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Investigating the Role of Asbestos Exposure in the Development of Small Duct Intrahepatic Cholangiocarcinoma

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Annotation: Intrahepatic cholangiocarcinoma (iCCA) is an uncommon liver cancer that has recently been categorized into two morphological subtypes: small duct and large duct. Emerging evidence points to asbestos as a potential risk factor for iCCA; however, no prior studies have explored the association between asbestos exposure and iCCA subtypes. This study aimed to investigate the relationship between asbestos exposure and the morphological classification of iCCA.

A total of 50 patients who underwent surgical resection for iCCA were prospectively enrolled. Asbestos exposure was evaluated using the standardized questionnaire from the patient of medical city of Baghdad. Histopathological analysis of the resected specimens identified 36 cases of small duct iCCA (sd-iCCA) and 14cases of large duct iCCA (ld-iCCA).

Among the sd-iCCA group, five patients had confirmed or probable occupational exposure to asbestos, whereas none of the ld-iCCA cases were classified as

occupationally exposed. Other forms of asbestos exposure—such as possible occupational, familial, or environmental—were documented in 15 sd-iCCA cases and 2 ld-iCCA cases. Notably, 12 sd-iCCA patients (33.3%) and 7 ld-iCCA patients (50.0%) were considered unlikely to have been exposed to asbestos.

These findings suggest a stronger association between asbestos exposure and the small duct subtype of iCCA, implying that asbestos fibers may act as a parenchymal rather than ductal carcinogenic factor. As this is a preliminary investigation, further validation through case-control studies or larger independent cohorts is warranted.

Keywords: Asbestos, cholangiocarcinoma, iCCA, occupational disease.

Introduction

Intrahepatic cholangiocarcinoma (iCCA) represents the second most common primary liver cancer (PLC), accounting for 10–15% of PLCs [1]. Although iCCA remains a rare malignancy in Europe and the United States, its incidence is rising globally, with significant geographic variability reflecting diverse etiological factors. In Eastern countries, the high incidence has been attributed to endemic liver fluke infections, hepatolithiasis, and chronic biliary conditions [2]. In contrast, up to 40% of iCCA cases in Western populations lack identifiable risk factors [3–5]. Notably, in Japan, iCCA has recently been recognized as an occupational disease among printing workers due to solvent exposure [6].

A strong correlation between iCCA histological subtype and its underlying etiology has been well established. According to the latest WHO classification, small duct iCCA (sd-iCCA) is associated with non-biliary cirrhosis and chronic hepatitis—similar to the intrahepatic risk profile of hepatocellular carcinoma—while large duct iCCA (ld-iCCA) is linked to chronic biliary diseases such as cholangitis, hepatolithiasis, and liver fluke infections, which resemble the risk factors for extrahepatic and hilar cholangiocarcinomas [1].

Recent studies have suggested an increased risk of cholangiocarcinoma (CCA) in individuals occupationally exposed to asbestos fibers. Farioli et al. reported a heightened risk of CCA in a case–control study nested within the Nordic Occupational Cancer (NOCCA) cohort across four Nordic countries [7]. The association between asbestos exposure and CCA was stronger for iCCA than for extrahepatic cholangiocarcinoma (eCCA), confirming previous findings from an Italian case–control study [8], which indicated a fourfold increased risk of developing iCCA in asbestos-exposed individuals.

Further investigations in Casale Monferrato (Piedmont, Italy), a region with high asbestos exposure, revealed the presence of asbestos fibers within the biliary tree and gallbladder [9,10], and more importantly, within the tumor tissue of iCCA patients [11]. Although the exact mechanism by which inhaled or ingested asbestos fibers reach the liver remains unclear, the most plausible hypothesis is hematogenous dissemination via the pulmonary and portal lymphatic systems [11,12]. Once in the liver, asbestos fibers may induce chronic inflammation, disrupting the balance between cell proliferation and apoptosis [13,14]. Additionally, thinner fibers may preferentially lodge in smaller bile ducts, potentially explaining the stronger association with iCCA compared to eCCA [7,8]. To date, no substantial evidence links asbestos exposure to hepatocellular carcinoma, with only a single report describing five cases [15].

