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Cholangiocarcinoma and Occupational Exposure to Asbestos: Insights From the Italian Pooled Cohort Study

Stefania Curti[1*], Mena Gallo[1], Daniela Ferrante[2], Francesca Bella[3], Lorenza Boschetti[4], Veronica Casotto[5], Marcello Ceppi[6], Daniela Cervino[7], Lucia Fazzo[8], Ugo Fedeli[5], Paolo Giorgi Rossi[9], Lucia Giovannetti[10], Paolo Girardi[11], Cecilia Lando[6], Enrica Migliore[12], Lucia Miligi[10], Enrico Oddone[13], Vincenza Perlangeli[7], Roberta Pernetti[13], Sara Piro[10], Cinzia Storchi[9], Rosario Tumino[3], Amerigo Zona[8], Manuel Zorzi[5], Giovanni Brandi[1,14], Stefano Ferretti[15], Corrado Magnani[2], Alessandro Marinaccio[16], Stefano Mattioli[17], and Working Group[‡]

[1]Department of Medical and Surgical Sciences, University of Bologna, Italy
[2]Unit of Medical Statistics, Department of Translational Medicine, Università del Piemonte Orientale and Cancer Epidemiology Unit, CPO-Piemonte, Novara, Italy
[3]Syracuse Cancer Registry, Provincial Health Authority of Syracuse, Italy
[4]Health Protection Agency of Pavia (ATS Pavia), Pavia, Italy
[5]Epidemiological Department, Azienda Zero, Veneto Region, Padua, Italy
[6]Clinical Epidemiology Unit, IRCCS-Ospedale Policlinico San Martino, Genoa, Italy
[7]Department of Public Health, Azienda USL di Bologna, Italy
[8]Department of Environment and Health, Istituto Superiore di Sanità, Rome, Italy
[9]Epidemiology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[10]Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[11]Department of Environmental Sciences, Informatics and Statistics, Ca' Foscari University of Venice, Venice, Italy
[12]Unit of Cancer Epidemiology, Regional Operating Center of Piemonte (COR Piemonte), University of Torino and CPO-Piemonte, Turin, Italy
[13]Department of Public Health, Experimental and Forensic Medicine - University of Pavia, Pavia, Italy
[14]Oncology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
[15]Emilia-Romagna Cancer Registry, Ferrara Unit, Local Health Authority, Ferrara; and University of Ferrara, Italy
[16]Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Italian Workers' Compensation Authority, Rome, Italy
[17]Department of Environmental and Prevention Sciences, University of Ferrara, Italy

[‡]WORKING GROUP

Alessia Angelini[1], Fabiano Barbiero[2], Fabio Barbone[3], Lisa Bauleo[4], Alessandra Binazzi[5], Massimo Bovenzi[6], Carol Brentisci[7], Caterina Bruno[8], Achille Cernigliaro[9], Elisabetta Chellini[10], Marco De Santis[8], Germano Fiorillo[11], Paolo Galli[12], Manuela Giangreco[13], Ferdinando Luberto[†14], Andrea Martini1, Stefania Massari[5], Simona Menegozzo[11], Domenico Franco Merlo[15], Paola Michelozzi[4], Patrizia Perticaroli[16], Walter Sebastiano Pollina Addario[9], Elisa Romeo[4], Francesca Roncaglia[14], Stefano Silvestri[17]

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*Corresponding Author: Stefania Curti; E-mail: stefania.curti@unibo.it

[1]Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy
[2]Department of Medical Area (DAME), University of Udine, Udine, Italy
[3]Department of Medical Sciences, University of Trieste, Trieste, Italy
[4]Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Rome, Italy
[5]Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Italian Workers' Compensation Authority, Rome, Italy
[6]Unit of Occupational Medicine, Department of Medical Sciences, University of Trieste, Trieste, Italy
[7]Unit of Cancer Epidemiology, Regional Operating Center of Piemonte (COR Piemonte), University of Torino and CPO-Piemonte, Torino, Italy
[8]Department of Environment and Health, Istituto Superiore di Sanità, Roma, Italy
[9]Regional Health Authority of Sicily, Palermo, Italy
[10]ex ISPRO, Florence, Italy
[11]Unit of Occupational Medicine - Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Napoli, Italy
[12]Department of Public Health, Azienda USL di Bologna, Italy
[13]Institute for Maternal and Child Health, IRCCS "Burlo Garofalo", Trieste, Italy
[14]Epidemiology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[15]Scientific Department, Azienda USL-IRCCS Reggio Emilia, Reggio Emilia, Italy
[16]Prevention Department, ASUR Marche, Senigallia, Italy
[17]Department of Translational Medicine, Università del Piemonte Orientale and CPO Piemonte, Novara, Italy

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ABSTRACT

Background: *Recent studies supported the association between occupational exposure to asbestos and risk of cholangiocarcinoma (CC). Aim of the present study is to investigate this association using an update of mortality data from the Italian pooled asbestos cohort study and to test record linkage to Cancer Registries to distinguish between hepatocellular carcinoma (HCC) and intrahepatic/extrahepatic forms of CC.* **Methods:** *The update of a large cohort study pooling 52 Italian industrial cohorts of workers formerly exposed to asbestos was carried out. Causes of death were coded according to ICD. Linkage was carried out for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registries.* **Results:** *47 cohorts took part in the study (57,227 subjects). We identified 639 causes of death for liver and bile duct cancer in the 44 cohorts covered by Cancer Registry. Of these 639, 240 cases were linked to Cancer Registry, namely 14 CC, 83 HCC, 117 cases with unspecified histology, 25 other carcinomas, and one case of cirrhosis (likely precancerous condition). Of the 14 CC, 12 occurred in 2010-2019, two in 2000-2009, and none before 2000.* **Conclusion:** *Further studies are needed to explore the association between occupational exposure to asbestos and CC. Record linkage was hampered due to incomplete coverage of the study areas and periods by Cancer Registries. The identification of CC among unspecific histology cases is fundamental to establish more effective and targeted liver cancer screening strategies.*

1. Introduction

Cholangiocarcinoma (CC) is a malignant tumor that arises from biliary epithelium at any portion of the bile duct system and represents the second most common primary liver malignancy. CC are commonly divided into intrahepatic (ICC) and extrahepatic (ECC) forms (including perihilar and distal CC) [1]. These two forms differ in terms of risk factors, incidence and clinical presentation [2].

