Association Between Aspirin Use and Biliary Tract Cancer Survival

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Aspirin use and survival from biliary tract cancer

Subtitle: Aspirin use and biliary tract cancer survival

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Tweet: Aspirin use may extend survival after biliary tract cancer diagnosis
Twitter handle: ssjac79
Introduction

Biliary tract cancers (BTCs) are rare, with a worldwide incidence of <2/100,000 individuals.\(^1\) The five-year survival rate is ~5-15\%, with a median survival of <1 year.\(^1\) Between 60-70\% of patients present with late-stage disease (e.g. inoperable or metastatic tumors) owing to lack of symptoms.\(^2\) Consequently, there is a critical need for treatments that improve BTC survival.

Aspirin has been proposed as a treatment to reduce cancer mortality as it may slow cancer growth through the inhibition of both cyclooxygenase-2, which promotes inflammation and cell proliferation,\(^3\) and platelet aggregation, which may slow the metastatic spread of cancer.\(^4\) We investigated post-diagnosis aspirin use and BTC survival.

Methods

We obtained data, including all-cause deaths, on adult patients diagnosed with BTC between 1990-2017 from the United Kingdom’s Clinical Practice Research Datalink (CPRD), an electronic medical record database. We identified cancers using Read codes for gallbladder cancer (GBC), cholangiocarcinoma, ampulla of Vater cancer (AVC), and overlapping lesions of the biliary tract. We excluded patients with previous cancer, except for non-melanoma skin cancer.

Ever use of post-diagnosis aspirin was defined as \(\geq 1\) prescription recorded in the CPRD on or after the BTC diagnosis date. We used Cox proportional hazards regression models to estimate the cancer site-specific hazard ratios (HRs) and 95\% CIs for the association between time-dependent post-diagnosis aspirin use and overall survival. Patients who received an aspirin prescription within 30 days of diagnosis entered the model as users. The time scale began at diagnosis until death, exit, or end of follow-up (truncated at 10 years). We adjusted for the following covariates \textit{a priori}: age at diagnosis, sex, comorbidities, statin use at diagnosis, indicators of a healthy lifestyle, and year of diagnosis. We fit separate models for each BTC type.
and stratified the baseline hazard by pre-diagnosis aspirin use (yes/no). We estimated adjusted survival curves using a marginal approach to remove the sex and age effects on aspirin use, accounting for the time-dependent exposure. We conducted analyses using SAS (version 9.4; SAS Institute Inc) and survival curves in R Studio (version 1.1.453).

Results
Among the eligible 2,934 BTC patients, 667 (23%) had GBC; 1,559 (53%) cholangiocarcinoma; 224 (8%) AVC; and 484 (16%) overlapping. There were 2,415 deaths (82%) with a median survival of 5.8 (IQR: 2 – 15) months. Two-hundred and fifty-six (9%) patients were aspirin users at baseline, with an additional 349 (12%) patients initiating aspirin after diagnosis. Ninety-six percent of aspirin users were prescribed a 75 mg dose. Compared to non-users, aspirin users were more likely to be older, current statin users, and pre-diagnosis aspirin users, and to have heart disease and comorbidities.

Aspirin use was associated with decreased risk of death in GBC (HR: 0.63, 95% CI: 0.48, 0.83), cholangiocarcinoma (HR: 0.71, 95% CI: 0.60, 0.85), AVC (HR: 0.44, 95% CI: 0.26, 0.76), and overlapping BTC patients (HR: 0.68, 95% CI: 0.50, 0.92) (Table). The survival probabilities are shown in the Figure. Incident users with no previous history of aspirin use had a larger benefit from post-diagnosis aspirin use than prevalent users, though all had a reduction in risk.

Discussion
We observed a reduced risk of death for post-diagnosis aspirin users across all BTC types. Platelet activation protects tumor cells from elimination, enhances metastatic cell growth, and enables cancerous cells to spread via the bloodstream. Aspirin may slow metastatic spread of cancer cells through inhibition of platelet aggregation, improving BTC survival. A limitation of our analysis is the lack of data on stage and chemotherapy regimens received (if any). However, most BTCs are diagnosed at late stage with <10% of patients presenting with
resectable tumors and 50% of tumors metastasizing to the lymph nodes.\textsuperscript{1} The survival benefit of aspirin observed in our study are on par with the current standard of care.\textsuperscript{2}

**Author Contributions:** Drs Sarah S. Jackson and Jill Koshiol had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jill Koshiol

Acquisition, analysis, or interpretation of data: Sarah S. Jackson, Ruth M. Pfeiffer, Zhiwei Liu, Lesley Anderson, Huei-Ting Tsai, Shahinaz M. Gadalla, and Jill Koshiol

Drafting of the manuscript: Sarah S. Jackson

Critical revision of the manuscript for important intellectual content: Ruth M. Pfeiffer, Zhiwei Liu, Lesley Anderson, Huei-Ting Tsai, Shahinaz M. Gadalla, and Jill Koshiol

Statistical analysis: Sarah S. Jackson and Ruth M. Pfeiffer.

