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Asbestos Exposure and Increased Risk of Intrahepatic Cholangiocarcinoma: Enough to Infer Causality?

Brandi G, Tavolari S. Asbestos and Intrahepatic Cholangiocarcinoma. Cells 2020;9:421.

Cholangiocarcinoma (CCA), the second most common primary hepatic malignancy after hepatocellular carcinoma, is a lethal disease that often evades early diagnosis and defies treatment, thereby displaying one of the highest mortality-to-incidence ratio of any solid neoplasm (Nat Rev Clin Oncol 2018;15:95–111). In the face of such common clinical features as clinical aggressiveness, limited treatment options, and high rates of recurrence after resection, CCA is notable for high epidemiologic, anatomic, and biological heterogeneity. As a matter of fact, not only the tumor is classified into 3 anatomic subtypes, intrahepatic (iCCA, 20% of all CCAs), perihilar, and distal tumor, but each of these subtypes is associated with different risk factors, from cirrhosis to flukes and bile duct stones, with evidence of a substantial geographic variability.

The majority of CCAs have a sporadic onset, with the consequent lack of screening accounting for biliary tumors to be almost invariably detected at an advanced stage. On the top of this clinical heterogeneity, the neoplastic biliary epithelium evolves a myriad of genetic and epigenetic modifications that are under thorough investigation as potential targets for developing precision medicine based treatments (Hepatology 2020 Feb 11 https://doi.org/10.1002/hep.31175 [Epub ahead of print]; J Hepatology 2020;72:95–103). Yet, none of these genetic markers has proven to help early diagnosis, the only pragmatic approach to override the dismal prognosis of CCA. With all the caveats of a misclassification that may have occurred in the years when iCCA was not coded separately from extrahepatic CCA (eCCA), in the last decades the overall incidence of CCA has been on the raise worldwide, in part paralleling the increasing burden of chronic liver diseases (J Hepatol 2019;71:104–114; Cancer 2020;126:2666-2678. This is particularly true for iCCA, a tumor that is increasingly detected as a hepatic mass lesion during surveillance for hepatocellular carcinoma in patients with cirrhosis, whereas for the many patients with a sporadic CCA early diagnosis remains an unrealistic objective.

Along this line, a better understanding of the concerned risk factors may be of interest. Because liver diseases related to occupational exposure fell under the radar of the hepatologists (J Hepatol 2019;71:1022-1037), questions have been raised about the potential role of workplace exposure to chemicals and metals as possible risk factors for liver cancer and CCA. Although thorotrast and 1,2 dichloropropane are recognized risk factors for human CCA, evidence for other chemicals remains contradictory. In the 1970s, a study of Swedish painters reported excess cancer of the intrahepatic bile ducts and an excess of biliary cancer was also reported for rubber workers, yet both cohorts were exposed to many chemicals, making their results difficult to interpret with reference to specific agents (J Occup Med 1970;12:333–341; Br J Ind Med 1986;43:257–262). A few years later, in an epidemiologic study of 1271 employees in a fiber production plant in South Carolina, exposure to methylene chloride was initially associated to increased mortality ratio from biliary cancer, with 4 observed deaths versus 0.35 expected, to give a standardized mortality ratio of 20. Although all of the deaths from biliary cancer occurred among the workers with $\geq$10 years of employment and $\geq$20 years since first employment, a subsequent reanalysis of the same cohort failed to confirm a significant association between methylene chloride and CCA deaths (Scand J Work Environ Health 1990;16:247–251). More recently, a study from Japan provided insights on a possible association of CCA with prolonged exposure to solvents in proof-printing workers, because either iCCA or eCCA was histologically diagnosed in 11 of 62 workers who were exposed to 1,2-dichloropropane for 1–17 years (mean, 6 years), with 27 individuals also exposed to dichloromethane for 1–12 years (mean, 4 years) (Occup Environ Med 2013;70:508–510).

Further expanding the list of chemicals with a potential association with CCA, a review article has been published enlisting the case reports, cohorts and case control studies

on an association between occupational exposure to the well-known lung carcinogen asbestos and risk of developing biliary cancer (Cells 2020;9:421–436). According to the authors, the potential for asbestos to cause biliary tumors is grounded on an excess risk of liver/biliary tract cancers in exposed workers from 15 cohort studies. However, most studies did not distinguish liver from biliary tract cancers; thus, the evidence essentially reflects liver cancer risk. Owing to the global burden of asbestos exposure and the high proportion of iCCA patients lacking any known risk factor for this disease worldwide, the authors suggest asbestos to be listed as a possible risk factor for iCCA with all the inherent implications for policies of primary and secondary prevention.

