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# Title page

## Prevention of biliary cancer with statins: still a long way to go

**Short title:** Statins and biliary tract cancers

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**Abbreviations:** BTC, Biliary tract cancers; CCA, cholangiocarcinoma; dCCA, distal cholangiocarcinoma; iCCA, intra-hepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

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Biliary tract cancers (BTCs) are a heterogeneous group of rare, highly fatal tumors affecting the gall bladder, ampulla of Vater and bile ducts. The latter represents the second most common primary tumors of the liver and are further differentiated into intra-hepatic (iCCA), perihilar (pCCA) and distal (dCCA) cholangiocarcinomas. While the anatomical differentiation of BTCs holds relevant implications in patient management, all biliary tumors share late stage at diagnosis and poor outcome. Biliary tumors seem to differ in terms of temporal trends, with iCCA being on the rise worldwide compared to the extra hepatic ones that appear to be declining. A recent study in 32 selected countries from Europe, the Americas, and Australasia over the 1995-2016 period reported an increase in mortality rates for iCCA that was counterbalanced by a decline or levelling off of mortality due to extrahepatic cancers (Bertuccio *et al.* 2019).

While the determinants of BTCs risk are largely undefined, attention has been addressed to disorders of lipid metabolism and their inherent ability to boost inflammatory and immune-mediated reactions of the bile tree, which might in part account for the pathogenic link that has emerged between BTCs and biliary diseases as cholelithiasis, infection with bacteria and parasites, and primary sclerosing cholangitis. Along this line, and considering the limited chances of effective therapy of BTCs, an anti-inflammatory drug like aspirin (Choi *et al.* 2016; Liu *et al.* 2005; Petrick *et al.* 2015; Lapumnuaypol *et al.* 2019) and inhibitors of hepatic synthesis of cholesterol (Peng *et al.* 2015; Liu *et al.* 2018) have been investigated for they ability to prevent BTCs.

Recently, a nested case-control study based on the UK Clinical Practice Research Datalink (CPRD) highlighted the potential of statins to prevent BTCs(Liu *et al.* 2018). The study, including 3118 patients with BTCs matched with 15,519 cancer-free individuals and valid information on drug use based on a well recognized administrative data linkage system, found an inverse association between statins use and BTCs. This positive message rested on a valid study design given that the UK CPRD is representative of the UK population, that was established more than 30 years ago and contains

information on ~8.5% (13.3 million) of the UK population provided by general practitioners. The adjusted relative risk was 0.88 for current users of statins (95% confidence interval, CI, 0.79 to 0.98), in the presence of a dose risk relationship, with a relative risk of 0.76 (95% CI, 0.64-0.91) for the highest number of prescriptions, and 0.81 (95% CI, 0.68-0.96) for the highest cumulative dose. After adjusting for body mass index, smoking, alcohol and diabetes, all well recognized risk factors for BTCs and hence possible confounders, the reduced risk associated with statin use was similar for individual types of BTCs, i.e., 708 gallbladder tumors, 1678 cholangiocarcinomas, 228 ampulla of Vater adenocarcinomas and 500 mixed tumours. Noteworthy, the observed associations were not influenced by gender and year of tumor diagnosis and persisted in patients with a pre-neoplastic condition like diabetes. Relevant to data interpretation, however, are some missing informations like the prevalence of other risk factors for cholangiocarcinoma, namely chronic hepatitis B and C, though delineation and quantification of these associations remain unclear. Further, the authors acknowledge how the study was underpowered for the analysis of individual types of BTCs and individual statins (hydrophilic versus lipophilic), and how the lack of assessment of compliance rates among persons taking statins could have led to potential exposure misclassification.

**Comment**

Pharmacological prevention stands as an attractive option to reduce the mortality burden of BTCs, with the understanding that prevention may counteract the high rates of treatment failures that are driven by late stage at diagnosis, resulting from the lack of surveillance programs, and by the well-known tumor chemo resistance. However, working against such an approach are the distinct morphological phenotypes of BTCs that have been recently associated with different genetic defects and biological pathways that drive tumor development and progression. This is not a trivial point, as these anatomical and biological barriers, which ease molecular characterization of BTCs finalized to the development of

a personalized medicine, at the same time harness development of broadly effective preventive measures. Confirming the complexity of BTCs is the identification of the association between selected subtypes of CCA and cirrhosis, infection with hepatitis B and C viruses, obesity and tobacco smoking, while the associations of these factors with gallbladder and ampulla of Vater cancers are less well defined (Choi *et al.* 2016; Randi *et al.* 2006). Along this line, a strong association has been delineated also between such benign biliary diseases as bacterial and parasitic infection, cholelithiasis and primary sclerosing cholangitis and extra hepatic biliary cancer, where a disorder of lipid regulation might either trigger or be associated to inflammation and pro inflammatory immune responses of pathogenic relevance.

