marrero C. Aspirin use and risk of cholangiocarcinoma: External validation with big data. *Hepatology*. 2017;65(4):1421-1422. doi:10.1002/hep.28920

4. Lapumnuaypol K, Tiu A, Thongprayoon C, et al. Effects of aspirin and non-steroidal anti-inflammatory drugs on the risk of cholangiocarcinoma: a meta-analysis. *QJM*. 2019;112(6):421-427. doi:10.1093/qjmed/hcz039

5. Kim M-H, Chang J, Kim WJ, Banerjee S, Park SM. Cumulative dose threshold for the chemopreventive effect of aspirin against gastric cancer. *Am J Gastroenterol*. 2018;113(6):845-854. doi:10.1038/s41395-018-0097-5

6. Chaiteerakij R, Yang JD, Harmsen WS, et al. Risk factors for intrahepatic cholangiocarcinoma: association between metformin use and reduced cancer risk. *Hepatology*. 2013;57(2):648-655. doi:10.1002/hep.26092