Although the incidence of ECC was stable or decreased in the last decades in Nordic Countries [3], an increase in the incidence of ICC was reported in the majority of countries worldwide [4]. In 2003-2017 in Italy, the average annual incidence rate for ICC was 1.8 and 1.1 per 100,000 person-years in

men and women, respectively [5]. In 2008-2012 in the same country, the age-standardised incidence rate of ICC was higher than ECC with a ratio of 1.2:1 [6].

In Italy, an increase of ICC mortality from 0.01 per 100,000 person-years in 1980 to 0.59 per 100,000 person-years in 2003 was reported [7]. In 2010-2014, age-standardised mortality rates from ICC reached the value of 1.00 per 100,000 person-years for men and 0.67 per 100,000 person-years for women [8]. Moreover, a slightly uptrend in survival from ICC has been reported in 2003-2017 [5]. With respect to ECC, mortality rates increased in the period 1980-1994, however a decreasing trend from 1995 to 2003 has been detected [7]. In 2010-2014, age-standardised mortality rates for ECC were 0.21 and 0.13 per 100,000 person-years in men and women, respectively [8].

Known/putative risk factors for CC include viral hepatitis B and C, liver fluke infections (e.g., *Clonorchis sinensis, Opistorchis viverrini*), primary sclerosing cholangitis, cholelithiasis/choledocholithiasis, hepatolithiasis, liver cirrhosis, non-alcoholic steatohepatitis, congenital/inherited conditions, personal habits like heavy alcohol consumption, cigarette smoking, and conditions such as obesity [9]. Despite this, in Western Countries about 50% of CC cases arise 'de novo' and no known risk factors are identified [10].

Recent cohort studies investigated the role of occupational exposure to chemical substances and risk of CC [11-13]. An increased risk for CC was found in printing workers exposed to 1,2-dichloropropane and/or dichloromethane [11-12].

The putative association of CC with occupational/environmental exposure to asbestos was investigated as well [14]. A case-control study reported a fourfold increased risk of ICC among ever exposed at work compared with never exposed (adjusted Odds Ratio [OR] 4.8, 95% Confidence Interval [95%CI] 1.7–13.3) [15]. Suggestive evidence that asbestos exposure might be associated with ECC was also observed [15]. A nested case-control study in the Nordic Occupational Cancer (NOCCA) cohort reported an increased risk of ICC with cumulative exposure to asbestos (≥15.0 f/mL × years vs never exposed: OR 1.7, 95%CI 1.1-2.6) [16]. Furthermore, a recent study carried out on ICC patients classified in small duct (sd-ICC) and large duct morphological subtypes (ld-ICC) suggested that sd-ICC might be more frequently associated to asbestos exposure than ld-ICC [17].

How asbestos inhaled or ingested fibres may reach the biliary tract is still an open question. It can be hypothesized that asbestos fibres might reach the bloodstream through the pulmonary and the portal lymphatic system [18-19]. In the liver, asbestos fibres might be trapped in Hering's channels and the terminal bile ductules, where they may cause direct damage on stem cell niche. At the same time, asbestos fibres may act indirectly, causing prolonged chronic inflammation in the same environment [20-21]. Of note, two recent studies detected the presence of asbestos fibres in the biliary tree/gallbladder and CC specimens of patients living in a highly polluted area [18, 22].

The aim of the present study is to investigate the association between occupational exposure to asbestos and risk of CC using an update of mortality data from the Italian pooled cohort study of workers formerly exposed to asbestos [23] and to test record linkage to Cancer Registries to distinguish between hepatocellular carcinoma (HCC) and ICC/ECC forms.

2. Methods

This study is based on the update of a large cohort study pooling 52 Italian industrial cohorts of former exposed to asbestos including a cohort of wives of asbestos cement workers and a cohort of Italian crocidolite miners in Australia [23]. In 2015, the pooled cohort study consisted of 43 cohorts mainly involved in asbestos cement industry, rolling stock construction and maintenance, and shipbuilding [24-29].

The update of the follow-up of the pooled cohort study was carried out based on the following steps: i) vital status and cause of death were ascertained through local Registrar's Offices; ii) in the case of decedents, local Registrar's Offices or Local Health Authority Registries of Causes of Death provided the cause of death, coded according to the International Classification of Disease (ICD, 8th, 9th and 10th revisions); and iii) the coordinating unit pooled the information of the different cohorts, including gender, date of birth, vital status, date of follow-up (either date of death for decedents or date

of the most recent observation for alive/lost subjects), cause of death for decedents, start/end date of each period of employment. For the different cohorts, the date of follow-up varied according to the most recent available update of mortality data and was comprised between 2018 and 2021 [23].

For the present study, we intended to identify those CC cases arising from the pooled cohort study in order to distinguish between HCC and CC and to further classify CC into ICC or ECC forms. Considering that the cause of death regarding liver/biliary tract neoplasms could be misclassified or classified with three-digit ICD codes, an attempt was made to perform a linkage for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registries. The linkage procedures were carried out by each Cancer Registry according to a deterministic approach based on the following variables: name, surname, date and place of birth. These procedures were performed for any subjects enrolled in the study independently of spatio-temporal coverage of Cancer Registry. Each Cancer Registry forwarded the anonymised data to the coordinating unit including date of incidence, morphology and topography code.

The study included the following causes of death coded according to ICD codes, namely: i) 155 (Malignant neoplasm of liver and intrahepatic bile ducts, specified as primary) and 156 (Malignant neoplasm of gallbladder and bile ducts) for ICD-8; ii) 155 (Malignant neoplasm of liver and intrahepatic bile ducts) and 156 (Malignant neoplasm of gallbladder and extrahepatic bile ducts) for ICD-9; and iii) C22 (Malignant neoplasm of liver and intrahepatic bile ducts), C23 (Malignant neoplasm of gallbladder), and C24 (Malignant neoplasm of other and unspecified parts of biliary tract) for ICD-10. Whereas possible, four-digit ICD codes were used.

