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Occupational and Environmental Cholangiocarcinoma-Related Toxic Exposures

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Keywords
Cholangiocarcinoma · Occupational exposures · Toxic exposures · Intrahepatic cholangiocarcinoma · Extrahepatic cholangiocarcinoma

Abstract
Cholangiocarcinoma (CCA) is a malignancy that originates from the epithelial cells of the biliary system. Despite advancements in medical diagnostic techniques, CCAs remain a challenge to detect due to their silent clinical progression, making it difficult to diagnose these diseases. There are several well-established risk factors for CCA, including biliary tract infection and inflammation. However, there is also growing evidence that community and occupational exposures play a significant role in the development of bile duct cancers. This review examines the geographical distribution of these risk factors and the importance of surveillance in individuals exposed to these toxins who are more prone to developing CCA.

Exposições Tóxicas Ocupacionais e Ambientais Relacionadas com o Colangiocarcinoma

Palavras Chave
Colangiocarcinoma · Exposições ocupacionais · Exposições tóxicas · Intra-hepáticas · Extra-hepáticas

Resumo
O colangiocarcinoma (CCA) é uma neoplasia maligna cuja origem reside nas células epiteliais do sistema biliar. Não obstante os progressos registados nos métodos de diagnóstico, a deteção dos CCA é um desafio, em virtude da sua progressão clínica silenciosa, tornando difícil o diagnostico desta entidade. Há diversos fatores de risco estabelecidos para o CCA, incluindo infeção e inflamação do trato biliar. Todavia, há também cada vez mais evidência de que as situações de exposição comunitária e profissional têm um papel significativo no desenvolvimento dos cancros das vias biliares. Esta análise aborda a distribuição geográfica destes fatores de risco e a

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importância da monitorização em indivíduos expostos a estas toxinas, os quais são mais propensos a desenvolver cancro das vias biliares.

Introduction

Cholangiocarcinoma (CCA) is a type of cancer that originates from bile duct epithelial cells. Classically, CCAs have been grouped together with gallbladder carcinomas, but a more recent classification categorizes it as intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) according to its anatomic location along the biliary tree [1]. pCCA arises from the left, right, and common hepatic ducts to the origin of the cystic duct, while dCCA arises from the common bile duct distal to the insertion of the cystic duct [2].

The most common risk factors for CCA include PSC, biliary duct cysts, chronic biliary tract inflammation, and, in certain geographic areas, parasitic infections such as liver fluke [3]. However, there exists a wide range of other occupational and environmental exposures that have been linked to the development of CCA, including 1,2-dichloropropane, aflatoxins, alcohol, arsenic, asbestos, dioxin, nitrosamines, polychlorinated biphenyls (PCBs), smoking, thorium dioxide, and vinyl chloride [4]. In this literature review, we explore the most common community and occupational exposures that have been associated with the development of CCA and examine the mechanisms by which they may play a role in carcinogenesis (Table 1).

Cholangiocarcinoma and Risk Factors

Clinical Features

CCAs are subdivided into iCCA, pCCA, and dCCA. The clinical features of the neoplasm are determined by the location of the tumor within these categories [25]. pCCAs can present with symptoms of biliary obstruction and cholestasis, such as painless jaundice, abdominal pain, and clay-colored stools [26]. iCCAs often present with more nonspecific symptoms, such as dull abdominal pain, and "B symptoms" such as night sweats, weight loss, and fatigue [27].

Diagnosis

CCAs are often discovered incidentally in routine imaging studies [28]. Diagnosis can be broken down into three groups: imagiological evaluations, endoscopic evaluations, and tumor markers/cytology [29] (shown in Fig. 1). Ultrasound (US) is the most common initial screening test for an abnormal hepatic panel, but it has been shown to have difficulty differentiating between iCCAs and HCC [30]. CT scans can differentiate between the two, as they appear as hypodense masses with irregular margins, but unlike US, CT does allow for differentiation based on enhancement versus washout in the arterial and venous delayed phases [31].