Despite growing evidence of asbestos as a risk factor for iCCA, no studies have yet explored its relationship with iCCA morphological subtypes. Therefore, the present study aims to assess the association between asbestos exposure and the histological classification of iCCA.

Methods

The study cohort was derived from the EtherBil study (ClinicalTrials.gov registration code NCT02184871), a monocentric prospective investigation approved by the local Ethical Committee (The study complies with the principles outlined in the **Declaration of Helsinki**, **Good Clinical Practice (GCP)** guidelines, and relevant regulatory frameworks.

For academic purposes, this work is submitted through the **College of Medicine, University of Baghdad**, and adheres to the institutional requirements for ethical research involving human subjects.

) under identification code EM221-2022_21/2019/U/Tess/AOUBo dated 11/04/2022. All patients provided written informed consent at the time of surgery. Individuals who underwent surgical resection for iCCA with available tumor tissue were prospectively enrolled.

A structured and standardized questionnaire was administered by trained interviewers either directly to patients or to their next of kin. The questionnaire collected comprehensive data on occupational and residential history, lifestyle habits, and clinical background. It consisted of three distinct sections:

- **Section 1:** General information, including personal data, lifestyle, and behavioral habits.
- **Section 2:** Adapted from the Italian National Mesothelioma Register (Registro Nazionale dei Mesoteliomi, ReNaM), this section gathered details on occupational history, family medical history, environmental and domestic exposure, and non-occupational asbestos exposure [21,22].
- **Section 3:** Clinical history, encompassing hepatic and non-hepatic pre-existing conditions and established risk factors.

Assessment of lifetime asbestos exposure was conducted by an occupational physician (SM) in accordance with ReNaM guidelines [23]. Exposure was classified into five categories: definite/probable occupational, possible occupational, environmental, familial, and unlikely exposure.

Histopathological evaluation was performed on formalin-fixed, paraffin-embedded surgical specimens. Tumor grading (Haematoxylin–Eosin), presence of microvascular invasion (MVI), and histological subtype were recorded. Classification into small duct (sd-iCCA) and large duct (ld-iCCA) subtypes followed the latest WHO guidelines [1]. Specifically, sd-iCCA exhibited a ductal or tubular architecture with variable desmoplastic stroma; neoplastic ducts were lined by cuboidal or columnar cells showing variable pleomorphism, inconspicuous nucleoli, and scant cytoplasm. In contrast, ld-iCCA resembled extrahepatic cholangiocarcinoma (eCCA), characterized by larger, branching ducts within a desmoplastic reaction, secretory cells with occasional mucin production, and frequent lymphovascular and/or perineural invasion (Fig. 2).

Immunohistochemical staining was performed using the Benchmark® Ultra automated system (Ventana Medical Systems, Inc., Roche Group, Tucson, AZ, USA). Antibodies included Keratin 7 (K7, rabbit monoclonal, clone Sp52, CC1S, prediluted; Roche), Keratin 19 (K19, mouse monoclonal, clone A53-B/A2.26, prediluted; Cell-Marque), and CD56 (mouse monoclonal, clone 123C3.D5, prediluted; Roche). K7 and K19 were utilized to confirm iCCA diagnosis, while CD56 was applied to support sd-iCCA subtype identification when necessary [1,24].

All study procedures were conducted in accordance with relevant ethical guidelines and regulatory standards.

Statistical Analysis

All statistical analyses were performed using STATA version 16 (StataCorp, College Station, TX, USA). Data were presented as means ± standard deviations, ranges, and frequencies. Pearson's chi-squared test, Fisher's exact test, and Kruskal–Wallis test were applied as appropriate. To assess the likelihood of asbestos exposure among sd-iCCA patients, a multivariable unconditional logistic regression model was constructed, adjusting for age (categorized as ≤55, 56–65, ≥66 years), gender, and alcohol consumption status (drinkers vs non-drinkers).

