REVIEW

Editorial Process: Submission:02/24/2022 Acceptance:06/11/2022

Cholangiocarcinoma Attributed to Occupation: A Systematic Reviews

Anantapat Seeherunwong[1], Naesinee Chaiear[1], Narong Khuntikeo[2], Chatchai Ekpanyaskul[3]*

Abstract

Background: The occurrence of a cluster of occupational cholangiocarcinoma(CCA) cases among Japanese workers at a small offset printing plant led to the hypotheses that occupational exposure was the root cause of this cancer. Numerous workplace carcinogens can be found at various jobs sites and are integral to various industrial processes. Therefore, a systematic evaluation of potential occupationally-related CCA and likely exposure types is needed. **Objective:** To conduct a systematic review on the cause of CCA in relation to occupation. **Methods:** The systematic review included papers published between 1980 and 2020. Databases included PubMed, Science Direct, CINAHL, ProQuest Medical Library, Springer, Wiley online library, and the Cochrane library. The review focused on CCA, intrahepatic CCA(as distinct from other types of liver cancer), and extrahepatic CCA(not including the gallbladder). While some occupations involve an expected risk of exposure to carcinogens, this study sought both primary reports on specific carcinogens or surrogates by occupation or industry title. Of the 65 English version abstracts, 18 studies were selected for in-depth review according to the eligibility criteria. Two occupational physicians independently assessed the relevance to the study objectives, data extractability, and data quality as per the Newcastle-Ottawa Scale. **Results:** The review revealed that ten observational studies met the eligibility criteria. There was heterogeneity of occupational exposure assessment and the reported results. The possible carcinogens statistical significantly related to the incidence or mortality of CCA risk included 1,2-dichloropropane (the highest RR = 32.40, 95%CI=6.40-163.90), asbestos (the highest OR=4.81, 95 % CI =1.73–13.33), endocrine-disrupting compounds (the highest OR =2.00, 95% CI=1.10–3.70), and rotating shift work (the highest HR =1.97, 95%CI=1.02-3.79). These carcinogens are classified as IARC class 1 and 2A. **Conclusions:** Despite the limited number of studies reviewed, the hypothesis of occupational risk for CCA was supported. Occupational health and safety measures may decrease exposure to these carcinogens, and surveillance in high-risk occupations or industries is urgently needed to prevent and control CCA.

Keywords: Cholangiocarcinoma- bile duct neoplasms- occupational disease- occupational exposure

Asian Pac J Cancer Prev, **23 (6)**, 1837-1845

Introduction

Cholangiocarcinoma (CCA) refers to primary malignant tumors originating from the biliary epithelium cells, including inside (intrahepatic) and outside (extrahepatic) the biliary tract, which includes the bile ductules—the hepatic duct, the cystic duct, the common bile duct to the ampulla of Vater—but excludes the gallbladder. CCA is sometimes known as bile duct carcinoma. It is the second-most common primary liver and bile duct malignancy and the cause of 10-15% of hepatobiliary malignancies and 3% of gastrointestinal malignancies (Tyson and El-Serag, 2011; Bergquist and von Seth, 2015). CCA is a rare tumor but causes 13% of all cancer-related deaths and occurs with varying geographical frequency (Kirstein and Vogel, 2016). Despite significant variable geographic incidence, the worldwide epidemiological data reveals an upward trend over the past few years (Banales et al., 2016), representing a public health problem in some regions, with an exceptionally high incidence in northeastern Thailand (Imsamran et al., 2015).

The respective key risk factor in Thailand vs. Korea and China is infestation with the parasitic liver fluke *O. viverrini* vs. *C. sinensis* from eating uncooked fish, and nitrosamines from various food sources (IARC, 2011). Currently, the incidence of CCA in Southeast Asia is in decline, (Kamsa-Ard et al., 2019) likely the result of controlling liver fluke infection risks. However, tools enabling early diagnosis remain elusive, so the window

[1]*Department of Community, Family and Occupational Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.*
[2]*Cholangiocarcinoma Screening and Care Program (CASCAP), Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.*
[3]*Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand.*
**For Correspondence: dr_chatchai@hotmail.com*

for timely chemotherapeutics or surgical interventions is missed, and survival is poor. In about 20% of CCA cases, there is no evidence of *O. viverrin*i infection (Itoh et al., 1994), so other risk factors are suspected, including chronic inflammation of the bile duct (Hussain and Al-Jashamy, 2013; Labib et al. 2019), behavioral risks such as alcohol consumption and smoking (Ye et al., 2013), medical use (Kamsa-ard et al., 2018), and metabolic syndrome. (Clements et al., 2020). Occupational risks for CCA are not on the list but could be more easily controlled, so further investigation is warranted.