The histological subtype groupings provided by Cancer Registries were based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes or earlier editions [30]. Cancer classification was made according to the European Network of Cancer Registries Recommendations [31].

For the present purpose, only a subset of cohorts established in an area covered by Cancer Registries were eligible for the study. In areas with no Cancer Registry coverage, a record linkage with hospital discharge records (HDR) was considered. This was the case of the three cohorts located in the province of Bologna, where the record linkage was performed using HDR classifying primary or concomitant diagnoses using ICD codes.

Standardized mortality ratios (SMR) were calculated according to causes of death for: i) liver and intrahepatic bile duct cancer; and ii) gallbladder and extrahepatic bile duct cancer [32]. For those cohorts included in the present study, workers contributed until their most recent date of observation. Age-, period-, sex-, region- and cause-specific rates were used as reference rates. Mortality rates for each region in which cohorts are located were used. The National Institute of Health (Istituto Superiore di Sanità, ISS) provided the set of rates based on mortality and population data (available since 1970) as supplied by the National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT). Consequently, analyses were restricted to person-years and events occurring after January 1st, 1970. Confidence intervals for SMRs were calculated according to the Poisson distribution of observed deaths at the 95% confidence value (95%CI) [32]. An alpha error of 0.05 was accepted. Analyses were carried out using OCMAP-plus cohort analysis program [33] and SAS 9.4 (SAS Institute Inc., USA).

3. Results

The update of the pooled cohort study consisted of 52 Italian industrial cohorts formerly exposed to asbestos. Of these, 47 participated in the study, including 44 cohorts established in an area covered by Cancer Registry and three located in the province of Bologna (i.e. Casaralta, Derbit, Officina Grandi Riparazioni). These 47 cohorts included 57,227 subjects (89.6% men, n=51,252). The description of the included cohorts along with Cancer Registries coverage is reported in Table 1. There is an overlap between cohorts and Registries, that is far from being complete both in time and in space. For instance, for Piedmont the largest cohorts (i.e. Eternit and wives of Eternit workers) were not located in an area covered by Cancer Registry. The vast majority of the

Table 1. Pooled Italian asbestos cohort study: description of the cohorts participating in the study.

Region	Company or cohort name	Location	Industrial Activity	Asbestos type	Year of activity	Total of subjects	Cancer Registry coverage (year of establishment)
Piedmont	Amiantifera [1,2]	Balangero	Miners	Chrysotile	1921-1989	974 men	Registry of Piedmont (1985): it covered only the city of Turin until 2007. Since 2008 the Registry has covered the province of Turin. Remaining provinces are not yet covered, but linkage was attempted because of internal migration and changes of residence. Incidence data were updated until 2019
	Eternit [3]	Casale Monferrato	Asbestos Cement	Chrysotile, crocidolite	1907-1986	3434 (2657 men)	
	Magliola	Santhià	Rolling stock maint and cons	Crocidolite, amosite	1901-1994	1563 (1415 men)	
	SACA [4]	Cavagnolo	Asbestos Cement	Chrysotile, crocidolite	1947-1982	869 (586 men)	
	SILA	Cigliano	Friction materials	Chrysotile	1924-active	421 (255 men)	
	Wives of Eternit workers [5]	Casale Monferrato	Wives workers	Chrysotile, crocidolite	1907-1986	1779 women	
Lombardy	Fibronit [6]	Broni	Asbestos Cement	Chrysotile, crocidolite, amosite	1932-1993	2012 (1841 men)	Registry of the province of Pavia: incidence data 2003 - 2018 were used
Liguria	Cantieri Navali Genoa [7]	Genoa	Shipyard	Mixed fibres	1933-active	3984 men	Registry of the province of Genova (1986): initially only the city, updated until 2016
Veneto	Compagnia Lavoratori Portuali	Venice	Harbour	Mixed fibres	1926-active	1956 (1954 men)	Registry of Region Veneto: the coverage has changed over the years. It covered the 27%, 33%, 45%, 49%, 53%, 96% and 100% of the population until 1987, 1988-1989, 1990-1997, 1998-2007, 2008-2012, 2013 and 2014-2018, respectively
	Edilit [8]	Vigodarzere	Asbestos Cement	Mixed fibres	1946-active	562 (339 men)	
	Fervet	Castelfranco Veneto	Rolling stock maint and cons	Crocidolite, amosite	1919-2008	970 (968 men)	
	Fincantieri	Venice	Shipyard	Mixed fibres	1940-active	4515 (4510 men)	
	Officine di Cittadella [9,10]	Cittadella	Rolling stock maint and cons	Mixed fibres	1946-2008	1255 (1244 men)	
	Officine Grandi Riparazioni FS	Vicenza	Rolling stock maint and cons	Mixed fibres	1919-active	1664 men	
	Officine Meccaniche Stanga [9,10]	Padua	Rolling stock maint and cons	Mixed fibres	1920-2008	2055 (2048 men)	

(*continued*)