Magnetic resonance imaging with contrast provides similar benefits and magnetic resonance cholangiopancreatography allows for anatomical visualization of the ductal system, which helps determine tumor resectability [32]. Compared with CT, magnetic resonance imaging is slightly superior in terms of tumor detection [33]. Positron emission tomography scans also help in diagnosis due to the high glucose uptake of the bile duct epithelium but can be limited with smaller/periductal infiltrating tumors [34]. The most beneficial use of positron emission tomography-CT is in detecting distant metastatic lesions [35].

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography are also useful in diagnosis, as samples of the lesion(s) can be taken [31]. EUS helps assess regional and extraregional lymph nodes, whereas endoscopic retrograde cholangiopancreatography allows for tissue samples via brush cytology, cholangioscopy-guided biopsies, and intraductal biopsies in addition to relief with stent placement. Traditionally, EUS has been a diagnostic tool, but its therapeutic applications have expanded, particularly for palliative care in CCA as well. In terms of cytology, the histologic appearance of CCA is similar to many metastatic tumors; however, when combined with fluorescence in situ hybridization, the specificity of the diagnosis increases [36]. Fluorescence in situ hybridization has a sensitivity and specificity of approximately 68% and 70%, respectively, in diagnosing CCA [37]. Next-generation sequencing has significant benefits in detecting CCA and identifying specific genomic alterations allows for personalized tumor directed therapy [38]. Tumor markers CA 19-9 and CEA are more useful in monitoring cancer recurrence after surgery, as they are otherwise nonspecific and can be elevated in other cancers or benign diseases [39, 40], although CA 19-9 is specific and sensitive for iCCA for people with PSC [41, 42].

Common Risk Factors of CCA

There are several established risk factors of CCA including parasitic infections, PSC, biliary duct cysts, hepatolithiasis, and toxins. Potential, however, less-

Table 1. Suspected mechanism of action for occupational exposures

Exposure	Association with the development of cholangiocarcinoma
1,2-dichloropropane	Mutagenic effects such as increased DNA breakage and transitional mutations from CG to TA; induction of inflammatory NFKB and TNF-alpha pathways, leading to DNA editing enzyme activation [5]
Aflatoxins	Stimulation of oval cells in knockout mice which can lead to the development of hepatocellular and/or cholangiocellular carcinomas [6]
Alcohol	Induction of CYP2E1 → conversion of ethanol into acetaldehyde → production of ROS → DNA damage + inhibition of DNA repair + decreasing hepatic retinoic acid; iron overload → DNA strand breaks and p53 mutations [7–9]
Arsenic	Arsenic's toxic metabolites are metabolized by the liver and then excreted through the biliary system. While the molecular mechanisms are not understood, the direct exposure of arsenic's metabolites to the biliary system may be oncogenic [10]
Asbestos	Release of pro-inflammatory cytokines in the bile ducts; epigenetic silencing; release of ROS; absorption of ionizing radiations; iteration of chromosomes during mitosis, resulting in chromosomal, histone, and RNA transcription [11, 12]
Dioxin, most commonly TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin)	Activation of the aryl hydrocarbon receptor, which leads to the activation of transcription factors and therefore affects downstream DNA and cell signaling pathways, including steroid hormones and endocrine systems [13–15]
Nitrosamines	Its metabolite N-nitroso dimethylamine (NDMA) has been shown to play a role in the carcinogenesis of CCA [16, 17]
Polychlorinated biphenyls (PCBs)	Weak association however evidence suggests that PCBs increase incidences of the liver, gallbladder, and biliary tract cancers [18, 19]
Thorium dioxide	Mutagenicity; most common mutations of A to G transitions of TP53 [20–22]
Tobacco	Nicotine potentially causes biliary fibrosis via cholangiocyte proliferation [23]
Vinyl chloride	Direct DNA mutation; base pair transitions during transcription lead to direct mutations in the RAS oncogenes and suppression of p53 suppressor genes [24]

established risk factors include inflammatory bowel disease, hepatitis B and C, cirrhosis, diabetes, obesity, alcohol use, smoking, and genetic polymorphism [3]. This paper focuses on specific community and occupational exposures contributing to CCA.

