data. A previous study concluded that use of data from these 4 prefectures was a provisionally acceptable way to evaluate cancer incidence trends in Japan.[4]

We obtained cancer incidence data from each prefectural population-based cancer registry for the period from 1985 through 2007. Cancer mortality data were obtained from vital statistics from 1985 through 2011. Cancers were classified according to the International Classification of Diseases for Oncology (ICD-O) for incidence and according to the ICD for mortality. The classification of ICD-O for incidence was converted into ICD codes. We used the ICD Ninth Revision (ICD-9) for data until 1994 and the 10th revision (ICD-10) for data from 1995 or later. We analyzed IHBD cancer (ICD-9, 155.1; ICD-10, C22.1) and EHBD cancer (ICD-9, 156.1; ICD-10, C24.0).

Statistical analysis

A previous study reported regional differences in IHBD and EHBD cancer mortality in Japan[5,6]; moreover, incidences of these cancers are believed to differ by region. Therefore, we employed a method used by the Monitoring of Cancer Incidence in Japan (MCIJ) Project[7–12] to estimate nationwide cancer incidence in Japan. This estimation method uses the arithmetic means of incidence rates, by site, sex, and 5-year age group, in the selected registries. Estimated nationwide cancer mortality in Japan was calculated using the same method, and observed cancer mortality was obtained from the vital statistics of the selected prefectures. Correction coefficients (ie, the ratios of estimated to observed cancer mortality) were subsequently calculated by site and sex. To avoid bias due to prefectural differences in cancer incidence and mortality, and to obtain corrected estimates, the estimated uncorrected cancer incidences according to site, sex, and 5-year age group were multiplied by correction coefficients for each year. In the present study, correction coefficients were calculated as the ratio of cumulative estimated mortality to observed mortality throughout the observation period instead for each year, to obtain stable estimates.

We calculated age-specific rates and age-standardized rates (ASRs; standardized to the 1985 model Japanese population, per 100 000 people) of IHBD and EHBD cancer incidence and mortality for all of Japan. The ASR of mortality was calculated for individual years, while the ASR of incidence was calculated for the following 2- or 3-year periods (due to low annual incidence rates): 1985–1986, 1987–1989, 1990–1992, 1993–1995, 1996–1998, 1999–2001, 2002–2004, and 2005–2007. To investigate differences in trends according to age group, we calculated ASRs at all ages (ASR_{all}), ASRs for age 30 to 49 years ($ASR_{30–49}$), and ASRs for age 50 years or older ($ASR_{\geq 50}$).

Long-term trends in ASRs of incidence and mortality were analyzed using a joinpoint regression model.[4,13–15] This model identifies the year in which significant changes in ASR trends occurred, which is called the joinpoint. We set the number of joinpoints to a minimum of 0 and a maximum of 2 (for incidence) or 4 (for mortality) to find the best-fit model using the Monte Carlo permutation method. We also estimated percentage change (PC) in ASR for each segment, which was a 2- or 3-year period for incidence and annually for mortality. A 2-tailed P value of less than 0.05 was considered significant. The analysis was performed using Joinpoint software (version 4.0.1) from the Surveillance Research Program of the National Cancer Institute.

RESULTS

Incidence

Table 1 shows the cumulative age-specific rates and ASRs of incidence and mortality throughout the observation period. The incidence rates of IHBD cancer for men and women were highest in age groups 80 to 84 and 75 to 79 years, respectively. However, high incidence rates were observed in older age groups in general.

Table 2 shows the results of joinpoint regression analysis of the ASRs of incidence and mortality, and Figure 1 shows trends in ASRs of incidence and mortality. The ASR_{all} and $ASR_{\geq 50}$ of IHBD cancer incidence among men increased by 9.1% and 8.6%, respectively, per 2- or 3-year period throughout the observation period ($P < 0.05$). The values for women also increased by 12.9% and 17.9%, respectively, per 2- or 3-year period until 1996–1998 ($P < 0.05$) and remained stable in recent years. The $ASRs_{30–49}$ of IHBD cancer incidence were stable throughout the observation period in both sexes.

All ASRs of EHBD cancer incidence among men were stable throughout the observation period. The ASR_{all} of EHBD cancer incidence among women decreased by 6.3% per 3-year period from 1993–1995 ($P < 0.05$), and the $ASR_{30–49}$ decreased by 18.3% per 2- or 3-year period throughout the observation period ($P < 0.05$). The $ASR_{\geq 50}$ among women was stable throughout the observation period.

The ASRs of EHBD cancer were 1- to 8-fold those of IHBD cancer. However, the differences between the ASRs of IHBD and EHBD cancer decreased over time, because those of IHBD cancer tended to increase or remain stable while those of EHBD cancer tended to decrease or remain stable. In particular, there were only small differences between the $ASR_{30–49}$ of IHBD and EHBD cancer incidence in recent years.