Region	Company or cohort name	Location	Industrial Activity	Asbestos type	Year of activity	Total of subjects	Cancer Registry coverage (year of establishment)
Emilia-Romagna	Artclit [11]	Cadelbosco Sopra	Asbestos Cement	Chrysotile, crocidolite	1965-1988	55 (54 men)	Registry of the province of Reggio Emilia: incidence data from Jan 1, 1996 were used
	Cemental [11]	Correggio	Asbestos Cement	Chrysotile, crocidolite	1952-1989	562 (486 men)	
	Cemiant [11]	Cadelbosco Sopra	Asbestos Cement	Chrysotile	1968-1991	119 (28 men)	
	Fibrotubi [11]	Bagnolo in Piano	Asbestos Cement	Chrysotile, crocidolite	1957-1993	295 (237 men)	
	ICAR Eternit [11]	Rubiera	Asbestos Cement	Chrysotile, crocidolite	1961-1992	578 (510 men)	
	Itamiant [11]	Castelnovo Sotto	Asbestos Cement	Chrysotile, crocidolite	1955-1993	1216 (910 men)	
	Officine Gallinari	Reggio Emilia	Rolling stock cons	Mixed fibres	1957-1992	1682 (1664 men)	
	Sidercam [11]	Boretto	Asbestos Cement	Chrysotile, crocidolite	1969-1993	143 (131 men)	
	Uprocem [11]	Boretto	Asbestos Cement	Chrysotile, crocidolite	1973-1993	68 (52 men)	
	Maranit [11]	Poggio Renatico	Asbestos Cement	Chrysotile, crocidolite	1962-1993	202 (185 men)	Registry of the province of Ferrara (established in 1987): incidence data 1991-2011 were used
	Superlit [11]	Novi di Modena	Asbestos Cement	Chrysotile, crocidolite	1954-1993	174 (168 men)	Registry of the province of Modena (established in 1989): incidence data updated till 2015
	Casaralta [12]	Bologna	Rolling stock maint and cons	Crocidolite, amosite	1919-1998	1851 (1807 men)	No Registry covered the province of Bologna: incidence data reported in hospital discharge records (HDR) were used instead. HDR data were available since 1988 (exhaustive since 2004)
	Derbit [13]	Castenaso	Asphalt rolls	Chrysotile	1964-1997	410 (338 men)	
	Officina Grandi Riparazioni FS	Bologna	Rolling stock maint	Mixed fibres	1908-2018	3115 (3070 men)	

Tuscany	Baraclit	Bibbiena	Asbestos Cement	Chrysotile	1943-active	1029 men	Registry of Region Tuscany (established in 1985): incidence data for residents of Florence and Prato until 2013, and incidence data for the whole Region since 2013. Incidence data updated until 2017
	Borma	Leghorn	Glassworks	Mixed fibres	1900-1992	2422 (1947 men)	
	Breda [14]	Pistoia	Rolling stock cons	Mixed fibres	1918-active	3705 (3525 men)	
	Cantieri Navali Apuania	Massa Carrara	Shipyard	Mixed fibres	1949-active	920 (890 men)	
	Compagnia Lavoratori Portuali	Leghorn	Harbour	Mixed fibres	1957-active	2637 (2596 men)	
	Fervet	Viareggio	Rolling stock maint and cons	Chrysotile	1910-1993	876 (869 men)	
	Fibronit [15]	Avenza	Asbestos Cement	Chrysotile, crocidolite	1935-1985	262 (200 men)	
	Officine Grandi Riparazioni FS	Florence	Rolling stock maint and cons	Crocidolite, amosite	1930-2005	1001 men	
	Sacfem	Arezzo	Rolling stock cons	Crocidolite	1945-1983	692 (688 men)	
	Saivo	Florence	Glassworks	Chrysotile	1915-1992	1374 (1080 men)	
	Saline	Volterra	Rock salt workers	Chrysotile, amosite	1900-1992	489 (368 men)	
	Santa Lucia [16]	Pistoia	Industrial ovens cons	Chrysotile, crocidolite	1962-active	249 (233 men)	
	Signani	Aulla	Ship furniture	Mixed fibres	1945-1994	1338 (1314 men)	
	Siri	Sesto Fiorentino	Insulation	Mixed fibres	1951-1989	220 (219 men)	
	Veronit	Leghorn	Asbestos Cement	Chrysotile, crocidolite	1950-1989	159 (130 men)	
Sicily	Eternit	Syracuse	Asbestos Cement	Chrysotile, crocidolite	1953-1992	867 (608 men)	Registry of the province of Syracuse (1999)
	Sacelit [17,18]	San Filippo Mela	Asbestos Cement	Chrysotile, crocidolite	1958-1993	204 (177 men)	Registry of the province of Catania (2003)
Italy	Australian Blue asbestos [19]	Wittenoom (Australia)	Italian miners in Wittenoom	Crocidolite	1943-1967	300 (299 men)	Cancer Registry coverage according to residence

Abbreviations: Cons, construction; Maint, Maintenance. References related to cohorts included in the study are reported in Supplementary Table 1.

Table 2. Causes of death for liver and bile duct cancer in the 47 cohorts participating in the study (44 cohorts covered by Cancer Registry and three located in the province of Bologna) by calendar period.

	Causes of death for liver and bile duct cancer*							
	44 cohorts, N=639				3 cohorts, N=59			
	Cancer Registry, n (%)				**HDR, n (%)**			
	<2000	**2000-2009**	**2010-2019**	**Total**	**<2000**	**2000-2009**	**2010-2019**	**Total**
Cases identified by record linkage	73 (22.8)	83 (44.9)	84 (62.7)	240 (37.6)	5 (17.2)	12 (60.0)	3 (30.0)	20 (33.9)
Cases not identified by record linkage	247 (77.2)	102 (55.1)	50 (37.3)	399 (62.4)	24 (82.8)	8 (40.0)	7 (70.0)	39 (66.1)

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*
Abbreviations: HDR, Hospital Discharge Records.

included cohorts were involved in asbestos cement industry (n=19, 40.4%), rolling stock construction and maintenance (n=12, 25.5%), and shipyard/harbour (n=6, 12.8%). We identified 639 causes of death for liver and bile duct cancer in the 44 cohorts covered by Cancer Registry along with 59 cases identified in the three cohorts located in the province of Bologna (Table 2).

On the basis of the causes of death identified in the 47 cohorts, mortality for 'liver and intrahepatic bile duct cancer' did not increase (men: SMR 1.02, 95%CI 0.94-1.11; women SMR 0.98, 95%CI 0.68-1.35) as well as for 'gallbladder and extrahepatic bile duct cancer' (men: SMR 0.93, 95%CI 0.76-1.14; women: SMR 1.02, 95%CI 0.65-1.53).

Of the 639 causes of death referring to the 44 cohorts established in an area covered by Cancer Registry, 240 cases were identified by record linkage (Table 2). The proportion of cases identified by record linkage increased with Cancer Registry coverage 22.8% before 2000, 44.9% in 2000-2009, and 62.7% in 2010-2019. This was expected considering the increasing coverage of Cancer Registries as described in Table 1.

