Published in final edited form as:

JAMA Oncol. 2020 May 01; 6(5): 784. doi:10.1001/jamaoncol.2020.0125.

Aspirin for Biliary Tract Cancer: Is There Truly Survival Benefit? – Response

Sarah S. Jackson, PhD, MPH, Ruth M. Pfeiffer, PhD, Jill Koshiol, PhD, MPH

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD USA

We thank Dr. Bergquist and colleagues for their interest in our article¹ on the association between aspirin and biliary tract cancer (BTC) survival in the UK's Clinical Practice Research Datalink (CPRD). We agree that our results cannot be the sole justification to incorporate aspirin into the standard management of BTCs. For that, careful replication of our findings and, if possible, a randomized clinical trial are needed to provide further evidence. We also agree that our analysis has limitations that are typical with the use of electronic databases for observational research. We appreciate the opportunity to respond to these limitations beyond what was discussed in our article.

Although all observational studies are subject to error, not all potential sources of error will nullify the results. For instance, surgical status is not a strong enough confounder to completely explain our findings.¹ Klatskin tumors are very rare, making up ~3% of cholangiocarcinomas;² therefore, the benefit of surgical resection for a small subset of these BTC cases is unlikely to confound our results. Furthermore, failure to account for surgery in cholangiocarcinoma patients would not explain our findings for the other BTCs.

The survival curves we presented are a graphical presentation of the differences between 2 groups accounting for time-varying aspirin use.¹ We agree fewer events occur after 12 months than within the first year. However, this does not impact the associations represented by the hazard ratios, which should be interpreted as averages over the investigated time period. Clearly, there is no information contributing to those estimates when there are no more events the aspirin group.

To reduce misclassification bias we required 2 or more prescriptions recorded in CPRD to classify patients as aspirin users, which is a valid measure of adherence for chronic medications.³ Because aspirin is available over the counter in the UK, some true aspirin users may have been misclassified as non-users. This misclassification would dilute our findings by making the 2 groups more alike, in which case the true survival benefit would be higher than what we reported.

We chose not to link to the National Cancer Data Repository (NCDB) or Office of National Statistics data because they only cover a percentage of the practices in England (~57% of the CPRD).⁴ Case ascertainment is not usually a concern in studies of survival wherein

Corresponding Author: Sarah S. Jackson, PhD, MPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6-E210, Rockville, MD 20892 (sarah.jackson@nih.gov).

Conflict of Interest Disclosure: None reported

both comparison groups are patients with cancer. Validation studies show high levels of concordance between NCDR and CPRD for both cancer incidence and mortality.⁴ On the other hand, a linked analysis would have reduced sample size, power, and generalizability.⁴ While lack of data on stage is a limitation, BTCs are nearly always fatal with short survival time after diagnosis, largely due to the late stage at diagnosis; it is likely mortality was due to late-stage BTC in this analysis.

Although, our study¹ has limitations that hamper any analysis of electronic medical data, the big advantage is that our results can truly be thought of as representative of the case population, and not a selected subset.

References

1. Jackson SS, Pfeiffer RM, Liu Z, et al. Association Between Aspirin Use and Biliary Tract Cancer Survival. *JAMA Oncol.* 2019.
2. Surveillance E, and End Results (SEER) Program (www.seer.cancer.gov). SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2018 Sub (1975-2016) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the 11 2018 submission.
3. Strom BL, Kimmel SE, Hennessy S. *Pharmacoepidemiology*. Sixth edition. ed. Hoboken, NJ: Wiley-Blackwell; 2020.
4. McDonald L, Schultze A, Carroll R, Ramagopalan SV. Performing studies using the UK Clinical Practice Research Datalink: to link or not to link? *Eur J Epidemiol.* 2018;33(6):601–605. [PubMed: 29619668]