Toxic Exposures

1,2-Dichloropropane

1,2-dichloropropane (1,2-DCP) is a chemical used in the production of organic chemicals, paint stripping, and as an ink removal agent in the printing industry in Japan, until it was banned in 2012 [43]. A large body of evidence linking 1,2-DCP to CCA comes from a single printing plant in Osaka, where a high incidence of CCA (17/111) in young patients with similar intensity of exposure led to the conclusion that 1,2-DCP was the cause of the disease [44]. Furthermore, exposure to 1,2-DCP has been linked to additional plants, with significant results in the middle exposure (RR: 14.9, 95% CI: 4.1–54.3) and high exposure category (RR: 17.1, 95% CI: 3.8–76.2) [45].

The mechanism of action by which 1,2-DCP causes CCA is not yet fully understood, but studies have shown that it can cause mutagenic effects, including increased breakage in DNA and increased transitional mutations from CG to TA, through the formation of extra DNA adducts on G residues [5]. In addition, DNA editing enzyme activation has been shown to increase in in vitro studies due to the induction of inflammatory NFKB and TNF-alpha pathways [46] (shown in Fig. 2).

Aflatoxins

Aflatoxins, which are well associated with HCC, do not have established correlations with CCAs in humans [47]. A review of the literature revealed only a

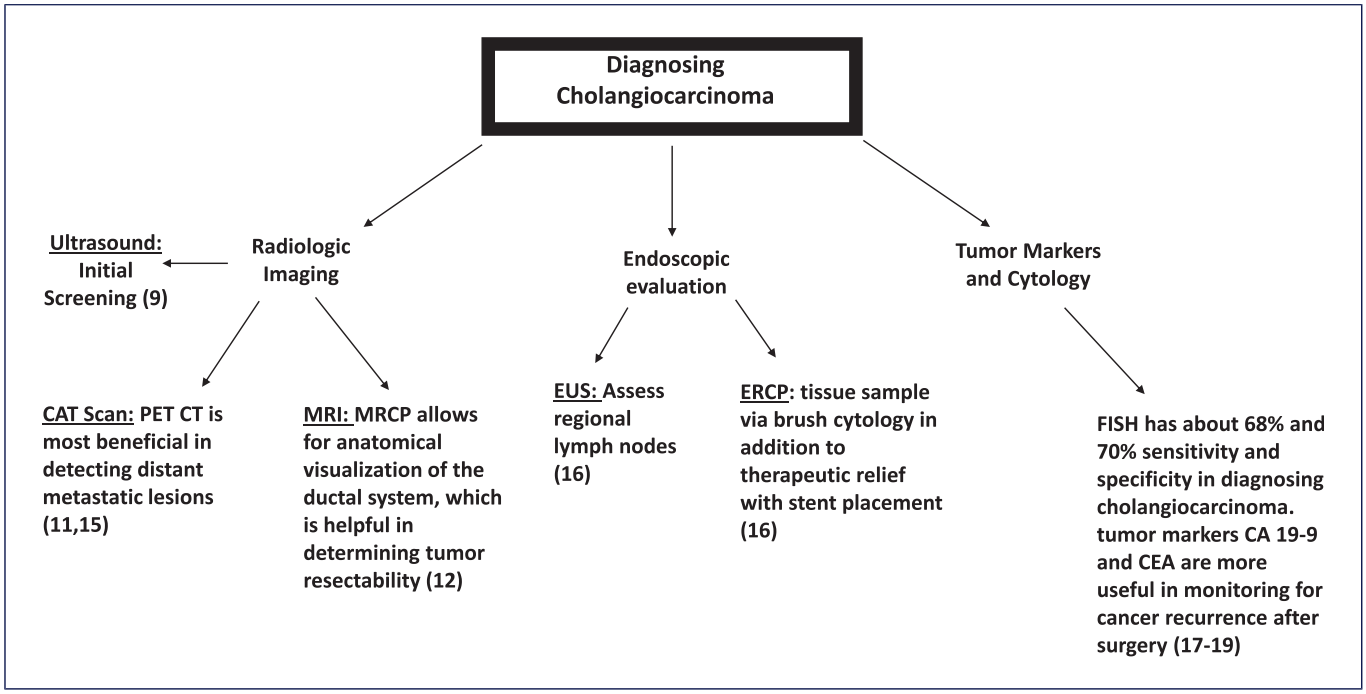

Fig. 1. Cholangiocarcinoma can be diagnosed by a number of different mechanisms. Radiologic imaging allows for the visualization of mass. Endoscopic evaluation allows for visualization and sampling of the mass as well as therapeutic stent placement. Cytology allows for more specific tissue analysis.