The site (topography) and the histology (morphology) of the 240 liver/biliary tract neoplasms linked to registry data were reported in Table 3.

Fourteen CC were identified, namely nine ICC, one ECC, one neoplasm involving both intrahepatic and extrahepatic bile ducts, and three cases not further classified. 83 HCC were present as well. In addition to that, we observed 117 cancers with unspecified histology (i.e. no morphology information available) and 25 carcinomas other than CC or HCC. Of note, one case of cirrhosis was identified (likely a precancerous condition considering that data retrieved from Cancer Registry were dated two months before the date of death). The classification of the 240 cases identified in the 44 cohorts covered by Cancer Registry according to ICD-O and calendar period is reported in Table 4.

No cases of CC were reported before 2000. Two ICC were identified in 2000-2009, while seven ICC, one ECC and four CC were reported in 2010-2019. The proportion of HCC was about one-third across the three time periods.

The description of the 14 cases of CC identified in the 44 cohorts covered by Cancer Registry is reported in Table 5.

These 14 cases of CC were characterised by: i) mean age of 72.9±10.7 years (range 58-89); ii) average of time since first exposure (TSFE) of 45.4±10.7 years (range 30-70); and iii) mean duration of exposure of 18.1±8.6 years (range 2-34). Out of 14 cases, 13 were men. A subgroup of 21 cases with unspecified histology and with topography codes referring to bile ducts showed the same characteristics as those experienced by these 14 CC cases (Supplementary Table 2). In the three cohorts established in the province of Bologna, we identified 59 causes of death for liver and bile duct cancer (Table 2). Of these, 20 cases were linked to HDR data (either as primary or concomitant disease). The description of the findings is reported in Table 6.

Table 3. Causes of death for liver and bile duct cancer identified by record linkage in the 44 cohorts covered by Cancer Registry (N=240).

Causes of death*	Cases identified by Cancer	ICD-O			
ICD-9	**Registry Linkage, n (%)**	**Morphology code**	**Topography code**	**Classification**	**n**
155-Malignant neoplasm of liver and intrahepatic bile ducts	40 (16.7)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	26
			C22.1-Intrahepatic bile duct	Unspecified	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	13
155.0-Malignant neoplasm of liver, primary	62 (25.8)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	22
			C22.1-Intrahepatic bile duct	Unspecified	1
		8001/3-Malignant tumor cells	C22.0-Liver	Unspecified	2
			C48.2-Peritoneum, NOS	Unspecified	1
			-	Unspecified	1
		8140/3-Adenocarcinoma	C22.0-Liver	Other ca.	1
			C18.9-Colon, NOS	Other ca.	1
			C80.9-Unknown primary site	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	29
			-	HCC	2
		-	C22.0-Liver	Cirrhosis	1
155.1-Malignant neoplasm of intrahepatic bile ducts	4 (1.7)	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	Unspecified	2
			C24.0-Extrahepatic bile duct	Unspecified	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
155.2-Malignant neoplasm of liver, not specified as primary or secondary	21 (8.8)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	8
			C18.9-Colon, NOS	Unspecified	1
			C38.4-Pleura, NOS	Unspecified	1
		8001/3-Malignant tumor cells	C22.0-Liver	Unspecified	1
		8010/3-Malignant epithelial tumor	C18.0-Cecum	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	9
156-Malignant neoplasm of gallbladder and extrahepatic bile ducts	4 (1.7)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
			C24.1-Ampulla of Vater	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	1

(*continued*)

Causes of death*	Cases identified by Cancer	ICD-O			
ICD-9	**Registry Linkage, n (%)**	**Morphology code**	**Topography code**	**Classification**	**n**
156.0-Malignant neoplasm of gallbladder	10 (4.2)	8000/3-Malignant tumor	C23.9-Gallbladder	Unspecified	2
		8010/3-Malignant epithelial tumor	C23.9-Gallbladder	Other ca.	1
		8090/3-Basal cell carcinoma, NOS	C44.5-Skin of trunk	Other ca.	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	5
		8480/3-Mucinous adenocarcinoma	C23.9-Gallbladder	Other ca.	1
156.1-Malignant neoplasm of extrahepatic bile ducts	5 (2.1)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	1
			C24.0-Extrahepatic bile duct	Unspecified	1
		8010/3-Malignant epithelial tumor	C23.9-Gallbladder	Other ca.	1
		8140/3-Adenocarcinoma	C24.0-Extrahepatic bile duct	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
156.2-Malignant neoplasm of ampulla of Vater	1 (0.4)	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	Unspecified	1
156.9-Malignant neoplasm of biliary tract, unspecified site	7 (2.9)	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	Unspecified	5
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
			C24.9-Biliary tract, NOS	Other ca.	1
ICD-10					
C22-Malignant neoplasm of liver and intrahepatic bile ducts	1 (0.4)	8000/3-Malignant tumor	C25.0-Head of pancreas	Unspecified	1
C22.0-Liver cell carcinoma	32 (13.3)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	11
		8010/3-Malignant epithelial tumor	C22.0-Liver	HCC	2
		8130/2-Papillary transitional cell carcinoma	C67.9-Bladder, NOS	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	18