Many carcinogens occur in occupational settings, accounting for 4% of cancers. The International Labor Organization (ILO) estimates that 666,000 workers die each year due to occupational cancer (GBD 2017, 2018). These fatalities could be reduced if there were greater awareness of the risk factors of occupational health and understanding of protective safety measures; however, the occupational risk factor for CCA remains largely unknown because of the lack of data.

The risk factors for CCA related to occupation have been neglected since 2013 when there was an outbreak of 17 patients—who worked at an offset printing company—diagnosed with occupationally-related CCA. This incident was the result of exposure to carcinogenic chlorinated hydrocarbons. (Kubo et al., 2014). Therefore, the current systematic review aimed to conduct a comprehensive evaluation of undefined possible occupational risks for CCA. These findings can provide implications for cancer prevention, and proper management to reduce the number of deaths from this cancer.

Materials and Methods

This systematic review was conducted per the PREMA (Preferred Reporting Items for Systematic Review) checklist (Moher et al., 2009) under the aegis of the "CCA related to Occupational Causes" project. The Khon Kaen University Ethics committee approved the study for Human Research (No. HE641050). The scope was based on occupational exposure in terms of any agents, mixtures, exposure circumstances, job titles, and CCA outcomes, including the intrahepatic and extrahepatic bile ducts.

First, all relevant articles were systematically examined to identify the associations between occupation and CCA. The original research articles were hand-searching on the following electronic databases: MEDLINE or PubMed, ScienceDirect, CINAHL, ProQuest (including Dissertation and Theses Global), Springer, Wiley, and published between 1980 to December 2020. While general search engines, such as GoogleScholar, were not searched for relevant articles. Furthermore, an English language restriction was imposed in this search strategy. Second, the strategic search terms in keywords utilized for this study were [[occupation] AND [[cholangiocarcinoma] OR ["biliary tract cancer"] NOT ["gallbladder cancer"]] in the title and abstract. No other search conditions were applied. Third, EndNoteX was used to delete the duplicate records. Finally, the researcher censored the excluded records one by one, and no automation tools were used to avoid the inadvertent deletion of relevant information.

Initially, a total of 65 records were identified through database searches. After removing duplicates, 56 potentially relevant records were retrieved for the next step to screening the title, abstract, and type of publication. Incomplete full-text original articles in English; conference proceedings, unpublished results, personal communication, review articles, comments to the editor, editorial notes; and non-relevant studies related to non-occupational exposure such as environmental exposure, behavior, medical use, or non-human studies were excluded. Next, the passed screening articles were evaluated and checked for eligibility criteria. These articles may be included in the next step if they meet the following inclusion criteria: (1) the outcome of the study results were as follows: CCA, intrahepatic CCA separate analysis from other liver cancer such as hepatocellular carcinoma (HCC), or extrahepatic CCA separate analysis from gallbladder cancer or report biliary tract only; and (2) addressing relations to work in terms of occupational exposure or job title. The flow diagram that summarizes the selection process is in Figure 1.

Subsequently, ten articles passed the eligibility criteria; two occupational physicians independently reviewed the quality, risk of bias, and relevance to the objective study. This level of scrutiny was necessary because the included studies were observational, and their inclusion in this review was predicated on methodological quality as judged by the Newcastle-Ottawa Scale (NOS) (Wells, 2013). In terms of selection, comparability, exposure for case-control studies, or outcomes for cohort studies were utilized to evaluate the quality of non-randomized studies using a rating system with a zero to ten score. The studies with scores of six or more were considered to meet the quality standards for an in-depth review. Each of the qualified full-text articles was independently assessed and reviewed by AS and CE. When disagreements and uncertainties regarding eligibility occurred, it was resolved by discussions with NC. Statistical pooling was not possible due to the heterogeneity of the studies; therefore, the findings were presented as a narrative. Moreover, the scored articles also reviewed specific histological types and results. The results derived from those articles that did not separate intrahepatic CCA from other forms of liver cancer, nor the extrahepatic CCA from gallbladder cancer, were not included and reported in the final results of this study. (Table1)

Concerning the revision of the selected studies, the following data from each study were collected, and information was extracted from each study, as follows: (1) the study and the publication information (i.e., author names, publication year, and study location; (2) study characteristics (i.e., study design, study participants and periods, the selected outcome for analysis in the study, occupation and job assessment, confounders; and (3) the findings, i.e., the statistical parameters in the reports and the results were collected.

