Editorial

Rising trends in intrahepatic cholangiocarcinoma incidence and mortality: getting at the root cause

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Several epidemiologic studies over the years have demonstrated that there is a worldwide increase in the incidence of intrahepatic cholangiocarcinoma (ICC) (1-5). Given the aggressive biology of ICC and poor survival, it is not surprising that the mortality rate mirrors the incidence rate (6).

This begs the question; is rising incidence of ICC a true observation or "fake news" (7). Common culprits leading to misattribution include overdiagnosis (due to better diagnostic tools) or improvements in classification (8). A study by Sahib *et al*. convincingly argues against the overdiagnosis theory (7). Their findings suggest that the stage distribution and tumor size at diagnosis has not changed over time. However, to date, it has not been possible to address the notion that the rising incidence maybe due to improved classification of these tumors (8). For instance, prior to wide spread availability of more specific immunohistochemical panels, ICCs were classified as hepatocellular carcinomas or metastatic adenocarcinomas with unknown primary (9). Even at present, the diagnosis of ICC can be challenging and is a subject of discussion in multidisciplinary tumor boards. Similarly, improvements in multiphasic cross-sectional imaging and endoscopic technologies has made it possible to draw a more accurate distinction between ICCs and extrahepatic cholangiocarcinomas (9). This could also contribute to a false rise in the incidence of ICCs.

Despite limited evidence against misclassification (5), it is now recognized that ICCs represent a growing worldwide problem. Multiple factors are at play. A closer look at well-established risk factors can provide important clues in some instances. For example, ICC can occur as a sequelae of primary sclerosing cholangitis (10). Indeed, the rising incidence of PSC correlates with that of ICCs. Fluke infections of the biliary tract from *Clonorchis sinensis* (11) and *Opisthorchis viverrini* (12) could account for the cases in Southeast Asia but not the US. It is reasonable to assume that congenital conditions of the biliary tract such as choledochal cysts, Caroli's disease and congenital hepatic fibrosis are too rare to cause this rise in incidence. While chronic hepatitis B and C infections have been associated with ICCs in the East, this association is less characterized in the US patients (13). In reality, the vast majority of patients with ICC have no culpable risk factor.

Perhaps the answer is simpler than that. Cancer is a disease of old age and ICC is no exception. The rising incidence could merely be a reflection of an aging population. The paper by Beal *et al*. attempts to address this question using Age-Period-Cohort (APC) analysis (14). This statistical approach has been used by sociologists and epidemiologists for decades to parse out the contribution of each of the components in a myriad of social and health problems. Age effects are specific to individual patients. They reflect the risk of malignancy (or cancer-specific mortality) accrued with biologic age regardless of the period of time during which malignancy occurred or the battery of exposures that the patient's birth cohort (and hence the patient) has experienced. Period effects are external factors that might influence the onset of malignancy (or cancer-specific mortality) in that particular time period regardless

of the age of the patient or their birth cohort. For example, improvement in detection methods, changes in coding or abstraction of registries can introduce period effects. Finally, cohort effects are factors that may influence the incidence of malignancy (or cancer-specific mortality) because of an exposure that preferentially effected a particular birth cohort. For instance, people born from 1945 to 1965 (baby boomers) are 5 times more likely to have hepatitis C than other adults. Hepatitis C can lead to hepatocellular carcinoma and the occurrence of hepatocellular carcinoma in these patients can be attributed to a cohort effect.

To disentangle these effects in the context of ICC, Beal *et al*. note that cohort effects did not further add to the explanation of rising incidence of ICC any more than age and period effects. This suggests that a cohort effect such as hepatitis C exposure in "baby boomers" or another such risk factor is unlikely to account for rising incidence of ICC. In reporting of their analysis, the authors chose to report on gender-specific mortality rate rather than the morality rate of all patients. They find significant cohort effects for males but not so for females. The explanation for this observation cannot be addressed with analysis in this paper.

This study is important in that it provides evidence against birth cohort effects in the rising incidence of ICC. The data demonstrate that the age- and period-effects dominate the rising incidence and mortality of ICC. However, there are several limitations. The chief among them is the identification problem with APC models (15). What that means is that the three attributes are colinear. If we know the age of an individual and what period they are being measured, we can quickly determine their birth cohort (as the authors did). Because of collinearity it is impossible to completely disentangle the cohort- *vs*. age- *vs*. period-effects. Certain, a priori assumptions can improve the robustness of the findings generated through the APC analysis. These assumptions need to be theory-driven rather than data-driven. Under these assumptions, by constraining one attribute, the APC approach can highlight the significance of the other two attributes (14,15). Given the current knowledge of ICC incidence and mortality, theory-driven assumptions cannot be made with confidence limiting the robustness of these findings.

In summary, these observations should be seen as a stepping stone for future studies rather than definitive evidence against birth-cohort effects. Since age-effects are individual-specific effects, wide spread adoption of germline testing and genome wide association studies may provide in-depth mechanistic understanding of age-effects. Other clues can come from large-scale case control epidemiologic studies.

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Footnote

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