C22.1-Intrahepatic bile duct carcinoma	11 (4.6)	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	Unspecified	1
			C24.9-Biliary tract, NOS	Unspecified	2
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.0-Liver	CC	1
			C22.1-Intrahepatic bile duct	ICC	5
			C24.0-Extrahepatic bile duct	ECC	1
			C24.9-Biliary tract, NOS	CC	1
C22.9-Malignant neoplasm of liver, not specified as primary or secondary	27 (11.3)	8000/3-Malignant tumor	C22.0-Liver	Unspecified	14
			C22.1-Intrahepatic bile duct	Unspecified	1
			C26.9-Gastrointestinal tract, NOS	Unspecified	1
		8140/3-Adenocarcinoma	C22.0-Liver	Other ca.	1
			C26.9-Gastrointestinal tract, NOS	Other ca.	1
		8170/3-Hepatocellular carcinoma/ Hepatocarcinoma/Hepatoma	C22.0-Liver	HCC	9
C23-Malignant neoplasm of gallbladder	4 (1.7)	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	Unspecified	1
		8010/3-Malignant epithelial tumor	C24.8-Overlapping lesion of biliary tract	CC (involving both intrahepatic and extrahepatic bile ducts)	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C24.9-Biliary tract, NOS	CC	1
C24.0-Malignant neoplasm of extrahepatic bile duct	1 (0.4)	8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1
C24.1-Malignant neoplasm of ampulla of Vater	4 (1.7)	8000/3-Malignant tumor	C24.1-Ampulla of Vater	Unspecified	2
		8140/3-Adenocarcinoma	C24.1-Ampulla of Vater	Other ca.	2
C24.9-Malignant neoplasm of biliary tract, unspecified	6 (2.5)	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	Unspecified	3
			C24.9-Biliary tract, NOS	Unspecified	1
		8140/3-Adenocarcinoma	C23.9-Gallbladder	Other ca.	1
		8160/3-Cholangiocarcinoma (Bile duct adenocarcinoma or carcinoma)	C22.1-Intrahepatic bile duct	ICC	1

**Causes of death for liver and bile duct cancer coded according to ICD codes: ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24. Abbreviations: ICD-O, International Classification of Diseases for Oncology; CC, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; NOS, not otherwise specified; Other ca., all other specific morphology codes; Unspecified, unspecified histology (no morphology information available).*

Table 4. Classification of the 240 cases identified in the 44 cohorts covered by Cancer Registry according to ICD-O and calendar period.

	Cases identified by Cancer Registry linkage (N=240)			
	<2000, n (%)	2000-2009, n (%)	2010-2019, n (%)	Total, n (%)
Classification				
ICC	0 (0.0)	2 (2.4)	7 (8.3)	9 (3.7)
ECC	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.4)
CC	0 (0.0)	0 (0.0)	4 (4.8)	4 (1.7)
HCC	24 (32.9)	29 (34.9)	30 (35.7)	83 (34.6)
Other carcinomas	11 (15.1)	6 (7.2)	8 (9.5)	25 (10.4)
Unspecified	38 (52.0)	45 (54.2)	34 (40.5)	117 (48.8)
Cirrhosis	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.4)

Abbreviations: ICD-O, International Classification of Diseases for Oncology; CC, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; Other carcinoma, all other specific morphology codes; Unspecified, unspecified histology (no morphology information available).

4. Discussion

The present study includes 47 Italian cohorts of asbestos workers and is based on the update of a larger cohort study pooling 52 cohorts of workers formerly exposed to asbestos. This exploratory study was aimed to investigate the association between occupational exposure to asbestos and risk of CC and to distinguish between HCC and ICC/ECC performing a record linkage for those subjects who died for liver or bile duct cancer with data on histological subtype provided by Cancer Registry.

Considering the causes of death identified in the 47 cohorts, we did not find an excess mortality for 'liver and intrahepatic bile duct cancer' (SMR 1.02, 95%CI 0.94-1.11 and SMR 0.98, 95%CI 0.68-1.35 for men and women, respectively). To be noted that these estimates combined causes of death mainly from HCC and ICC that reported different trends in incidence and mortality. For that purpose, a record linkage to Cancer Registries was carried out.

We identified 14 CC in the 44 cohorts covered by Cancer Registry. Most of these (12 out of 14) emerged in the last decade (2010-2019). The HCC:CC ratio in 2010-2019 was about 2.6:1, far from an expected 8:1 as reported by Mancini et al [5]. Of note, a subgroup of 21 cases with unspecified histology and with topography codes referring to bile ducts reported the same characteristics of the aforementioned cases of CC such as frequent occurrence in the last 12 years, older age (mean, 79.3±8.7 years), and long TSFE (Supplementary Table 2).

More than 60% of cases with causes of death for liver and bile duct cancer were not identified by record linkage. This result by no means can be taken as an evaluation of the quality of death certification; this was rather expected since the overlap between Cancer Registries and cohorts in the present study was far from complete, both in time and in space, as shown in Table 1. Main reasons for this were related to deaths occurred before the establishment of the registry/HDR, and to partial spatio-temporal coverage. Therefore, this preliminary experience cannot be taken as an evaluation of quality of cohort follow-up or causes of death classification. It is worth noting that the proportion of cases identified by record linkage increased with calendar period (i.e. more than 60% in the last decade) with a peak of 94% in 2015 (15 out of 16 cases were identified by Cancer Registry). To be underlined that the observed heterogeneity in Cancer Registry coverage limited the identification of cases with causes of death for liver and bile duct cancer, especially for those cases occurred more than 20 years ago. This precluded the identification of those cases of liver cancer arose from the pooled cohort study in the past and their further classification into HCC and CC.

Table 5. Cases of cholangiocarcinoma (CC) identified in the 44 cohorts covered by Cancer Registry.

Region	Company or cohort name	Industrial activity	Gender	Cause of death	ICD-O		Incidence period	Age at death	Duration of exposure (years)	TSFE (years)
				ICD code*	Morphology code	Topography code				
Piedmont	Eternit	Asbestos Cement	Female	C23-Malignant neoplasm of gallbladder	8010/3-Malignant epithelial tumor	C24.8 - Overlapping lesion of biliary tract	2010-2019	89	20	70
Veneto	OGR-Vicenza	Rolling stock maint	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2000-2009	63	16	30
	Fincantieri	Shipyard	Male	156.1-Malignant neoplasm of extrahepatic bile ducts	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2000-2009	63	7	46
	Officine Meccaniche della Stanga	Rolling stock maint and cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	76	7	60
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	65	34	45
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	67	27	39
	Fincantieri	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	89	12	44
	OGR-Vicenza	Rolling stock maint	Male	C24.0-Malignant neoplasm of extrahepatic bile duct	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	73	20	44
	Lavoratori Portuali	Harbour	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	86	24	54

(*continued*)