Results

A total of ten occupational-related CCA types of research passed the eligibility and quality assessment

Table 1. Type of CCA Reported on the Articles which Included in This Systematic Review

Study	Intrahepatic CCA	Extrahepatic CCA	Gallbladder
Case-control study			
Farioli et al. (2018)	✓ [a]	✓	N/D
Brandi et al. (2013)	✓	✓	N/D
Ahrens et al. (2007)	N/D	✓ [b]	✓ [c]
Cohort study			
Kumagai et al. (2016)	✓ (combine to CCA)		N/D
Lin et al. (2015)	N/D	✓ [b]	✓ [c]
Hogstedt et al. (2013)	✓ [c]	✓	N/D
Vlaanderen et al. (2013)	✓ [a]	combine to extrahepatic CCA [c]	
Kumagai et al. (2013)	✓ (combine to CCA)		N/D
Malker et al. (1986)	N/D	✓ [b]	✓ [c]
Cross sectional study			
Okamoto et al. (2013)	✓	✓	N/D

✓, report in the included article; N/D, no data report in the included article; [a], separate coding or separate analysis from other liver cancer; [b], separate analysis from gallbladder and selected only extrahepatic CCA to report in the result of this study; [c], not included and report in the result of this systematic review

criteria by the NOS. They were observational studies including three case-control studies (Farioli et al., 2018; Brandi et al., 2013; Ahrens et al.,2007), six cohort studies (Kumagai et al. 2016; Lin et al.,2015; Vlaanderen et al., 2013; Hogstedt et al., 2013; Kumagai et al., 2013; Malker et al., 1986) and one cross-sectional study (Okamoto et al., 2013). Most of the studies were from Europe, particularly the Nordic countries. In addition, four studies—published in last decade between 2013 and 2016—were from Japan (Table 2). Eight of the studies concerned morbidity

