

Cholangiocarcinoma: from risk to prevention?

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In the oncology landscape, cholangiocarcinoma (CC) is a challenging disease in terms of both diagnosis and treatment (1).

Early diagnosis is still a target far from being reached, with most patients (>65%) resulting non-resectable at diagnosis (2).

As such, the diagnosis of CC often results in a poor prognosis *quoad vitam* with a median reported survival of 3–6 months for the unresectable cases (3).

In this setting any intervention moving toward an early diagnosis or even the possibility of primary prevention could be a revolutionary and life-sparing innovation in oncology.

In a recent paper Choi and colleagues from the Mayo Clinic suggest that the use of low-dose aspirin may prevent the insurgence of CC (4).

This retrospective study involved 2,395 patients diagnosed with CC at the Mayo Clinic from January 2000 through December 2014. All potential cases were identified by searching the Clinic database with the International Classification of Diseases-9 Clinical Modification codes for CC. All of the cases had been confirmed by histology.

The cohort of 2,395 cases included 1,169 (48.8%) intrahepatic CCs, 995 (41.5%) peri-hilar CCs, and 231 (9.6%) distal CCs.

Control subjects were recruited from the Mayo Clinic Biobank, a biorepository comprising a collection of blood samples and health information provided with informed consent. Most of these participants had at least 15 years of electronic medical record data, and at least two clinic visits per year. This procedure allowed the identification of 4,769 controls.

Logistic regression analysis was used to identify factors associated with CC development and to calculate odds ratios (ORs), adjusted odds ratios (AORs).

Aspirin use was also considered amongst the potential factors related to the incidence of CC.

To avoid biases and potential confounding factors influencing the chance of being prescribed aspirin, a multivariate analysis with propensity score adjustment was used to confirm the initial findings.

The authors found that primary sclerosing cholangitis (PSC) was the most significant risk factor (AOR =171). Liver cirrhosis (AOR =10.8, 95% CI: 6.5–18.0; P<0.001) and diabetes (AOR =2.8, 95% CI: 2.3–3.3; P<0.001) were also found to be independent risk factors.

CC cases were significantly less likely to report use of aspirin than controls (OR =0.41, 95% CI: 0.36–0.45; P<0.001). These results were not significantly altered after having been adjusted for other potential risk factors for CCA (AOR =0.34, 95% CI: 0.30–0.39; P<0.001). Also, multivariate analysis with propensity score adjustment did not substantially alter the associations (AOR =0.38, 95% CI: 0.33–0.44; P<0.001).

These findings are particularly interesting as they confirm on a very large population previous data that showed an AOR of 0.45 in a relatively small UK study of 81 patients (5).

Also, a Chinese study of 191 patients with extrahepatic bile duct cancer, demonstrated a comparable AOR of 0.48 (95% CI: 0.19–1.19) but statistical significance was not met (6).

Similar AORs in different studies coming from distant geographical areas would seem to confirm an actual protective effect of aspirin, but which are the

physiopathology elements behind these effect? The anticancer effect of aspirin has been first reported in studies of colon cancer (7) and is well known in oncology. Aspirin-mediated inhibition of both cyclo-oxygenase 2 (COX-2) activity and nuclear factor kB (NF-kB) activation are regarded as mechanisms of cancer prevention (8).

Specifically to cholangiocarcinogenesis, overexpression of COX-2 has been showed to be related to tumor growth and invasion in human CC cells (9). Finally, murine models showed that aspirin (as well as selective COX-2 inhibitors) inhibits vascular endothelial cell proliferation in CC, partially prevented neoplastic cell growth (4).

Considering the strong scientific rationale and the promising results of Choi's and previous studies, are we ready for aspirin-based prevention campaign for CC?

Unfortunately, large scale campaigns are difficultly feasible as CC remains a relatively rare disease. As such, the number of patients to treat in order to prevent a single CC in the general population would be very high and side-effects would probably outweigh the benefit. For these reason we are not going to see randomized double-blinded clinical trials of chemoprevention in the general population anytime soon.

Prevention of CC in high-risk patients, on the other hand, may be at hand.

As an initial step toward this goal, in their paper Choi and colleagues declare that they are planning to perform a case-control study comparing the protective effect of aspirin use in PSC patients, the population with the highest lifetime risk of developing CC.

Furthermore, the authors state that it will be of interest to study the relationship between genetic variations and the chemopreventive effect of aspirin in CC.

CC, indeed, is a complex disease encompassing a group of related but distinct malignancies characterized by a genetic heterogeneity (10). Advanced technologies such as next-generation sequencing could represent the best tool to assess whether the association between aspirin use and CC varies by polymorphisms, as already demonstrated for colorectal cancer (11).

The proposals of the authors should be fully endorsed; however some other considerations can be made.

First, lessons from clinical practice teach us that a radical surgical resection of early-stage CC in the setting of a multidisciplinary evaluation and follow-up of the patient can lead to a sustained disease-free survival. Relapse due to recurrence of resected tumour or de novo insurgence of new CC, however, occurs in a proportion of patients as high

as 60%, even after adjuvant chemotherapies (1).

Therefore, a question has to be raised: may patients who suffered from CC and are currently disease-free also benefit from aspirin chemoprevention?

Second, even if not evaluated by the authors, asbestos exposure is a hidden player for the development of CC (especially intrahepatic CC) (12). Therefore even patients who had a significant professional exposure to asbestos may be candidates for both screening and chemoprevention. In this regard, however, it should be noted that aspirin has not proven effective in preventing other asbestos-related malignancies in animal model and in a human cohort (13).

Finally, we are witnessing a progressive increase in the incidence of non-alcoholic fatty liver disease (NAFLD) and of its most aggressive form, i.e., non-alcoholic steatohepatitis (NASH) in many Western countries (14,15).

Even if NAFLD did not independently increase the risk of CC in Choi study, liver cirrhosis and diabetes did.

The retrospective design of the study (with the analysis of relatively old clinical data) may have concealed the actual magnitude of the NAFLD-related risk. Anyway, since NASH is now amongst the leading cause of liver cirrhosis, its role in cholangiocarcinogenesis is expected to increase over time. Patients with dysmetabolic cirrhosis should be aware that, should they receive aspirin prescription for their cardiovascular comorbidities, this drug may also help them in preventing one of the most dreadful complications of their liver disease. If future studies will demonstrate a protective effect of aspirin also toward the development of hepatocellular carcinoma, the most common liver cancer, the complex topic of anticoagulant/antiaggregant therapy in liver cirrhosis would gain a new element of debate.

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Footnote

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