Region	Company or cohort name	Industrial activity	Gender	Cause of death	ICD-O		Incidence period	Age at death	Duration of exposure (years)	TSFE (years)
				ICD code*	Morphology code	Topography code				
Emilia-Romagna	Officine Gallinari	Rolling stock cons	Male	C23-Malignant neoplasm of gallbladder	8160/3-Cholangiocarcinoma	C24.9-Biliary tract, NOS	2010-2019	86	2	38
Tuscany	Breda	Rolling stock cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.1-Intrahepatic bile duct	2010-2019	64	25	43
	Breda	Rolling stock cons	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C24.9-Biliary tract, NOS	2010-2019	58	18	36
	Lavoratori Portuali	Harbour	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C24.0-Extrahepatic bile duct	2010-2019	76	27	53
	Cantieri Navali Apuania	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8160/3-Cholangiocarcinoma	C22.0-Liver	2010-2019	71	22	40

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*

Abbreviations: Cons, Construction; ICD-O: International Classification of Diseases for Oncology; Maint, Maintenance; TSFE, time since first exposure.

Table 6. Causes of death for liver and bile duct cancer in the three cohorts of the province of Bologna linked to hospital discharge records (HDR)

	Cases identified by HDR linkage, N=20	HDR		
Causes of death*	**n (%)**	**ICD code**	**Primary/concomitant diagnosis**	**n**
ICD-9				
155.0-Malignant neoplasm of liver, primary	11 (55.0)	155.0-Malignant neoplasm of liver, primary	Primary	5
			Concomitant	2
		155.1-Malignant neoplasm of intrahepatic bile ducts	Primary	1
		155.2-Malignant neoplasm of liver, not specified as primary or secondary	Primary	3
155.1-Malignant neoplasm of intrahepatic bile ducts	1 (5.0)	155.2-Malignant neoplasm of liver, not specified as primary or secondary	Concomitant	1
155.2-Malignant neoplasm of liver, not specified as primary or secondary	3 (15.0)	155.0-Malignant neoplasm of liver, primary	Primary	2
			Concomitant	1
156.0-Malignant neoplasm of gallbladder	1 (5.0)	156.0-Malignant neoplasm of gallbladder	Primary	1
156.1-Malignant neoplasm of extrahepatic bile ducts	1 (5.0)	156.1-Malignant neoplasm of extrahepatic bile ducts	Primary	1
ICD-10				
C22.0-Liver cell carcinoma	3 (15.0)	155.0-Malignant neoplasm of liver, primary	Primary	2
		155.2-Malignant neoplasm of liver, not specified as primary or secondary	Primary	1

**Causes of death for liver and bile duct cancer coded according to ICD codes: ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*

For those cases identified by Cancer Registry, the vast majority (about 60%) reported cancers with unspecified histology and carcinomas other than CC or HCC. Therefore, for nearly 85% of cases, we were not able to distinguish between the two most common histological subtypes of liver cancer (i.e. HCC and CC) and this is relevant considering that these two forms differ in terms of aetiology and epidemiology [5,34].

This preliminary linkage study was aimed to identify cases of CC; however, the absolute numbers were too limited to evaluate the causal association between occupational exposure to asbestos and risk of CC. This pooled cohort study of asbestos workers has sufficient theoretical statistical power to study a rare disease like CC [35], but the overlap with Cancer Registries was too limited to evaluate all the cases notified by causes of death.

Recently, Mancini et al described the trends in liver cancer incidence in Italy using Cancer Registries data [5]. This study showed an increasing trend for ICC incidence along with a downward

and opposite trend for HCC. Moreover, the proportion of "other carcinomas and unspecified neoplasia types" out of all the cases of liver/bile duct neoplasms was 44% in men and 54% in women for 2003-2017. These figures were roughly in line with those reported in the present study. The proportion of ICC increased over the years (see Table 4). On the other hand, the proportion of HCC was stable across the three time periods. The majority of the cases identified by Cancer Registry linkage were other carcinomas/cases with unspecified histology. A global comparison of population-based cancer registry data reported that the proportion of unspecified histology cases of liver cancer ranged from the lowest levels in North America (6.2% of the total liver cases in men, 8.3% in women) to the highest levels in Southern Europe (40.5% and 48.8% in men and women, respectively) [34].

In high-income countries diagnosis of HCC and ICC through microscopic verification has decreased in favour of the use of ultrasound, computed tomography, and MRI imaging [36]. To some extent, this helps explaining the high proportion of unspecific histology cases in our study. This issue is related not only to the correct classification of ICC/ECC and HCC of "observed" cases, but also to the "expected" cases for each histological subtype. In fact, considering that only microscopically verified cases are counted for incidence and mortality estimates of histological subtypes of primary liver cancer, the burden of these diseases is widely underestimated.

To further address causality issues, other approaches should be taken into account such as case-control analysis and reevaluation of cases. For instance, cases with unspecified histology (i.e. no microscopic verification available) should be reevaluated by clinicians and pathologists based on hospital medical records along with imaging in order to differentiate the diagnosis of ICC, ECC, HCC, and other neoplasms. Clinical data, imaging together with microscopic verification should be considered to establish an accurate diagnosis.

In the framework of descriptive studies, it was suggested to reallocate the unspecific histology cases to HCC and ICC according to their relative proportion [34]. This scenario could be useful to provide more reliable incidence data; however, it would not help differentiate HCC and ICC for the purpose of causality assessment.

Some methodological considerations need to be addressed in addition to those relating to record linkage, already mentioned above. There is high variability in data quality for liver cancer from population-based cancer registries; high variability was shown also by coding of CC [37]. Changes in ICD-O classification over time have resulted in some misclassification of ICC and ECC. For instance, in 2000 the ICD-O-3 allows Klatskin tumours to be cross-referenced to either ICC (C22.1) or ECC (C24.0) [30]. Misclassification might also have occurred considering that it is not recommended to perform a biopsy in case of adverse clinical conditions of the patient, while the ENCR recommendations dissuaded to use specific morphological codes without microscopic confirmation [31].