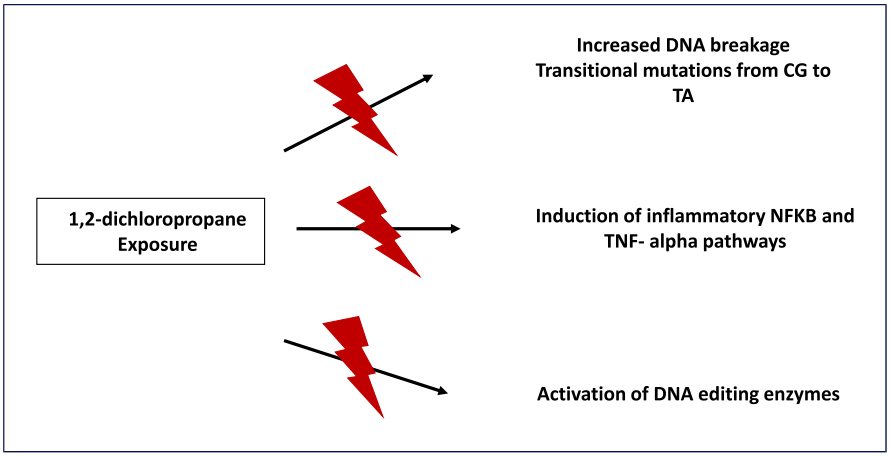

Fig. 2. Various pathways of 1,2-dichloropropane exposure. Mutagenic effects such as increased DNA breakage and transitional mutations from CG to TA; induction of inflammatory NFKB and TNF-alpha pathways, leading to DNA editing enzyme activation.

molecular study in knockout mice that were similarly susceptible as humans to aflatoxin's mutagenic effects. CCAs were produced when aflatoxin B was administered for a long period, most likely due to the stimulation of oval cells, which are thought to function as adult liver stem cells derived from hepatic progenitor cells that reside in the bile ducts. These cells can develop into hepatocellular and/or cholangiocellular carcinomas [6].

Alcohol

Alcohol consumption has been identified as a risk factor for the development of CCA. A meta-analysis published in the Journal of Hepatology found that heavy alcohol consumption, defined as 80 grams per day or the presence of alcoholic liver disease, was associated with an overall increased risk of iCCA (OR: 2.81, 95% CI: 1.52–5.21) [48]. Similarly, a study from the Liver Cancer Pooling Project revealed that heavy alcohol consumption,