Results

A total of forty patients were enrolled in the study, comprising 22 males (44%) and 28 females (56%), all of whom underwent liver resection for histologically confirmed intrahepatic cholangiocarcinoma (iCCA). The mean age at the time of surgery was 62.8 ± 12.1 years, with an age range of 35 to 80 years. Detailed clinical characteristics are presented in Table 1.

Asbestos exposure was classified according to the ReNaM guidelines. Five patients (12.5%) were categorized as having definite or probable occupational exposure, while six patients (15.5%) had possible occupational exposure. Environmental exposure was identified in six patients (15.5%), familial exposure in eight patients (25.0%), and sixteen patients (35.0%) were considered unlikely to have been exposed. The average duration of asbestos exposure was 32.8 ± 14.4 years, ranging from 15 to 65 years. These prolonged exposures were typically characterized by low or very low concentrations of asbestos fibers.

Hepatobiliary risk factors were present in 20 patients (55.0%), including hepatolithiasis or choledocholithiasis in 10 cases, alcoholic chronic hepatitis in 8, chronic hepatitis B virus (HBV) infection in 3, and chronic hepatitis C virus (HCV) infection in 3. Additionally, hepatic steatosis was observed in 12 patients.

When combining the various risk factors, 9 patients (22.5%) had no identifiable risk factors, 10 patients (25.0%) had hepatobiliary risk factors alone (3 with hepatolithiasis, 4 with alcoholic hepatitis, 3 with HBV, and 2 with HCV), 14 patients (30.0%) had both asbestos exposure and hepatobiliary risk factors (5 with hepatolithiasis, 5 with alcoholic hepatitis, 1 with HBV, and 2 with HCV), and 11 patients (20.0%) had asbestos exposure without any hepatobiliary risk factors. No significant differences were observed in the distribution of other risk factors between asbestos-exposed and non-exposed patients (data not shown)

Characteristic	Category	N (%)
Tumor Stage	Stage I	8 (18.6%)
	Stage II	8 (18.6%)
	Stage III	16 (37.2%)
	Stage IV	4 (9.3%)
	Not determined (n.d.)	7 (16.3%)
Surgical Margin Status	R0 (tumor-free margin)	23 (53.5%)
	R1 (tumor-involved margin)	12 (27.9%)
	Not determined	8 (18.6%)
Lymph Node Involvement	N+ (positive)	8 (18.6%)

	N0 (negative)	26 (60.5%)
	Not determined	9 (20.9%)
Systemic Treatment	Yes	32 (74.4%)
	No	11 (25.6%)
Serum CA 19.9 at Diagnosis	> 37 U/ml	18 (41.9%)
	< 37 U/ml	22 (51.2%)
	Not determined	3 (7.0%)
Hepatitis Profile	HCV	2 (4.7%)
	HBV	3 (7.0%)
	Autoimmune	3 (7.0%)
	No hepatitis/Other	35 (81.4%)
History of Alcohol Consumption	Yes	9 (20.9%)
	No	25 (58.1%)
	Not determined	9 (21.0%)
Smoke Abuse	Yes	22 (55.0%)
	No	18 (45.0%)
Diabetes Mellitus	Yes	5 (11.6%)
	No	32 (74.4%)
	Not determined	6 (14.0%)

Table 1. Main clinical characteristics of the 40 enrolled patients. *n.d.* not determined.

Histopathological features of intrahepatic cholangiocarcinomas (iCCAs) were analyzed in relation to asbestos exposure. No statistically significant differences were observed between exposure groups regarding age ($p = 0.20$, Kruskal–Wallis test), sex distribution ($p = 0.44$, Pearson's chi-squared test), or the presence of non-asbestos-related risk factors ($p = 0.987$, Pearson's chi-squared test; see above).

