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Professional exposure to asbestos and iCCA

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Q. Can professional exposure to chemicals cause iCCA? If so, could professional exposure to chemicals account for the mounting epidemic of iCCA?

One of the major issues in the field of carcinogenesis is the global iCCA incidence, that increased by 4%/y in the last two decades.[1] Epidemiological studies suggest a positive association between occupational exposure to some carcinogens and iCCA. Chronic exposure to 1,2-dichloropropane, an organic solvent, has been implicated as a causative factor for iCCA development among the young workers of a printing company in Osaka.[2] Currently, 38 out of 111 workers have developed an iCCA and none of them reported being exposed to other known risk factors for this disease. Of note, iCCA incidence increased with cumulative exposure to 1,2-dichloropropane (adjusted RR=14.9, 95%CI 4.1-54.3 for middle exposure category and adjusted RR=17.1, 95% CI 3.8-76.2 for high exposure category), suggesting an exposure-response link.[3] Moreover, whole-exome sequencing of the tumor tissue revealed a unique mutational profile and a frequency of somatic mutations 30-fold higher to that observed in common iCCA tissue samples, used as controls.[4] Although 1,2-dichloropropane may contribute to iCCA development, the number of subjects occupationally exposed to this compound is however limited and cannot account for the global increase of iCCA. It is therefore conceivable that other emerging risk factors are responsible for such an increase worldwide.

Q. Given your recent studies on asbestos, what is the evidence linking this compound to iCCA risk?

Based on my clinical experience, more than 40% of the iCCA patients that are diagnosed at our Centre lack any known risk factors for this disease, except for exposure to asbestos, evaluated according to the National Registry of Mesotheliomas (ReNaM) questionnaire. This observation led us to hypothesize that, among the emerging risk factors linked to iCCA development, asbestos may be one of the reasons most responsible for the increasing incidence of this disease at least in Italy, and perhaps, in other western countries.

Currently, the amount of epidemiological studies evaluating the link between iCCA risk and asbestos exposure is limited. Despite this possible association that has been suggested in some cohort studies, most of them reported estimates referred to the broad category of primitive liver cancers, without specific data on iCCA. The lack of specific data on iCCA in these studies can be ascribable to different causes. The first is related to the evolving WHO International Classification of Disease (ICD) coding system, which is internationally used by cancer registries to record different cancers; indeed, in this coding system, a specific code for iCCA has been reported only from version 8. A second important cause is linked to possible iCCA misclassification, as some iCCAs may be misdiagnosed as cancers of unknown primary, HCC or mixed HCC-iCCA. Despite the increase in iCCA incidence worldwide, this malignancy still represents a minority of the primary liver cancers. Therefore, relative risks estimated for liver cancers are mainly based on the vast majority of HCCs, with iCCAs playing a minor role. Secondly, only extremely large cohorts (as those based on nation-wide registers) have sufficient statistical power to capture a clear relationship between a specific risk factor and the development of a disease with low incidence.

Recently, two published case-control studies by our group highlighted the role of asbestos in iCCA development. In the first study, historical data from 69 iCCAs and 86 eCCAs occurring at our Center between 2006 and 2010 were analyzed. An OR = 4.81 (95% CI 1.73-13.33) for iCCA risk was reported among subjects occupationally exposed to asbestos for over 30 years, whereas limited evidence was found for eCCA (OR = 2.09, 95% CI 0.83-5.27)[5]. These findings have been confirmed in a case-control population-based study on the Nordic Occupational Cancer cohort, where 1458 iCCAs and 3972 eCCAs were analysed [6]. An increased risk of iCCA, but not of eCCA, was observed by cumulative exposure to asbestos: 0.1–4.9 f/ml x years, OR=1.1 (95% CI 0.9–1.3); 5.0–9.9 f/ml x years, OR=1.3 (95% CI 0.9–2.1); 10.0–14.9 f/ml x years, OR=1.6 (95% CI 1.0–2.5); ≥15.0 f/ml x years, OR=1.7 (95% CI 1.1–2.6). Overall, these two studies suggest that asbestos may represent a risk factor for iCCA, whereas the association with eCCA seems null or weak.

In order to provide further evidence about the link between asbestos exposure and iCCA development, we recently conducted a prospective case-control study on incident cases at our Centre. A total of 168 CCA cases (116 iCCAs and 52 eCCAs) and 185 controls (inpatients referring to our hospital for non-neoplastic diseases) were enrolled. The results obtained not only confirm the findings of our previous two studies on prevalent cases, but even reinforce the link between asbestos and iCCA risk. According to these data, asbestos fibers have been detected at the boundary between the healthy and neoplastic hepatic tissue of iCCA patients[7]. Based on these findings, we are currently performing next generation sequencing analysis in iCCA patients exposed and not-exposed to asbestos (EtherBil study, NCT02184871), in order to identify putative molecular biomarkers of asbestos exposure. Similarly to lung tumors, where a different molecular profile between asbestos-exposed and non-exposed patients has been reported[8-10], we observed a distinctive molecular profile in iCCA patients exposed to asbestos compared to iCCA patients not exposed, suggesting that asbestos could induce typical molecular alterations in target cells.

Q. Should workers with previous exposure to asbestos undergo screening for this liver cancer?

A link between asbestos and iCCA risk may explain, at least in part, the global increase of this disease,[11] but other hidden risk factors for iCCA, such as non-alcoholic steatohepatitis (NASH), are emerging, although with less impact on iCCA increase.[12] Since the latency period between asbestos exposure and disease development may be many decades (30-40 years), borrowing from the case of mesothelioma we should expect a further increase in iCCA incidence during the coming years, as the quantity of asbestos introduced into our environment increased until it was banned. In this context, surveillance procedures in subjects occupationally exposed to this compound and at high-risk of disease should be taken into serious consideration in the near future. These screening procedures could include Ca 19-9/CEA evaluation plus an ultrasonography that, based on the doubling time of iCCA growth and clinical practice, should be performed more frequently (at least every 4 months) than in HCC patients, in order to avoid cases with large unresectable iCCA at diagnosis. Moreover, the evaluation of circulating biomarkers of asbestos exposure should be assessed in these patients, but further studies are needed for their identification and potential translation into clinical practice. Undoubtedly, our knowledge of the molecular mechanisms underlying iCCA carcinogenesis is rapidly evolving, due to the current availability of high throughput analytical technologies such as next-generation sequencing. The employment of these methodologies has already made possible the identification of a distinctive molecular profile in patients with tumors of environmental origin, and our preliminary results in iCCA patients exposed to asbestos confirm this finding. Notably, the identification of molecular markers of exposure to asbestos could not only improve the monitoring of subjects exposed and at high-risk of disease, but also allow the development of more tailored strategies for the treatment of this dismal disease.

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