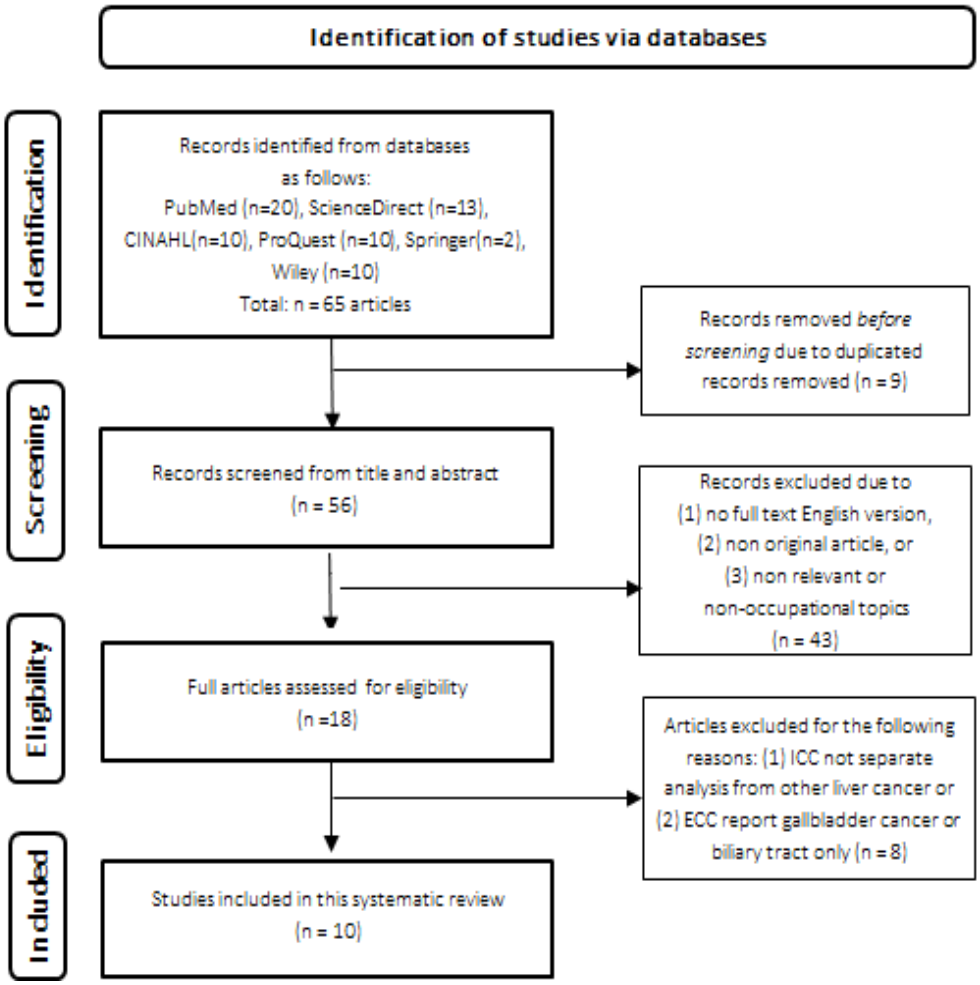

Figure 1. Steps of Article Selection in This Systematic Review

Table 2. Summarization of All Included Article for Systematic Review on CCA and Occupational Risks

Authors, year	Country	Participants in the study for analysis and periods	Method of occupation/job/ exposure assessment	Selected outcome for analysis in this study	Findings	Adjusted for confounders
Farioli et al. (2018)	Nordic countries (Finland, Norway, Sweden and Iceland)	Case: 8,231 total CCA cases (1,458 intrahepatic CCA, 3,972 extrahepatic CCA, and 2,801 unidentify subtype) Control: total 37,389 population controls (6,773 control for intrahepatic CCA and 18,221 control for extrahepatic CCA) between 1960-2005	Job-exposure matrix from Nordic Occupational Cohort Study (NOCCA) for asbestos exposure	Reports on cancer registries for each country. CCA coding as follows: Finland ICD-7:155.0, 155.2 Norway ICD-8: 155.1, 156.1, 156.2 Sweden ICD-7: 155.0, 155.2, 155.3; ICD-9: 155.1, Iceland ICD-10: C22.1, C24.0, C24.1	Cumulative asbestos exposure > 15 f/mL x years with trend (p for trend 0.001) and total CCA risk, OR=1.2(95%CI=1.0-1.4) Intrahepatic CCA risk, OR=1.7 (95% CI =1.1-2.6), OR =1.7(95% CI =1.1-2.5) for 10-year-lag, OR =2.1(95% CI =1.2-3.7) for 20-year-lag ,OR =2.3 (95% CI =0.6-8.8) for 30-year-lag Extrahepatic CCA risk OR=1.1 (95% CI =0.8-1.4 ; p for trend 0.503)	Year of birth, gender, country
Brandi et al. (2013)	Italy	Case: 100 cases (41 intrahepatic CCA and 59 extrahepatic CCA) Control: population mixed hospital controls (149 control for intrahepatic CCA, 212 control for extrahepatic CCA) between 2006-2010	Retrospective assessed job titles from working life history and calendar period for asbestos exposure	Histologically confirmed intrahepatic CCA and extratrahepatic CCA	Occupational exposure to asbestos and intrahepatic CCA risk, adjusted OR =4.81 (95 % CI =1.73–13.33), extrahepatic CCA risk, adjusted OR= 2.09 (95 % CI =0.83–5.27) ,	Birth year, sex, region of residence
Ahrens et al. (2007)	Six European countries (Denmark, France, Italy, Germany, Spain, and Sweden)	Case: 80 cases: Men aged 35 to 75 years with extrahepatic bile duct cancer and cancer of the ampulla of Vater with histologically confirmed Control: 1856 matched population and patient controls between 1995 and 1997	Evaluated on the basis of the core questionnaire and self-reported job descriptions