Histological evaluation revealed that 32 tumors (80.0%) were classified as small duct iCCA (sd-iCCA), while 8 tumors (20.0%) were large duct iCCA (ld-iCCA). Microvascular invasion (MVI) was identified in 17 cases (42.5%). According to WHO grading criteria, 3 tumors (7.5%) were grade 1, 22 (55.0%) were grade 2, and 14 (35.0%) were grade 3. Most tumors exhibited a tubular histotype, with the exception of three predominantly solid tumors (two sd-iCCA and one ld-iCCA) and one mucinous ld-iCCA.

The distribution of iCCA subtypes in relation to asbestos exposure is summarized in Table 2. Key findings include:

- **Definite/probable occupational asbestos exposure** was documented in five cases, all of which were sd-iCCA. No ld-iCCA cases were reported in this exposure category.
- **Possible occupational exposure** was observed in five sd-iCCA cases and one ld-iCCA case.
- **Overall asbestos exposure** (including occupational, environmental, and familial sources) was identified in 21 sd-iCCA patients (65.6%) and 3 ld-iCCA patients (37.5%).
- **Unlikely asbestos exposure** was noted in 11 sd-iCCA cases (34.4%) and 5 ld-iCCA cases (62.5%). Statistical comparison between exposed and non-exposed groups yielded a p-value of 0.229 (Fisher's exact test), with an odds ratio (OR) of 3.2 and a 95% confidence interval (CI) of 0.6–15.9.

Asbestos Exposure Type	sd-iCCA (N = 36)	ld-iCCA (N = 14)
Unlikely	12 (33.3%)	7 (50.0%)
Environmental exposure	7 (19.4%)	4 (28.6%)
Familial exposure	6 (16.7%)	1 (7.1%)
Occupational (possible)	5 (13.9%)	2 (14.3%)

exposure		
Occupational (definite/probable) exposure	6 (16.7%)	0 (0.0%)
Total	**36 (100.0%)**	**14 (100.0%)**

Table 2: Distribution of Small-Duct and Large-Duct iCCA Subtypes According to Asbestos Exposure Categories (ReNaM Guidelines)

This table illustrates the classification of intrahepatic cholangiocarcinoma (iCCA) subtypes—small duct (sd-iCCA) and large duct (ld-iCCA)—among the enrolled patients, stratified by asbestos exposure categories as defined by the Italian National Mesothelioma Register (ReNaM). Exposure levels include definite/probable occupational, possible occupational, environmental, familial, and unlikely exposure.

- e OR (adjusted for age, gender, alcohol drinking, smoking status and HBV/HCV chronic hepatitis) for being exposed to asbestos was 3.5 (96% CI 0.6–92.7) for sd-iCCA patients, considering ld-iCCA patients as reference.

No di erences among the exposure groups were found as far as the other histopathological variables are concerned (*data not shown*).

Discussion

Our findings indicate that intrahepatic cholangiocarcinomas (iCCAs) of the small duct subtype (sd-iCCA) may be more frequently associated with asbestos exposure compared to the large duct subtype (ld-iCCA), with exposure rates of 64.8% versus 36.5%, respectively. Notably, a previously published case–control study reported that only 12.0% of control subjects from the general population had occupational asbestos exposure [8]. In contrast, our study identified occupational exposure in 32.4% of sd-iCCA patients, while only one ld-iCCA case (13.5%) fell into this category.

This observation is particularly relevant given that sd-iCCA has been traditionally linked to hepatocellular or parenchymal risk factors—such as viral hepatitis—rather than biliary (ductal) risk factors like cholelithiasis, which are more commonly associated with ld-iCCA and extrahepatic cholangiocarcinoma (eCCA) [16,17]. These results suggest that prolonged asbestos exposure, either alone or in combination with other established risk factors, may represent an additional parenchymal risk factor for sd-iCCA. This hypothesis aligns with previous studies by Farioli et al. and Brandi et al., which demonstrated an elevated risk of iCCA in individuals exposed to asbestos fibers [7,8].