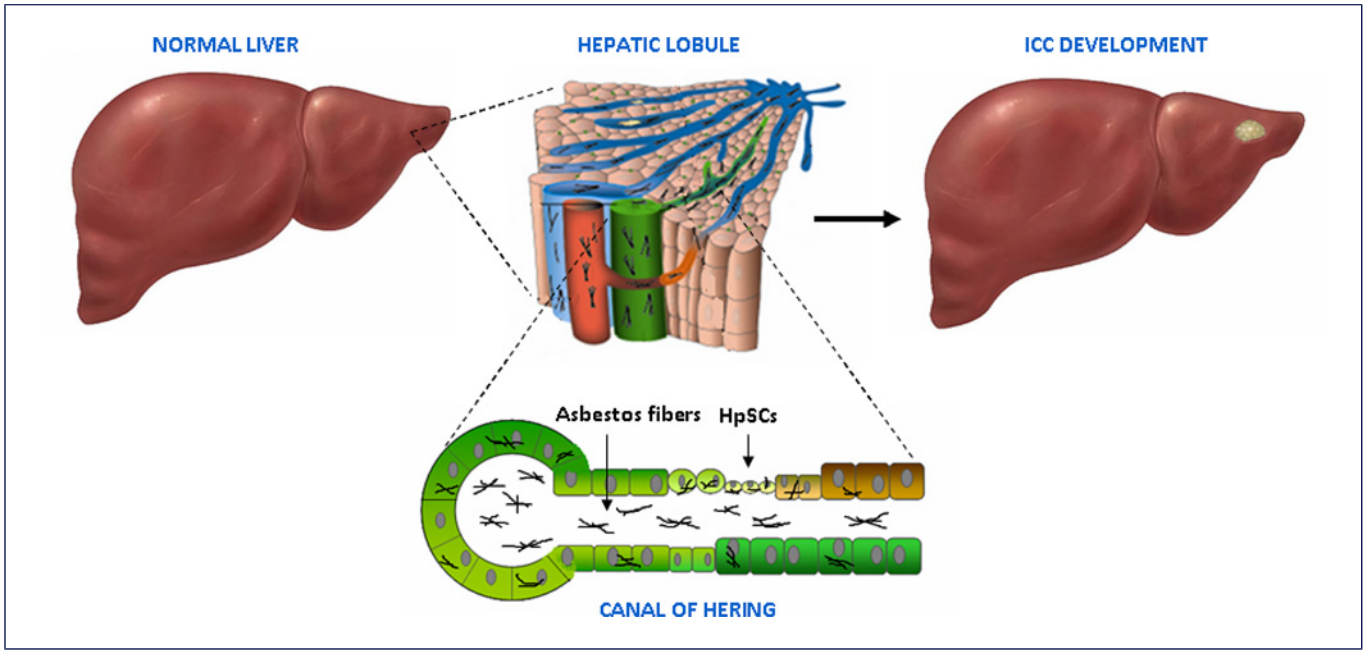

Fig. 3. Trapped asbestos fibers within smaller bile ducts, particularly at the level of the canals of Hering, where they may exert carcinogenic effects, inducing HpSC malignant transformation and eventually ICC development. Reproduced with permission, MDPI, Basel, Switzerland (https://creativecommons.org/licenses/by/4.0), Brandi G, Tavolari S. Asbestos and intrahepatic cholangiocarcinoma. *Cells* 2020;9.

categorized as more than five drinks per day, may be associated with an increased risk for iCCA, although this finding did not reach statistical significance (HR: 1.68, 95% CI: 0.99–2.86) [7]. The mechanism by which alcohol may contribute to CCA formation is thought to involve the induction of CYP2E1, which breaks ethanol into acetaldehyde, leading to increased levels of reactive oxygen species, DNA damage, inhibition of DNA repair, decreased hepatic retinoic acid, and iron overload, resulting in DNA strand breaks and p53 mutations [8, 9]. However, a pooled analysis found that the risk of iCCA was similar between alcohol consumption groups and non-drinkers (RR: 1.09, 95% CI: 0.87–1.37) [49].

Arsenic

There may be a potential carcinogenic effect of arsenic in drinking water on developing CCA. A recent study showed that although no correlation was observed between elevated measured arsenic levels in groundwater and CCA in the USA, there were associations in Taiwan and India [50]. In Taiwan, there was found to be an increased risk for both intrahepatic and extrahepatic CCA; whereas in India, there was found to be an increased risk for extrahepatic CCA only [50]. Although arsenic exposure can occur in certain occupations such as mining and refining processes (such as gold, lead, zinc, and copper), no studies were found that relate arsenic exposure in the workplace to CCA [10].

Asbestos

Asbestos is a well-known carcinogen that causes primary thoracic cancers, including mesothelioma [1]. A case-control analysis of 155 consecutive patients found an increased risk of iCCA in workers exposed to asbestos (OR: 4.81, 95% CI: 1.73–13.33) and a possible link between exposure and extrahepatic CCA (OR: 2.09, 95% CI: 0.83–5.27) [2]. Asbestos may translocate to the biliary tract and interlobular bile ducts, which may explain the stronger correlation between asbestos exposure and iCCA, rather than extrahepatic CCA [51–54].

The mechanism by which asbestos induces CCA shares similarities with the pathway of the liver fluke in terms of translocation. Asbestos fibers may cross the alveolar barrier after inhalation or enter the gastrointestinal mucosa after ingestion, entering the circulatory and lymphatic systems and becoming lodged in the smaller bile ducts [4] (shown in Fig. 3). Macrophages attempt to phagocytose these fibers, but cannot digest fibers longer than 20 micrometers, leading to the release of pro-inflammatory cytokines and activation of the

EGFR pathway [11]. Additionally, asbestos can also induce mutagenicity through various pathways such as epigenetic silencing, the release of reactive oxygen species, absorption of ionizing radiation, and physical interaction with chromosomes during mitosis, leading to chromosomal, histone, and RNA transcription errors [12].