and job-specific questionnaires. Then, they were converted to semi-quantitative variables (intensity, probability, and duration of exposure) for endocrine-disrupting compounds	ICD-9 revision: 156.1, 156.2 Note:excluded overlap histology, such as 156.0,156.8,156.9	High exposure to all endocrine-disrupting compounds and extrahepatic CCA (extrahepatic bile duct and the ampulla of Vater) risk, adjusted OR =2.0 (95% CI=1.1–3.7)	Age, country, gallstones
Kumagai et al. (2016)	Osaka, Japan	95 workers from a printing company during 1987 to 2006 found 17 CCA cases occurred between 1987-2012	JNIOSH experimental data which measured exposure concen-trations of 1,2-DCP and DCM	ICD-9: 155.1,156.1; ICD-10: C22.1, C24.0	Total CCA risk: All workers, SIR= 1,171 (95%CI=682-1,875); male, SIR=1,203(95%CI=701-1,927) ; female, SIR= <0.001(95%CI=0-9,426) ; 1,2-DCP workers, SIR= 1,019(95%CI =374-2,218) ; 1,2-DCP and DCM workers, SIR= 1,275(95%CI =636-2,280) Cumulative 1,2 DCP exposure, No lag time, p for trend <0.001 ; middle exposure, adjusted RR= 14.9(95% CI = 4.1-54.3) ; high exposure, adjusted RR= 17.1 (95%CI =3.8-76.2); 5-years-lag, p for trend <0.001 ; middle exposure, adjusted RR= 11.4 (95% CI= 3.3-39.6); high exposure, adjusted RR= 32.4 (95%CI =6.4-163.9) DCM exposure, No lag time, adjusted RR= 0.45(95% CI= 0.11-1.77); 5-years-lag, adjusted RR= 0.31(95% CI =0.07-1.34)	Sex, age, calendar year, DCM exposure
Lin et al. (2015)	Japan	-46,395 men recruited, 22,224 men aged 40–65 at baseline in 1988–1990 and followed through December 31, 2009 -follow up period 17 years, observed 71 ECC deaths	Using self-administered questionnaire collect the information on shift work	ICD-10: C24.0- 24.9 Note: Extrahepatic CCA separate analysis from gall bladder cancer (C23.0)	Rotating shift work and extraheptic CCA risk of death, adjusted HR = 1.97 (95 % CI= 1.02-3.79).	Age, BMI, history of cholelithiasis, diabetes, smoking, alcohol, perceived stress, sleep time Note: excluded all deaths within the first 2 years of follow-up
Hogstedt et al. (2013)	Swenden	-6,320 Swedish male chimney sweeps between 1958 to 2006 -2 ECC cases were observed	Occupational title from members of the national trade union database period 1918-1980 and alive in 1958; and 1981-2006	ICD-7: 155.2	Extrahepatic CCA risk: -Total cohort, SIR=1.60(95%CI=0.19-5.78) -Employment >30 years, SIR=4.19(95%CI = 0.51-15.14)	age, calendar year