Recent mechanistic models propose that highly penetrant, thin asbestos fibers—originating from inhalation (via systemic circulation) or ingestion (via portal circulation)—can reach the deepest regions of the liver parenchyma, including Hering's canals and terminal bile ductules, potentially initiating oncogenesis through multiple pathways [18]. One compelling hypothesis is that these fibers exert a direct oncogenic effect on hepatic stem cells residing within Hering's canals [19]. This direct damage to the stem cell niche may explain the absence of known morphological precursors in sd-iCCA, unlike ld-iCCA and eCCA, which are often associated with biliary intraepithelial neoplasia (BilIN) [1].

Indirect mechanisms may also contribute: asbestos fibers longer than 20 μm are resistant to complete phagocytosis by macrophages, thereby sustaining a chronic pro-inflammatory microenvironment [20]. In this context, Kupffer cells may also play a role in fiber deposition and the maintenance of inflammation [18].

The primary limitation of this study is its small sample size, which reduces statistical power and limits the ability to draw definitive causal conclusions. Additionally, iCCA is known to have a

wide range of risk factors unrelated to asbestos exposure [3]. The use of a questionnaire to assess exposure introduces the possibility of recall bias, which may have led to underreporting of asbestos exposure, particularly among ld-iCCA patients.

While selection bias cannot be entirely excluded, it is unlikely to have significantly influenced the observed differences in asbestos exposure between sd-iCCA and ld-iCCA patients. This is due to the monocentric nature of the study, conducted at a hospital that serves as a major referral center for bile duct neoplasms, with patients enrolled prospectively.

Importantly, the findings of this study strengthen the proposed association between asbestos exposure and intrahepatic cholangiocarcinoma (iCCA) [7,8], suggesting for the first time that such exposure may be more closely linked to the small duct histological subtype than to the large duct subtype. This observation holds considerable significance, especially given that environmental asbestos exposure is often underestimated or remains undocumented.

To confirm these preliminary results, further research is warranted through well-designed case–control studies or large-scale prospective cohort investigations. Such studies should account for other established risk factors for iCCA to better elucidate the role of asbestos in its pathogenesis.

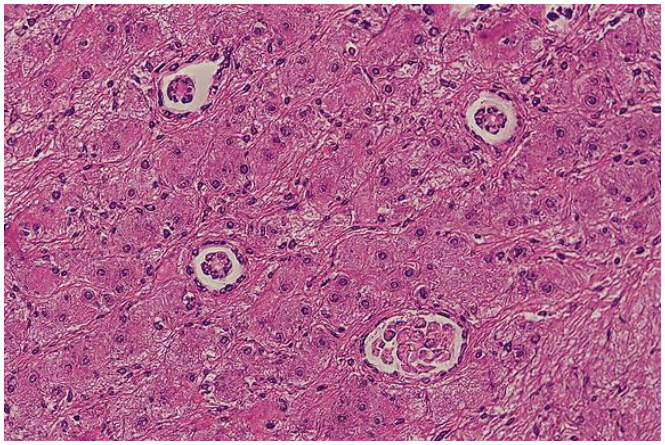

Figure 1. Histological architecture of normal liver parenchyma with small bile ducts. Hematoxylin and Eosin (H&E) stain showing small intrahepatic bile ducts lined by cuboidal epithelium, surrounded by dense fibrous stroma and hepatocytes. The ducts are regular in shape with clear lumina, and the stroma is composed of collagen fibers and scattered fibroblasts. Magnification: 20×.