Dioxin

Dioxin-like compounds (DLCs) are environmental pollutants that are byproducts of burning and other industrial processes [55]. Specific industrial processes include those that manufacture chemicals (such as herbicides, PCBs, chlorinated phenols, and chlorinated aliphatic compounds), those that burn fuels, and waste incinerators [55]. These compounds have been associated with a range of adverse effects, particularly in individuals with high levels of occupational exposure, those who consume contaminated food products, and those living near industrial factories [56]. Exposure to DLCs can occur through inhalation of dust, ingestion, and dermal contact with polluted soil [56].

Due to their long half-life (2–5 years) and toxicity potential, DLCs have been banned since the 1970s [55]. The most toxic of these compounds is TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin), which has been linked to immune system modulation, tumor promotion, and teratogenesis [57, 58]. The toxic effects of TCDD and other DLCs are mediated by activation of the aryl hydrocarbon receptor, a specific intracellular receptor [13, 14]. When TCDD diffuses into the plasma membrane and binds to aryl hydrocarbon receptor, it activates transcription factors and subsequently affects downstream DNA and cell signaling pathways, including steroid hormones and endocrine systems [15].

To assess and manage the risks posed by DLCs, the dioxin toxic equivalency factor is used as a worldwide approach [59]. To evaluate the carcinogenic effects and chronic toxicity of DLCs and PCBs, several 2-year rodent bioassays were conducted by the National Toxicology Program [59]. The results of these bioassays showed a dose-dependent increase in CCA incidence over the controls, such that rodents that received both TCDD and PCBs had a higher incidence of CCA, in addition to hepatocellular adenoma [59].

Nitrosamines

Nitrosamines are compounds derived from nitrous acid and secondary amines that can be found in various foods, drinking water, and tobacco products [60]. Food sources such as cured meats and smoked foods, which are more prevalent in the Asian diet, contain nitrosamines [61, 62]. While nitrosamines have not been proven to be carcinogenic to humans, some clinical trials and systematic reviews have suggested an increased risk of nasopharyngeal and gastric cancer in individuals with high nitrosamine intake [63–65]. However, a metabolite of nitrosamines, called N-nitroso dimethylamine (NDMA) has been shown to play a role in the carcinogenesis of CCA [66].

A review article studying CCA in Thailand looked at the liver fluke *Opisthorchis viverrini*, which is a causative factor in the development of CCA [67]. This liver fluke species has been shown to increase the production of nitrous oxide in the gut microbiome [68–70], which eventually leads to increased production of NDMA in the bile duct [16, 68, 71]. NDMA has been shown to play a role in the carcinogenesis of CCA, so it is speculated that diets rich in nitrosamines and those who smoke tobacco may be at increased risk [16, 17].

Polychlorinated Biphenyls

PCBs are a group of organic compounds composed of two benzene rings attached to 2–10 chloride atoms [72]. These compounds were widely used as dielectric and coolant fluids from 1930 to 1970 [73]. However, due to their carcinogenic properties as established through animal studies, their use was banned in the USA in 1979 [74]. Humans can be exposed to PCBs through various routes, including diet, air, and an occupational setting [75]. Animal models have shown that PCBs can lead to a wide range of systemic effects, including hypertension and hypercholesterolemia, as well as an increased incidence of neurological diseases [76–78].

PCBs are a weak causative factor in the development of CCA [18]. A study conducted in 1987 on workers at a factory exposed to PCBs found an increased incidence of the liver, gallbladder, and biliary tract cancers compared to controls [19]. A more recent study, with a small sample size of 15 patients, compared the levels of PCBs in patients with malignant and benign biliary tract cancer [18]. The study concluded that there was an increase in PCB concentration with age in these patients, and despite the ban on these compounds, there is still a significant concentration of PCBs in the bile of these patients [18].