Table 2. Continued

Authors, year	Country	Participants in the study for analysis and periods	Method of occupation/job/ exposure assessment	Selected outcome for analysis in this study	Findings	Adjusted for confounders
Vlaanderen et al. (2013)	Nordic countries (Finland, Iceland, Norway, and Sweden)	-74,949 individuals in the NOCCA study, contributing 1,373,940 person-years in men and 536,126 person-years in women from 1961-2005 - 29 intrahepatic CCA cases (men=21, women =8), 88 extrahepatic CCA, ampulla of Vater, gallbladder cases (men=53, women =35) were observed	Occupational category based on Nordic adaptations of the International Standard Classification of Occupations (ISCO- 1958)	ICD-10: C22.1, C24.0, C24.1 Note: Extrahepatic CCA not report due to combination with gallbladder cancer (C23.0) in analysis	Intrahepatic CCA risk: Male , all printers, SIR =2.34(95% CI=1.45-3.57) ; topographers; SIR= 2.01(95% CI=1.00-3.60) ; printers; SIR =3.54(95% CI=1.30-7.70); lithographers, SIR= 3.91(95% CI=0.47-14.1) ; bookbinders, SIR =1.17(95% CI=0.03-6.54) Female , all printers, SIR =1.95(95% CI=0.84-3.85) ; topographers, SIR =3.14(95% CI=0.65-9.17) ; printers, SIR =1.38(95% CI=0.03-7.68); lithographers, SIR =10.34(95% CI=0.26-57.6); bookbinders, SIR =0.50(95% CI=0.01-21.4)	Country, sex, 5-year age, 5-year calendar period category
Kumagai et al. (2013)	Osaka, Japan	-62 offset colour proof-printing men who exposed to 1,2-DCP and/ or DCM between 1991-2011 -11 workers were reported to have CCA	Japanese National Institute of Occupational Safety and Health (JNIOSH) experimental data which measured exposure to concentrations of 1,2-DCP and DCM	ICD-9: 155.1,156.1; ICD-10: C22.1, C24.0	Total CCA risk : all workers, SMR =2,900 (95% CI= 1,100-6,200), proof-printing, SMR= 5,000 (95% CI = 1,600-12,000), front room worker, SMR= 960 (95% CI= 24-5,400)	Sex, age, calendar year, cause-specific
Malker et al. (1986)	Sweden	-Swedish population using the Cancer-Environment Registry link occupation from the 1960 census - 764 biliary tract cancer (exclued gall bladder cancer) incidence cases from the National Swedish Cancer Registry between 1961-1979	Three-digit Industries and Occupation codes from International Standard Classification of Occupations (ILO,1958) and International Standard Industrial Classification of all economic activities (UN,1958)	ICD-7 revision: 155.2-155.9 Note: Biliary tract cancer separate analysis from gall bladder cancer	Extrahepatic CCA risk: Men trade, finance, real estate industry SIR = 1.20 ($p<0.05$) -insulation workers in the construction industry, SIR =10.60($p<0.05$) -gold, silver and silver-plating industry, SIR = 5.60 ($p<0.01$) Women -advertising and marketing, SIR=8.90,($p<0.01$) -carpet makers in the carpet making industry, SIR 4.50 ($p<0.05$)	Age, region
Okamoto et al. (2013)	Japan	201,937 workers and 168,420 family members in the printing and related industries in 2009 with 8,855 bile duct cancer cases and 107 were in printing and related industries between 2009-2012	Japan Health Insurance Association database link to industrial classification of workplaces which compose 42 categories, including printing and related industry	ICD-10; C22.1, C24.0	Printing industry workers Total CCA - all ages: male, SPRR =1.31(95%CI=0.91- 1.89); female, SPRR =1.01 (95%CI=0.42- 2.42) aged 30-49 years old: male, SPRR =1.78 (95%CI=0.63-5.00); female SPRR =1.52 (95%CI=0.17-13.79) Intrahepatic CCA - all ages: male, SPRR =1.79(=0.92-3.49); female, SPRR =1.07(95%CI=0.21-5.45) - aged 30-49 years old: male, SPRR = 3.03 (95%CI=0.52-17.56); female, SPRR =2.69 (95%CI=0.06-115.79) Extrahepatic CCA - all ages: male, SPRR =1.13(95%CI=0.73-1.76); female, SPRR =0.98(95%CI=0.35-2.78) - aged 30-49 years old: male, SPRR =1.26(0.34-4.71); female, SPRR =1.06(95%CI=0.06-17.79)	Sex, age

Note: -ICD-7, 155.0: liver cancer, primary/ 155.2-155.9: other cancers of biliary tract such as 155.2: extrahepatic CCA , 155.3 ampulla of Vater; -ICD-8 & ICD-9, 155.0: liver cancer, primary / 155.1: intrahepatic CCA / 156.1: extrahepatic CCA / 156.2: -156.9 other parts such as 156.2: ampulla of Vater, 156.8 over lapping site, 156.9 unspecified; ICD-10 code C22.1, intrahepatic CCA / C24.0: extrahepatic CCA / C24.1: ampulla of Vater / C24.8 over lapping site / C24.9 unspecified

outcomes, and two with mortality outcomes.

The studies differed with respect to exposure assessment, statistical analyses, and results, so a meta-analysis was not possible. Our review thus summarizes the results of the descriptive content. Cases of CCA were more incidence among printers such as offset proof-printing work exposed to 1,2-dichloropropane with SIR= 1,019, 95%CI=374-2,218 (Kumagai et al. 2016) or high mortality with SMR= 5,000, 95% CI = 1,600-12,000 (Kumagai et al., 2013). This carcinogen exposure had CCA risks with highest adjusted RR = 32.40, 95%CI=6.40-163.90 (Kumagai et al., 2016). When stratified by subtype, intrahepatic CCA was also more incidence in male printers with SIR=3.54, 95%CI=1.30-7.70 (Vlaanderen et al., 2013). The carcinogen resulting in a higher risk for intrahepatic CCA was asbestos with the highest adjusted OR =4.81, 95 % CI =1.73–13.33(Brandi et al., 2013). While extrahepatic CCA by definition excludes gallbladder cancer, there was an increased incidence of this type of cancer among trades and the finance industry(SIR =1.20, p <0.05), insulation workers in the construction industry(SIR =10.60, p <0.05), men in the gold and silver-plating industry (SIR =5.60, p <0.01), women in advertising and marketing (SIR =8.90, p <0.01), and the textile industry, including carpet and garment makers(SIR =4.50, p <0.05) (Malker et al., 1986). But SIR was no significantly associated with duration of employment (Hogstedt et al., 2013). The carcinogen risk to extrahepatic CCA occurrences or death had a high level of exposure to endocrine-disrupting compounds with adjusted OR =2.00, 95% CI=1.10–3.70 (Ahrens et al.,2007) and rotating shift work with adjusted HR =1.97, 95%CI=1.02-3.79 (Lin et al.,2015). The details are shown in Table 2.