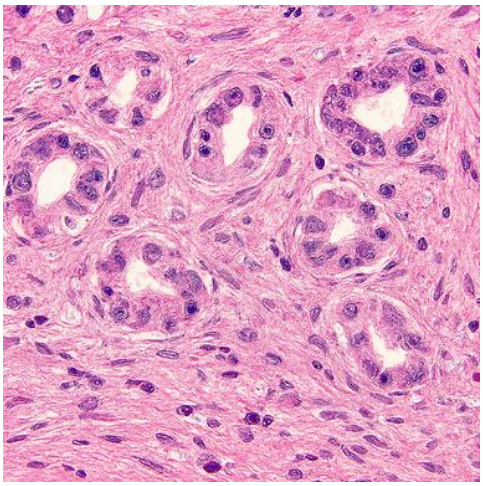

Figure 2. Small duct intrahepatic cholangiocarcinoma (sd-iCCA). H&E stain revealing malignant small ducts embedded in a desmoplastic stroma. The ducts are lined by cuboidal to low columnar epithelial cells with mild nuclear pleomorphism and hyperchromasia. The stroma is dense and fibrotic, with scattered inflammatory cells. Magnification: 20×.

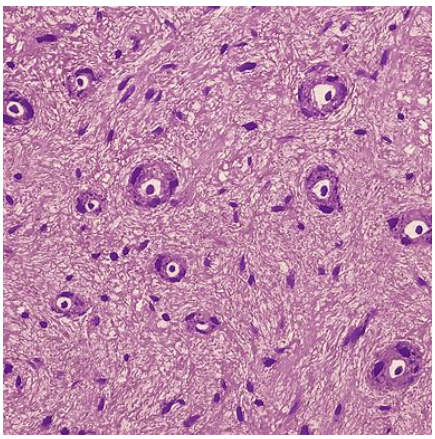

Figure 3. Dense desmoplastic stroma surrounding neoplastic ducts in sd-iCCA. H&E stain showing irregular small ducts within a collagen-rich stroma. The ducts are lined by uniform cuboidal cells with dark nuclei and minimal atypia. Fibroblasts and inflammatory cells are dispersed throughout the stroma. Magnification: 20×.

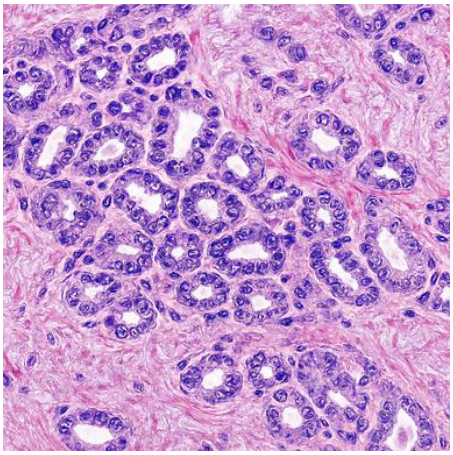

Figure 4. Glandular pattern of sd-iCCA with inflammatory infiltration. H&E stain demonstrating small glandular structures with cuboidal epithelium and central lumina. The surrounding stroma contains dense collagen fibers, fibroblasts, and lymphocytes. The ducts are unevenly distributed across the field. Magnification: 20×.