Italy as well as other countries with high socio-demographic index have been characterised by unfavourable trend of liver cancer driven by unidentified factors other than HBV, HCV, and alcohol consumption [38]. These along with differences in terms of aetiology and epidemiology of HCC, ICC and ECC should be taken into account for future investigations considering the potential role of asbestos exposure as well.

A variety of non-occupational risk factors contributed to the onset of CC [9]. No data on personal habits and medical conditions of the subjects included in the pooled cohort study were available. Alcohol drinking, smoking habits, and other liver diseases might play a role in the development of CC. These confounders are more common among subjects with low socio-economic status [39-41] like workers formerly exposed to asbestos. This might overestimate the risk of CC in our cohort. However, in a recent case-control study on CC and asbestos, Brandi et al reported slightly higher estimates (adjusted for smoking status and socioeconomic class) than those reported in the univariate analysis [15].

Occupational risk factors other than asbestos might be considered as well. IARC classified 1,2-dichloropropane and dichloromethane in Group 1 (carcinogenic to humans) and 2A (probably

carcinogenic to humans), respectively [42]. However, these solvents were not commonly used in the industrial sectors included in the present study. Nevertheless, it is within the bounds of possibility that these chemical substances, or other substances whose carcinogenicity is not yet known, could have contributed to the development of CC.

5. Conclusions

Present data show feasibility along with limits of using record linkage of mortality records with Cancer Registry records to identify cases of CC and to further classify them into ICC or ECC forms. The real burden of ICC and ECC related to occupational exposure to asbestos needs to be further investigated. The high proportion of unspecific histology cases hampered to firmly support the hypothesis of a causal association between occupational exposure to asbestos and the risk of CC.

Further studies are needed to explore the association between occupational exposure to asbestos and CC, including multicentre case-control studies with microscopically verified cases of ICC and ECC along with estimates of occupational and non-occupational exposure to asbestos. The identification of ICC/ECC and HCC among unspecific histology cases is of paramount importance to better understanding the epidemiology of these diseases and establish more effective and targeted liver cancer screening strategies.

Supplementary Materials: Supplementary Table 1, Supplementary Table 2.

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Institutional Review Board Statement: The study was submitted to the University of Eastern Piedmont Ethics Committee (Authorization CE 164/21, July 28th, 2021) and to the competent Ethics Committees of each participating institution.

Informed Consent Statement: The processing of the data is carried out in compliance with data protection laws for statistical and scientific purposes and only with operations strictly essential for conducting the study.

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Declaration On The Use Of Ai: none

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. References related to cohorts included in the study.

Company or cohort name	References
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Officine Meccaniche della Stanga [9,10]	[9] Simonato L, Tessari R, Canova C. [Controversy unsupported by data]. *Med Lav.* 2004;95:412-413. [10] Tessari R, Canova C, Simonato L. [Epidemiological investigation on the health status of employees in two factories manufacturing and repairing railway rolling stock: a historical perspective study of mortality]. *Med Lav* 2004;95:381-391.
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Company or cohort name	References
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Supplementary Table 2. Cancers with unspecified histology and topography codes referring to bile ducts identified in the 44 cohorts covered by Cancer Registry.

				Cause of death	ICD-O					
Region	**Company or cohort name**	**Industrial activity**	**Gender**	**ICD code***	**Morphology code**	**Topography code**	**Incidence period**	**Age at death**	**Duration of exposure (years)**	**TSFE (years)**
Piedmont	Amiantifera di Balangero	Chrysotile Mine	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	93	28	67
	Eternit	Asbestos Cement	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2010-2019	79	26	54
	Eternit	Asbestos Cement	Male	C23-Malignant neoplasm of gallbladder	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	73	3	44
	SACA	Asbestos Cement	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	82	0.33	57
Liguria	Cantieri Navali Genova	Shipyards	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	83	17	44
	Cantieri Navali Genova	Shipyards	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	1990-1999	65	17	27
	Cantieri Navali Genova	Shipyards	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	87	27	72
Veneto	Officine Grandi Riparazioni FS	Rolling stock maint	Male	155-Malignant neoplasm of liver and intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	1990-1999	77	37	55
	Compagnia lavoratori Portuali	Harbour	Male	155.0-Malignant neoplasm of liver, primary	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	77	35	54
	Officine Grandi Riparazioni FS	Rolling stock maint	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	58	2	35

	Fincantieri	Shipyard	Male	155.1-Malignant neoplasm of intrahepatic bile ducts	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2000-2009	84	5	45
	Fincantieri	Shipyard	Male	156.1-Malignant neoplasm of extrahepatic bile ducts	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	77	25	51
	Fincantieri	Shipyard	Male	156.2-Malignant neoplasm of ampulla of Vater	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2000-2009	88	1	47
	Fincantieri	Shipyard	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	85	3	50
Emilia-Romagna	ICAR Eternit	Asbestos Cement	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	79	19	36
	Cemental/ ICAR Eternit	Asbestos Cement	Male	156.9-Malignant neoplasm of biliary tract, part unspecified site	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2000-2009	71	2	43
Tuscany	Cantieri Navali Apuania	Shipyard	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	81	3	34
	Compagnia lavoratori Portuali	Harbour	Male	C22.1-Intrahepatic bile duct carcinoma	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	87	26	52
	Borma	Glassworks	Female	C22.9-Malignant neoplasm of liver, not specified as primary or secondary	8000/3-Malignant tumor	C22.1-Intrahepatic bile duct	2010-2019	93	5	74
	Borma	Glassworks	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.0-Extrahepatic bile duct	2010-2019	76	22	43
	Fervet	Rolling stock maint and cons	Male	C24.9-Malignant neoplasm of biliary tract, unspecified	8000/3-Malignant tumor	C24.9-Biliary tract, NOS	2010-2019	71	0.01	49

**ICD-8 codes: 155 and 156; ICD-9 codes: 155 and 156; and ICD-10 codes: C22, C23 and C24.*
Abbreviations: Cons, Construction; ICD-O, International Classification of Diseases for Oncology; Maint, Maintenance; TSFE, time since first exposure.