This led investigators at Mayo Clinics, Rochester, to consider the potential chemopreventive effect of aspirin on CCA (Choi *et al.* 2016), since aspirin is an anti-inflammatory drug with inhibitory properties on COX-2, nuclear factor JB and DNA mismatch repair proteins as well as anti-platelet effects, both thought to play a pathogenic role in carcinogenesis (Dovizio *et al.* 2012). In a large case-control study of Caucasian patients with CCA (1169 intrahepatic, 995 perihilar, and 231 distal cancers) a significant inverse association between aspirin use and CCA was reported, with 2.7-fold to 3.6-fold decreased risk for the three cancer subtypes, though the lack of information on duration and dosing of aspirin did not allow to establish a dose-response relationship and to disentangle the anti inflammatory from the anti platelet effects of aspirin (Choi *et al.* 2016). In addition, a pooled analysis of over 1 million individuals from 10 US prospective cohort studies and including 225 cases of iCCA reported a significant 36% reduced risk of iCCA in men only (Petrick *et al.* 2015), and a Chinese case-control study with 368 cancers of the gallbladder, 191 of the extrahepatic bile duct and 68 of ampulla of Vater found a significant reduced risk of gallbladder cancer and nonsignificant reductions in the risk of bile duct and ampullary cancers associated with aspirin use (Liu *et al.* 2005). Noteworthy, a recent meta-analysis,

including the 3 aforementioned studies as well as two additional case-control studies, provided an overall relative risk of CCA for aspirin use of 0.56 (95% CI, 0.32-0.96) (Lapumnuaypol *et al.* 2019).

While the potential for aspirin as a chemopreventive agent has been documented with several other gastrointestinal cancers (Cuzick *et al.* 2015), there is more limited data on the use of statins in cancer chemoprevention. This hypothesis was fostered by studies in human cells documenting the ability of these compounds to inhibit a number of pathways involved in carcinogenesis like insulin-like growth factor 1 (IGF1) and cell proliferation while inducing cell apoptosis (Buranrat *et al.* 2016; Lee *et al.* 2016; Miller *et al.* 2011). In two meta-analyses, the relative risk of developing hepatocellular carcinoma, the commonest primary malignancy of the liver, was around 0.6 for statins users versus non users, in the presence however of significant heterogeneity across study locations and study design that raises concern for selection bias (Pradelli *et al.* 2013; Singh *et al.* 2013).

Scanty data is available on statins use and the risk of BTCs. A record linkage based on the National Health Insurance program in Taiwan (Peng *et al.* 2015), based on a case control study of 3,174 CCA cases, provided a relative risk of 0.80 (95% CI 0.71-0.90) for statins users versus non users, with some evidence for the risk to decline for longer use for most statins preparations. Thus, the two available record-linkage studies, from Taiwan (Peng *et al.* 2015) and UK (Liu *et al.* 2018), produced consistent and similar results, both with relative risk estimates of BTCs around 0.8 for ever statins users, and some evidence of a dose-risk relationship. Both studies have an optimal design to address favorable and unfavorable side effects of medications, since the scope for recall and selection bias is low in record linkage studies, though prescription may not be a perfect measure of use. A pooled analysis of the two studies using a fixed effect model highlights an overall relative risk for ever use of statins of 0.87 (95% CI 0.80-094) and of 0.79 (95% CI 0.71-089) for longest term use

We should however acknowledge that record linkage studies based on administrative data may be shadowed by limited availability of information on confounding. In the UK CPRD, the relative risks

were adjusted for body mass index, smoking, alcohol and diabetes, which are recognized risk factors for BTCs, and hence possible confounders. No information, however, was available on viral hepatitis B and C, which are major causes of iCCA and also extra hepatic CCA, and the same was true in the Taiwan study, too; therefore, no allowance for these factors was possible. What remains unclear is whether viral hepatitis can be a relevant confounder in the inverse relationship between statins and BTCs, a doubt that can only be wiped out by studies including valid information on these variables. By the same token, in the Taiwan study information on parasite infections, mainly liver flukes, which are known to play a role on BTCs (Randi *et al.* 2006), was lacking, as well as information on aspirin and physical activity, which have been inversely related to hepatobiliary cancers risk, too (Baumeister *et al.* 2018; Bosetti *et al.* 2009; Choi *et al.* 2016; Liu *et al.* 2005; Petrick *et al.* 2015). While these latter factors were not allowed for in the analyses on statins, it is unlikely that they had a major confounding role on the statin-related risk estimates.

It should be mentioned, moreover, that in a Swiss record linkage study (Bietry *et al.* 2016) statins were inversely related to cholecystectomy, with relative risks of 0.85 for current users and 0.77 for long-term users. Since gallstones are key risk factors for gallbladder cancer (Randi *et al.* 2006), and are likely to play a role in extra hepatic CCA too, such a favorable impact of statins on gallstones may, at least in part, accounts for the inverse relationship with BTCs observed in the UK CPRD.