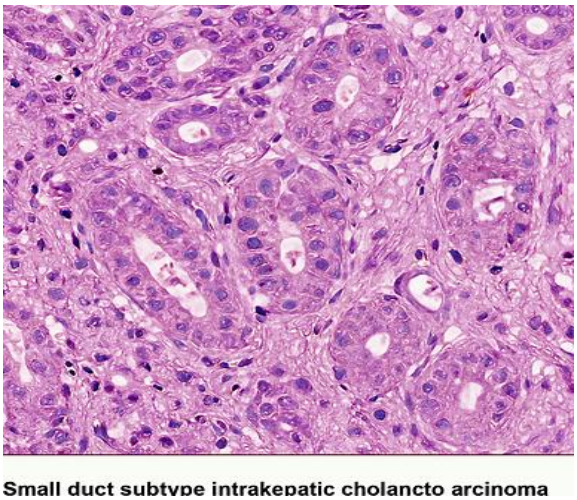

Figure 5. Neoplastic ducts in sd-iCCA with minimal atypia. H&E stain showing small ducts lined by cuboidal epithelial cells with round nuclei and pale cytoplasm. The ducts are embedded in a dense desmoplastic stroma with scattered inflammatory cells and microvasculature. Caption: *Small duct subtype intrahepatic cholangiocarcinoma (sd-iCCA) stained, showing cuboidal epithelium with minimal atypia, surrounded by dense desmoplastic stroma.* Magnification: 20×.

Pathological Features of iCCA Subtypes

Histological examination revealed distinct morphological characteristics between the two subtypes of intrahepatic cholangiocarcinoma (iCCA).

(a) On Haematoxylin–Eosin staining, small duct iCCAs (sd-iCCA) displayed small, uniform ducts and tubules lined by cuboidal epithelial cells with minimal atypia. These structures were embedded within a dense desmoplastic stroma.

(b) Immunohistochemical analysis showed CD56 positivity in sd-iCCA cases, consistent with current diagnostic guidelines.

(c) In contrast, large duct iCCAs (ld-iCCA) exhibited large, branching ducts lined by epithelial cells ranging from cuboidal to columnar, often containing variable mucinous components.

(d) CD56 immunostaining was typically negative in ld-iCCA cases. All images were evaluated at 20× magnification.

Statistical Analysis

To assess the association between asbestos exposure and iCCA subtype, patients with ld-iCCA were used as the reference group. Multivariable unconditional logistic regression was performed to estimate odds ratios (OR) and 95% confidence intervals (CI), following the method of Breslow and Day [25]. The model was adjusted for age (categorized as ≤55, 56–65, ≥66 years), gender, smoking status (ever vs never smokers), and history of chronic hepatitis B or C (HBV/HCV: yes/no). A significance level of $\alpha = 0.05$ was adopted for all statistical tests.

Conclusions

This study provides preliminary evidence supporting a potential association between asbestos exposure and the small duct subtype of intrahepatic cholangiocarcinoma (sd-iCCA). While no statistically significant differences were observed in demographic or clinical variables between exposure groups, a higher proportion of sd-iCCA cases were linked to occupational and environmental asbestos exposure compared to large duct iCCA (ld-iCCA). These findings suggest that asbestos fibers may act as a parenchymal carcinogenic factor, possibly contributing to sd-iCCA pathogenesis through direct or indirect mechanisms involving hepatic stem cells and chronic inflammation.

Although limited by sample size and potential recall bias, the prospective design and centralized recruitment strengthen the reliability of the observations. Further large-scale, multicenter studies are warranted to validate these results and to better understand the etiological role of asbestos in iCCA subtypes, particularly in the context of other established hepatobiliary risk factors.

Recommendations

Based on the findings of this pilot study, the following recommendations are proposed:

1. **Further Research:** Large-scale, multicenter prospective studies are essential to confirm the observed association between asbestos exposure and the small duct subtype of iCCA, while accounting for confounding variables and established hepatobiliary risk factors.
2. **Improved Exposure Assessment:** Future studies should incorporate more objective methods for evaluating asbestos exposure, such as environmental sampling or biomarker analysis, to reduce reliance on self-reported data and minimize recall bias.
3. **Pathological Surveillance:** Routine histopathological classification of iCCA into small and large duct subtypes should be emphasized, particularly in regions with known asbestos exposure, to better understand etiological patterns.

4. **Public Health Awareness:** Awareness campaigns should be developed to highlight the potential carcinogenic effects of asbestos, especially in occupational settings, and to encourage early screening in exposed populations.
5. **Policy Implications:** Regulatory bodies should consider revisiting occupational safety standards and exposure limits for asbestos, given its possible role in liver carcinogenesis beyond mesothelioma and lung cancer.

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