Editorial

Increasing mortality of intrahepatic cholangiocarcinoma in the US: are gender-specific risk factors important?

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Intrahepatic cholangiocarcinoma (iCCA) is an often-fatal malignancy, with an annual incidence rate that closely approximates the mortality rate (1,2). The poor prognosis of these cancers is due in part to their nonspecific clinical presentation and the often-late stage at diagnosis—which is not amenable to curative treatment. While understanding the underlying biology of iCCA is important for early detection and therapy development, there is also a need to ascertain the temporal trends of the disease incidence and mortality. A thorough appraisal of trends in iCCA incidence and mortality would inform strategies for the prevention and identification of high-risk populations for screening and surveillance. Many studies have shown that the incidence and mortality rates of iCCA have increased in the US over the last few decades (1-6), but while some of these studies suggest that the increase in iCCA incidence appears to have plateaued (2,5), others show continuous rise of both the incidence and mortality of iCCA in the US (3,4,6).

The study by Beal *et al*. (7) reports an interesting approach to understanding trends in iCCA incidence and mortality in the US by investigating the contributions of age-period-cohort (APC) effect (7). The investigators retrospectively analyzed iCCA incidence data from the Surveillance Epidemiology and End Results program of the National Cancer Institute (SEER 9 sites, 1973 to 2012) and iCCA mortality data from the Centers for Disease Control and Prevention's WONDER database (1999 to 2015). The results show an overall increase in iCCA incidence in the US over time, with increasing incidence in all successive age groups and all birth cohorts. The authors further noted that birth cohort effects influenced the iCCA incidence rates in both men and women. Mortality rates for iCCA also increased over time, with nearly identical rates of increase in men (72%) and women (70%) from 1999 to 2015. Interestingly, while the mortality rates differed across birth cohorts in men, they did not differ across birth cohorts in women. It should be noted that the findings of increasing incidence of HCC in the US is in contrast to findings from a previous study (2) that suggested a plateauing of the incidence rate for iCCA in the US. Although both studies used data from SEER to estimate incidence, the study by Beal *et al.* (7) had longer follow-up and showed a continued rise in iCCA incidence in recent cohorts in the US. Moreover, the study poses an important question as to why iCCA mortality rates differ across birth cohorts in men and yet did not differ across birth cohorts in women.

While the observed trend of increasing incidence of iCCA could be attributed to the increasing prevalence of potential risk factors, such as obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, alcoholic liver disease and hepatitis C virus infection (8,9), the reasons for the gender differences in iCCA mortality trends between the birth cohorts are not entirely clear. In general, gender differences in cancer outcomes can result from variation in biological modifiers of tumor behavior, such as male and female hormones, or variation in prognostic factors, such as insurance status and adherence to treatment regimen. In this same context, the differences in iCCA mortality trends across the birth cohorts in men could have been caused by differential rates of pre-disposing factors or differences in treatment-related factors between the birth cohorts in men; whereas among women, these factors may

have been relatively stable across the cohorts. It is also possible that these could have been caused by statistical fluctuations, rather than reflect biological or behavioral differences between men and women. While the observed trends in mortality in women remain to be fully validated and understood, the study does provide additional evidence of increasing incidence and mortality of iCCA in the US. Overall, these observations lend support for comprehensive risk prevention strategies and timely clinical management of iCCA patients in order to minimize the societal impact of the trends in incidence and mortality.

Presently, the causes of iCCA are not completely understood and no single diagnostic test or clinical feature can reliably detect these tumors at an early stage before they progress to incurable disease. In light of the current trends in incidence and mortality, concerted efforts are needed to comprehensively characterize the risk factors of iCCA for targeted prevention. Further, combinations of clinical evaluations (e.g., signs of biliary obstruction or abnormal liver function tests), imaging modalities, elevated serum levels of cancer antigen 19-9 (CA19-9), and occasionally tissue biopsy, are often used for surveillance and diagnosis of iCCA (10). Even tissue biopsy can sometimes lead to misdiagnosis of iCCA as hepatocellular carcinoma, with the correct diagnosis ultimately made on explant pathology. Identification of robust biological markers of iCCA development, with optimal sensitivity and specific, are therefore needed to foster early detection efforts. In the meantime, implementation of programs to reduce the prevalence of known or suspected risk factors of iCCA (e.g., diabetes, obesity, and metabolic syndrome), targeted surveillance of high-risk groups with a combination of clinical examination, imaging scans and serum CA19-9 levels, and initiation of early treatment soon after diagnosis could all have a significant impact on reducing the incidence and mortality of these deadly cancers.

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Footnote

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References

1. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33:1353-7.
2. Petrick JL, Braunlin M, Laversanne M, et al. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. Int J Cancer 2016;139:1534-45.
3. Shaib YH, Davila JA, McGlynn K, et al. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? J Hepatol 2004;40:472-7.
4. Antwi SO, Mousa OY, Patel T. Racial, Ethnic, and Age Disparities in Incidence and Survival of Intrahepatic Cholangiocarcinoma in the United States; 1995-2014. Ann Hepatol 2018;17:604-14.
5. Tyson GL, Ilyas JA, Duan Z, et al. Secular trends in the incidence of cholangiocarcinoma in the USA and the impact of misclassification. Dig Dis Sci 2014;59:3103-10.
6. Mosadeghi S, Liu B, Bhuket T, et al. Sex-specific and race/ethnicity-specific disparities in cholangiocarcinoma incidence and prevalence in the USA: An updated analysis of the 2000-2011 Surveillance, Epidemiology and End Results registry. Hepatol Res 2016;46:669-77.
7. Beal EW, Tumin D, Moris D, et al. Cohort contributions to trends in the incidence and mortality of intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr 2018;7:270-6.
8. Shaib YH, El-Serag HB, Davila JA, et al. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. Gastroenterology 2005;128:620-6.
9. Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221-8.
10. Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95-111.

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