All in all, given the rarity of biliary cancers, data on a possible favorable effect of statins on BTCs risk remain scanty and hence inconclusive, also in consideration of the moderate inverse association and dose-risk relationship, and of the limited information on confounding factors in administrative record linkage datasets. This however should not discourage further investigation on BTCs prevention with statins, the consistency of the findings from large Taiwanese and British datasets, and the presence of plausible biological and mechanistic interpretations indicating that such an inverse relationship is possible.

**References**

Baumeister, S. E., S. Schlesinger, K. Aleksandrova, C. Jochem, M. Jenab, M. J. Gunter, et al. 2018. 'Association between physical activity and risk of hepatobiliary cancers: A multinational cohort study', *J Hepatol*.

Bertuccio, P., M. Malvezzi, G. Carioli, D. Hashim, P. Boffetta, H.B. El-Serag, et al. 2019. 'Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma', *J Hepatol*, in press.

Bietry, F. A., O. Reich, M. Schwenkglenks, and C. R. Meier. 2016. 'Statin use and risk of cholecystectomy - A case-control analysis using Swiss claims data', *Expert Opin Drug Saf*, 15: 1577-82.

Bosetti, C., S. Gallus, and C. La Vecchia. 2009. 'Aspirin and cancer risk: a summary review to 2007', *Recent Results Cancer Res*, 181: 231-51.

Buranrat, B., L. Senggunprai, A. Prawan, and V. Kukongviriyapan. 2016. 'Simvastatin and atorvastatin as inhibitors of proliferation and inducers of apoptosis in human cholangiocarcinoma cells', *Life Sci*, 153: 41-9.

Choi, J., H. M. Ghoz, T. Peeraphatdit, E. Baichoo, B. D. Addissie, W. S. Harmsen, et al. 2016. 'Aspirin use and the risk of cholangiocarcinoma', *Hepatology*, 64: 785-96.

Cuzick, J., M. A. Thorat, C. Bosetti, P. H. Brown, J. Burn, N. R. Cook, et al. 2015. 'Estimates of benefits and harms of prophylactic use of aspirin in the general population', *Ann Oncol*, 26: 47-57.

Dovizio, M., S. Tacconelli, C. Sostres, E. Ricciotti, and P. Patrignani. 2012. 'Mechanistic and pharmacological issues of aspirin as an anticancer agent', *Pharmaceuticals (Basel)*, 5: 1346-71.

Lapumnuaypol, K., A. Tiu, C. Thongprayoon, K. Wijarnpreecha, P. Ungprasert, M. A. Mao, and W. Cheungpasitporn. 2019. 'Effects of Aspirin and Non-Steroidal Anti-Inflammatory Drugs on the Risk of Cholangiocarcinoma: A Meta-Analysis', *QJM*.

Lee, J., E. M. Hong, J. A. Jang, S. W. Park, D. H. Koh, M. H. Choi, et al. 2016. 'Simvastatin Induces Apoptosis and Suppresses Insulin-Like Growth Factor 1 Receptor in Bile Duct Cancer Cells', *Gut Liver*, 10: 310-7.

Liu, E., L. C. Sakoda, Y. T. Gao, A. Rashid, M. C. Shen, B. S. Wang, et al. 2005. 'Aspirin use and risk of biliary tract cancer: a population-based study in Shanghai, China', *Cancer Epidemiol Biomarkers Prev*, 14: 1315-8.

Liu, Z., R. Alsaggaf, K. A. McGlynn, L. A. Anderson, H. T. Tsai, B. Zhu, et al. 2018. 'Statin use and reduced risk of biliary tract cancers in the UK Clinical Practice Research Datalink', *Gut*.

Miller, T., F. Yang, C. E. Wise, F. Meng, S. Priester, M. K. Munshi, et al. 2011. 'Simvastatin stimulates apoptosis in cholangiocarcinoma by inhibition of Rac1 activity', *Dig Liver Dis*, 43: 395-403.

Peng, Y. C., C. L. Lin, W. Y. Hsu, C. S. Chang, H. Z. Yeh, C. F. Tung, et al. 2015. 'Statins are associated with a reduced risk of cholangiocarcinoma: a population-based case-control study', *Br J Clin Pharmacol*, 80: 755-61.

Petrick, J. L., V. V. Sahasrabuddhe, A. T. Chan, M. C. Alavanja, L. E. Beane-Freeman, J. E. Buring, et al. 2015. 'NSAID Use and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: The Liver Cancer Pooling Project', *Cancer Prev Res (Phila)*, 8: 1156-62.

Pradelli, D., D. Soranna, L. Scotti, A. Zambon, A. Catapano, G. Mancia, et al. 2013. 'Statins and primary liver cancer: a meta-analysis of observational studies', *Eur J Cancer Prev*, 22: 229-34.

Randi, G., S. Franceschi, and C. La Vecchia. 2006. 'Gallbladder cancer worldwide: geographical distribution and risk factors', *Int J Cancer*, 118: 1591-602.

Singh, S., P. P. Singh, A. G. Singh, M. H. Murad, and W. Sanchez. 2013. 'Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis', *Gastroenterology*, 144: 323-32.