Comment. This review discusses many aspects of asbestos toxicology and intends to provide evidence for a causal association between asbestos exposures and iCCA. However, because of incomplete data only vague inferences can be made about causality. The why (ie, assessment of asbestos exposure; self-reported, questionnaires, no punctual measurements) is necessarily approximate, and the what (ie, iCCA may reflect misclassification; liver metastases interpreted as iCCA). In such circumstances, causal inferences would require coherence of results across studies and strong associations, which is not the case. Findings from cohort studies as reported in Table 2 of the article by Brandi and Tavolari (Cells 2020;9:421–436) are inconsistent, and the association was significant in about one-half of the studies and thus is inadequate to make an inference on biliary tract cancers and specifically iCCA.

More valid information comes from case control studies of workers recruited in Italy and Nordic countries. The Italian study included 41 cases of iCCA and 149 controls from heterogeneous sources, plus 59 cases of eCCA and 212 controls (Cancer Causes Control 2013;24:911–918). There was a significant association between self-reported asbestos exposure and iCCA, with an odds ratio (OR) of 4.8 (95% confidence interval [CI], 1.7–13.3). However, no significant association was found for eCCA (OR, 2.09). A nested case-control study from a routine database, the Nordic Occupational Cancer cohort, included 1458 cases of iCCA and 3972 of eCCA (Occup Environ Med 2018;75:191–198). There was some association with iCCA, with an OR of 1.2 for ever exposure, of borderline significance, increasing to 1.7 (95% CI, 1.1–2.5) for the highest exposure level. There was no association with eCCA.

An intriguing question relates to the levels of cumulative exposures to asbestos fibers that are possibly associated with iCCA. It seems that they are quite high, possibly at the highest cumulative exposure level shown in this study. If so, iCCA would occur in the same range of cumulative exposures associated with lung tumors and with mechanisms of carcinogenesis likely different from that of mesothelioma. Suggesting a biological plausibility for such an association, the article discusses several studies that report finding of asbestos fibers in bile and biliary epithelium of exposed workers as well as of patients with CCA who live in geographical areas of Italy credited for high exposure to asbestos. These studies, however, are not informative on what dose is associated with iCCA.

Owing to the global burden of asbestos exposure and the high proportion of patients with iCCA lacking any known risk factor for this disease worldwide, the authors engage in inferences to the best explanation drawing the conclusion that asbestos should be listed as a possible risk factor for iCCA, with all the inherent implications for policies of primary and secondary prevention. There remain, however, major difficulties for causal inference. First, the excess risks are moderate, and hence a role of bias and confounding in observational studies can partly or largely explain the apparent association with iCCA. Further, the absence of association with the more common eCCA is not supportive of a role of asbestos on biliary tract carcinogenesis. The association limited to iCCA indicates that asbestos fibers are present within the liver only, but may also reflects misclassification of liver metastases as iCCA.

Thus, the issue of asbestos exposure and iCCA risk, despite several suggestive evidences, remains undefined and, more important, unquantified. This reflects essentially 2 major difficulties: (i) quantifying past asbestos exposure and (ii) validating, on epidemiologic data, the diagnosis if iCCA versus other intrahepatic neoplasms, that is, the more common hepatocellular carcinoma, and—even more important—liver metastases, mainly from lung and other strongly asbestos-related neoplasms.

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Utility of Surveillance and Screening Colonoscopy in Older Adults

Calderwood AH, Holub JL, Greenwald DA, et al. Yield and practice patterns of surveillance colonoscopy among older adults: an analysis of the GI quality improvement consortium. Am J Gastroenterol 2019;114:1811–1819.

As the US population ages, there is a need for guidance on colorectal cancer screening with colonoscopy in patients above the age of 75. Current guidelines recommend a risk–benefit discussion between the elderly patient and provider, but there is substantial variability in how physicians approach colorectal cancer screening in the elderly, which is due to limited knowledge about the benefits and risk of colorectal cancer screening in this age group. To address this need, Calderwood et al performed a retrospective study