Obtained funding: Jill Koshiol

Administrative, technical, or material support: Sarah S. Jackson, Zhiwei Liu, and Huei-Ting Tsai

Study supervision: Jill Koshiol

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**Disclaimer:** Dr. Tsai is currently an employee of the US Food and Drug Administration. This manuscript reflects the views of the author and does not necessarily represent FDA’s views or policies. This study is based on data from the CPRD database September 2018 release, obtained from the UK Medicines and Healthcare Products Regulatory Agency (Copyright © 2018). The interpretation and conclusions contained in this study are those of the authors alone. This study was approved by the National Institutes of Health Human Research Protection Program and the Independent Scientific Advisory Committee of the CPRD (Protocol 17_160.R)

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References

1. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clinical epidemiology*. 2014;6:99-109.
2. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer discovery*. 2017;7(9):943-962.
3. Langley RE, Burdett S, Tierney JF, Cafferty F, Parmar MK, Venning G. Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy? *British journal of cancer*. 2011;105(8):1107-1113.
4. Gasic GJ. Role of plasma, platelets, and endothelial cells in tumor metastasis. *Cancer metastasis reviews*. 1984;3(2):99-114.
5. Therneau TM, Crowson CS, Atkinson EJ. Adjusted Survival Curves. 2015; [https://cran.r-project.org/web/packages/survival/vignettes/adjcurve.pdf](https://cran.r-project.org/web/packages/survival/vignettes/adjcurve.pdf). Accessed April 8, 2019.
6. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nature reviews Cancer*. 2011;11(2):123-134.
Table 1. Time-dependent associations between post-diagnosis aspirin use and overall survival for each biliary tract cancer site

| Post-diagnosis aspirin use | Gallbladder | Cholangiocarcinoma | Ampulla of Vater | Overlapping |
|----------------------------|-------------|--------------------|-----------------|-------------|
| n\(^b\) | HR (95% CI) | n\(^b\) | HR (95% CI) | n\(^b\) | HR (95% CI) | n\(^b\) | HR (95% CI) |
| No. of events/No. at risk | 553/667 | 1,321/1,559 | 142/224 | 399/484 |
| Non-users | 530 | 1.0 (Ref) | 1,255 | 1.0 (Ref) | 164 | 1.0 (Ref) | 380 | 1.0 (Ref) |
| Users | 137 | 0.63 (0.48, 0.83) | 304 | 0.71 (0.60, 0.85) | 60 | 0.44 (0.26, 0.76) | 104 | 0.68 (0.50, 0.92) |

Among individuals who used aspirin pre-diagnosis

| No. of events/No. at risk | 194/195 | 497/497 | 59/59 | 156/157 |
|----------------------------|---------|---------|-------|---------|
| Non-users | 97 | 1.0 (Ref) | 269 | 1.0 (Ref) | 24 | 1.0 (Ref) | 81 | 1.0 (Ref) |
| Prevalent users\(^c\) | 98 | 0.69 (0.50, 0.94) | 228 | 0.78 (0.65, 0.95) | 35 | 0.41 (0.22, 0.79) | 76 | 0.76 (0.54, 1.07) |

Among individuals who did not use aspirin pre-diagnosis

| No. of events/No. at risk | 359/472 | 824/1,062 | 83/165 | 243/327 |
|----------------------------|---------|-----------|-------|---------|
| Non-users | 433 | 1.0 (Ref) | 986 | 1.0 (Ref) | 140 | 1.0 (Ref) | 299 | 1.0 (Ref) |
| Incident users\(^c\) | 39 | 0.57 (0.28, 1.17) | 76 | 0.37 (0.21, 0.64) | 25 | 0.21 (0.03, 1.56) | 28 | 0.34 (0.12, 0.94) |

\(^a\)Adjusted for sex, history of heart disease, statin use (current, former, never), presence of comorbidities, age at diagnosis, and year of diagnosis. Aspirin use was modeled as time-dependent and the baseline hazard was stratified by pre-diagnosis aspirin use.

\(^b\)The results presented used Cox regression where aspirin was modeled as time-dependent (e.g. individuals could switch between use and non-use status), the numbers (n) represent any aspirin use after BTC diagnosis.

\(^c\)Prevalent users were defined as patients with two or more aspirin prescriptions before BTC diagnosis. Incident users were defined as patients who only initiated aspirin use on or after BTC diagnosis date.

\(P\)-values for interaction was estimated by putting a cross-product term in the models for post-diagnosis use and pre-diagnosis use.
Figure 1. Adjusted survival curves of overall survival among post-diagnosis aspirin users and non-users by cancer site.

Survival curves were weighted by age and sex distributions of the cohort with aspirin use modeled as time-dependent variable. Numbers shown are estimated survival at one year with 95% CIs computed based on the quantiles of the corresponding bootstrap distribution function with 1,000 replications.
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Aspirin use

Gallbladder

- 61% (95% CI: 31%, 100%)
- 27% (95% CI: 16%, 47%)

Cholangiocarcinoma

- 62% (95% CI: 42%, 98%)
- 26% (95% CI: 19%, 35%)

Ampulla of Vater

- 85% (95% CI: 33%, 83%)
- 52% (95% CI: 18%, 43%)

Overlapping

- 61% (95% CI: 34%, 100%)
- 27% (95% CI: 16%, 46%)

Survival probability

Months since cancer diagnosis

Aspirin use

No aspirin use