Smoking

Smoking is one of the leading causes of cancer, due to the many toxic chemicals it contains, such as carbon monoxide and cyanide, as well as nicotine, which is the

addictive component of tobacco [4]. The impact of smoking on CCA is not well studied in cohort studies. Previous case-control studies have had mixed results, with some concluding that smoking increases the likelihood of CCA, while others found no impact [79, 80]. A recent experimental study with mice showed that nicotine causes biliary fibrosis via cholangiocyte proliferation, which may point to the mechanism by which smoking could induce CCA [23].

A recent retrospective study conducted in China analyzed 55,806 smokers and looked at the incidence of extrahepatic CCA in this sample [81]. The results of the study showed that exposure to both active and passive tobacco smoke increased the mortality risk from CCA [81]. Furthermore, the results correlated with the increased prevalence of CCA in China, which has increased along with the incidence of smoking in China since the 1980s [81, 82].

Thorium Dioxide

Thorium dioxide, also known as thorotrast, was a radiographic contrast agent that was used in USA, Europe, and Japan until it was banned in 1960. Thorium has a half-life of approximately 400 years, which results in a lifetime of alpha radiation exposure with an estimated latency period between exposure and diagnosis of 16–45 years [83]. Thorotrast has been linked to a wide range of malignancies, primarily liver cancer, including hepatocellular carcinoma, angiosarcoma, and cholangiosarcoma. This link was first documented during World War II due to increased use of thorotrast and found a 300-fold increased risk of CCA specifically [84].

A literature review points to the mechanisms by which thorotrast induces CCA as most likely being mutagenic [20]. In the liver, thorotrast is aggregated in Kupffer's cells, which is then slowly released and absorbed by hepatocytes [21]. Through alpha radiation-induced nucleotide base deletions, transitions, and transformations, repeated cycles of replication cause multiple errors that eventually lead to uninhibited growth, microsatellite instability, and gene silencing, ultimately resulting in tumor growth [20]. It has been found that in cases of thorotrast-induced CCAs, mutations of A to G transitions of TP53 were more than 2 times higher than in non-thorotrast CCAs [22].

Additionally, thorotrast may also destabilize microsatellite motifs by hypermethylating the hMLH1 promoter region [85]. Since the contrast agent has been banned since the 1960s, the number of CCA associations with thorotrast has been minimal [85].

Vinyl Chloride

Vinyl chloride is a synthetic, colorless gas that does not occur naturally and is often used in the production of polyvinyl chloride, a material commonly used in pipes, insulators, and packaging materials [86]. The mechanism by which vinyl chloride induces CCA is thought to be through direct DNA mutation, rather than through secondary cytotoxicity [24]. Reactive metabolites of vinyl chloride, such as 2-chloroethylene oxide, 2-chloroacetaldehyde, and other cyclical structures, can cause base pair transitions during transcription, leading to mutations in the RAS oncogenes and suppression of p53 suppressor genes [24].

Conclusion

CCA is a highly malignant cancer of the biliary tract that can be difficult to detect and treat, as individuals often present with nonspecific symptoms and are often in the later stages of tumor progression. Established risk factors of CCA include parasitic infections, PSC, biliary duct cysts, hepatolithiasis, and toxins. Potential, however, less-established risk factors include inflammatory bowel disease, hepatitis B and C, cirrhosis, diabetes, obesity, alcohol use, smoking, and genetic polymorphism [3]. However, there has been limited research on the relationship between environmental factors and CCA. This literature review aimed to compare various environmental exposures and their critical role in the carcinogenesis of CCA. Thorium dioxide, 1,2-dichloropropane, and asbestos are some of the more common risk factors that have been studied, but this review also examined less-known exposures and specific industries that have been shown to play a role in CCA development. Further research is needed to fully understand the importance of the cumulative effect of environmental factors in the development and progression of CCA, which would aid in the understanding of the disease onset and progression. Future studies can assess whether greater surveillance would be beneficial for individuals exposed to these toxins who are at a higher risk of developing CCA.

Statement of Ethics

Ethical review and approval were not required, as the study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tianyu She, Nairuti Shah, and Nathan Starkman: literature review and draft of the manuscript. Benna Jacob, Julie Lieman, Amandeep Kaur, and Neal Shah: literature review and critical review of the manuscript and assistance with figures and tables. Marc Wilkenfeld supervised all of above and came up with original article concept and design. All authors critically reviewed and approved the final manuscript.

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