Discussion

This systematic review investigated the occupational risk for CCA extracted from ten analytical observational studies, including a case-control study, a cohort study, and a cross-sectional analytic study. The main findings were that carcinogen identification and occupational exposure knowledge supported prevention and surveillance activities, and compensation for exposed workers. Several studies focused on occupations offset printing following reports of excess CCA among printing workers (Kumagai et al., 2013; Okamoto et al., 2013; Vlaanderen et al., 2013; Kumagai et al., 2016); however, there has been growing interest in other carcinogens over the last two decades as researchers investigate whether other occupations also have workplace-associated cancers. As a result, occupation is one of the causes of CCA, and four possible carcinogens have been identified.

Chlorinated hydrocarbons containing 1,2 dichloropropane (1,2-DCP) as well as dichloromethane (DCM) or methylene chloride—are classified as group 1 (confirmed) and group 2 (suspected) carcinogens by the International Agency for Research on Cancer (IARC) (IARC, 2017). This classification confirms the likely relationship between workers only exposed to 1,2 dichloropropane (1,2-DCP) or co-exposure with dichloromethane (DCM), and a higher probability of CCA than those only exposed to dichloromethane (DCM) (Kumagai et al., 2013). These substances are not only used in offset printing, but also in print media production, toner replacement, cleaning agents used in gold and silver-plating, degreasing agents, and paint removers. Crucially, these occupational carcinogens mainly enter the body through the respiratory tract. Studies in both Europe and Japan reported an increased risk of developing CCA in cases of cumulative exposure, particularly more than ten years. Only one study reported no statistically significant increase in the risk of developing CCA in these occupations (Okamoto et al., 2013). The mechanism of carcinogenesis remains unclear but appears to be related to glutathione S-transferase (GST) and CYP2E1 and induced chronic inflammation of the bile ducts (Yanagiba, 2016; Wang et al., 2019). This mechanism has been confirmed in murine studies, wherein exposed animals were found to have abnormal bile duct epithelial cells, especially those having multiple substance exposures (Wang et al., 2019). This pattern also found an increased risk in workers; such that the duration of exposure range among CCA patients was between six years and one month to 16 years and one month (average 12 years and six months) (Kubo et al.,2018). The age range was between 25-45 years (average 36 years) and younger than sporadic CCA (Kaneko et al., 2015).

Another occupational carcinogen associated with increased incidence of CCA is asbestos—an IARC group 1 carcinogen. Some occupations may be linked to exposure to asbestos, such as insulation work and wholesale construction (Brandi et al., 2013). Cumulative asbestos exposure in Nordic countries > 15 f/mL x years, < 20-year-lag, showed a trend for intrahepatic CCA development not extrahepatic CCA (Farioli et al., 2018). The possible hypothesis is that asbestos fibers enter the body through alveolar respiration or ingestion through the gastrointestinal mucosa, spreading throughout the body via the vascular and lymphatic systems. Asbestos fibers can translocate to all organs, including the bile duct where it may become stuck in the small biliary duct causing chronic inflammation with the production of oxygen radicals, cytokines, and growth factors leading to impaired cell proliferation and apoptosis that may initiate cancer of the bile duct (Miserocchi et al., 2008). However, this mechanism is debated (Manning et al., 2002) as chronic inflammation may lead to stem cell-derived carcinogenesis, where HpSC malignant transformation represents the first step of a process that eventually becomes cancerous. In sum, a relationship between asbestos and intrahepatic CCA has been confirmed, but none with extrahepatic CCA.

Endocrine-disrupting compounds, including several exogenous agents or mixtures, is another class of carcinogens. They mimic hormones and disrupt the normal functioning of the endocrine system, such as interference through hormone growth control, metabolism, and bodily functions. These disruptions may lead to a carcinogenic effect. Common endocrine-disrupting compounds

used in the workplace include estrogens, alkylphenols, phthalates, oils with PCB, bisphenol A, chlorophenols, or pentachlorophenol, phenylphenol, and pesticides. In agricultural countries, exposure to pesticides containing endocrine-disrupting compounds in the workplace is a risk for extrahepatic biliary tract cancer among men, particularly extrahepatic bile duct and the ampulla of Vater. Ahren et al., (2007) found that high exposure to all endocrine-disrupting compounds was irritant the extrahepatic bile duct. Polychlorinated biphenyls could also be a candidate for strong risk factor (Schmeisser et al., 2010). Unfortunately, this study was excluded as the outcome was combined with gallbladder cancer. Some occupational exposures with possible hormonal effects, such as exposure to pesticides, have been reported to increase the risk of hepatobiliary cancer among men (Cocco, 1997; Brown, 1992); however, the epidemiologic studies on cancer of the extrahepatic biliary tract have mentioned small population sizes and problems with quantitatively assessing exposure to xenobiotics, particularly endocrine-disrupting compounds (Jeephet et al., 2016).

Finally, one occupationally-related factor that is shift work. About 15-20% of workforces in industrialized countries engage in night shift work and more in developing countries. This work pattern disrupts the circadian rhythm and increases cancer risk in various organs. According to the IARC, night shift work is classified as a group 2A carcinogen (IARC, 2010). Many studies, including animal and biomarker research, show that shift work causes a suppressive effect by light-at-night on melatonin levels. This hormone is not only a primary circadian pacemaker but also possesses well-established oncostatic properties and is a cancer hallmark. The reduction of melatonin could be a carcinogenicity mechanism and broadly applied to explain the incidence of different cancer types, including biliary duct cancer(Lin et al., 2015). In addition, animal studies have shown that circadian dysregulation disrupts homeostasis of the bile duct, which could be linked to cancer development. However, this review found only one study on mortality risk (Lin et al., 2015). A 17-year follow-up found that an increased relative mortality risk was apparent in extrahepatic bile duct cancer among rotating shift workers.

The review had some limitations, including the exploration of CCA risk (i.e., variation in study designs and occupational assessments), resulting in heterogenecity and difficulty conducting meta-analysis (Table 2). This study systematically searched for and selected only full, peer-reviewed articles on authorized databases or articles in English only, so this study may be missed some relevant studies in other languages. As a strength, though, the review searched a broad spectrum of databases and included rechecked references in selected articles. Lastly, inconsistent CCA classification may hinder the interpretation of occupational risks in epidemiological studies. Most cancer registries combine CCA with other hepatobiliary malignancies, including HCC and gallbladder cancer. This study only included results on intrahepatic CCA and excluded HCC or extrahepatic CCA by filtering out gallbladder cancer. The intent was to decrease misclassification for a definite diagnosis using the International Classification of Disease (ICD) or histopathological reports.

In term of application, the diagnosis of occupational cancer was obscured as physicians routinely neglected to take an occupational history. For example, only one-quarter of physicians included occupation in their medical records (Alex et al., 2013; Manotham et al., 2015). There is thus inadequate information to diagnose occupational cancer or to confirm the association between a specific occupation and cancer. The current systematic review may help raise awareness among health providers regarding employment-related CCA-inducing carcinogens, thereby providing grounds for workers to seek better exposure controls and compensation, and benefits for occupational cancer.

In conclusion, this systematic review revealed four primary occupational carcinogens statistically significant related to CCA risk, including 1,2 dichloropropane (1,2-DCP) or co-exposure with dichloromethane (DCM), asbestos, endocrine-disrupting compounds, and rotating shift work. Besides these, offset printing, typesetting, construction, gold and silver plating, advertising, and marketing, and garment or carpet makers in the textile industry resulted in increased morbidity or mortality of CCA. The study has limitations and requires careful interpretation due to the variety of study designs, occupational exposure assessment, and only a few cases and studies. CCA still urgently requires investigation, and the occupational etiology and cancer prevention need further examination following occupational medicine protocols.

Author Contribution Statement

Conceptualization: NC, NK, CE. Data curation: AS, CE. Formal analysis: AS, CE. Funding acquisition: NC. Methodology: NC, NK, CE. Project administration: NC. Visualization: CE. Writing - original draft: AS. Writing - review & editing: NC, NK, CE.

Acknowledgements

The authors thank Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Funding Statement

This research was funded by the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Ethical Declaration

The Khon Kaen University Ethics Committee for Human Research approved the project (No. HE641050).

Conflict of Interest

The authors have no conflicts of interest associated with the material presented in this paper.

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