The ASRs of IHBD and EHBD cancer incidence among men were 1- to 2-fold and 2- to 4-fold, respectively, those among women.

Mortality

High mortality rates were observed in older age groups (Table 1).

Trends in IHBD cancer mortality markedly changed (Table 2 and Figure 1). There were dramatic increases in all

Table 1. Cumulative age-specific and age-standardized rates (ASRs) of the incidence (1985–2007) and mortality (1985–2011) of IHBD and EHBD cancer

	Incident				Mortality			
	IHBD[a]		EHBD[b]		IHBD		EHBD	
	Men	Women	Men	Women	Men	Women	Men	Women
0–4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5–9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10–14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15–19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20–24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
25–29	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
30–34	0.0	0.1	0.2	0.1	0.0	0.0	0.1	0.1
35–39	0.1	0.2	0.5	0.2	0.1	0.1	0.2	0.1
40–44	0.4	0.3	1.0	0.4	0.2	0.1	0.5	0.3
45–49	0.7	0.5	1.6	0.9	0.4	0.2	1.2	0.7
50–54	1.6	0.7	3.3	1.9	0.8	0.4	2.5	1.5
55–59	2.4	1.3	6.7	3.8	1.4	0.8	5.1	2.8
60–64	3.9	1.8	13.0	5.9	2.4	1.3	9.3	4.9
65–69	5.4	2.6	22.5	10.4	3.7	1.9	16.6	8.8
70–74	7.3	3.8	34.1	18.0	5.2	2.9	27.1	14.7
75–79	6.3	5.0	49.1	27.7	7.0	3.9	41.1	23.7
80–84	7.9	4.4	67.1	43.2	8.6	4.9	59.3	35.5
85–	5.9	3.4	82.8	55.9	8.9	5.8	74.6	49.2
ASR_{all}[c]	1.2	0.7	5.6	3.1	0.9	0.5	4.4	2.5
ASR_{30-49}[d]	0.3	0.2	0.8	0.4	0.2	0.1	0.5	0.3
$ASR_{\geq 50}$[e]	4.0	2.2	19.8	10.9	3.1	1.7	15.9	9.1

[a]Intrahepatic bile duct.
[b]Extrahepatic bile duct.
[c]Age-standardized rate at all ages.
[d]Age-standardized rate for age 30 to 49.
[e]Age-standardized rate for age 50 years or older.

ASRs for both sexes in 1995, and APCs between 1993 and 1995 were extremely large (approximately 60% per year). Since 1996, the ASR_{all} and $ASR_{\geq 50}$ of IHBD cancer mortality increased among men (1.8% and 1.9% per year, respectively) and women (both 1.2% per year) ($P < 0.05$). However, ASR_{30-49} remained stable in both sexes after 1996.

The ASR_{all} and $ASR_{\geq 50}$ of EHBD cancer increased until 1992 and decreased thereafter in men (−0.9% and −0.8% per year, respectively) and women (−1.9% and −1.8% per year, respectively) ($P < 0.05$). The ASR_{30-49} decreased among men and women by 2.8% and 4.4% per year, respectively, throughout the observation period.

The ASRs of EHBD cancer since 1995 were 1- to 5-fold those of IHBD cancer. The differences between the ASRs of IHBD and EHBD cancer decreased, because the ASRs of IHBD cancer tended to increase or remain stable while those of EHBD cancer tended to decrease since 1992. In particular, there were only small differences between the ASR_{30-49} of IHBD and EHBD cancer in recent years.

The ASRs of IHBD and EHBD cancer among men were 1- to 2-fold those among women.

DISCUSSION

Using 4 selected population-based cancer registries and vital statistics, we examined IHBD and EHBD cancer incidence and mortality in Japan. Regarding overall ASRs and those in people 50 years or older, IHBD cancer incidence and mortality increased or remained stable in both sexes. EHBD cancer incidence was stable in men and decreased or remained stable in women, while EHBD cancer mortality decreased since 1992 in both sexes. Regarding ASRs in people aged 30 to 49 years, IHBD cancer incidence and mortality were stable, while EHBD cancer incidence and mortality remained stable or decreased throughout the observation period.

A possible explanation for the marked increase in IHBD cancer mortality in 1995 is the adoption of ICD-10 as the classification for causes of death and the simultaneous revision of the death certificate form. The Japanese Ministry of Health, Labour and Welfare reports that these changes affected mortality statistics. In particular, as a result of these changes the liver cirrhosis mortality rate decreased, while liver and IHBD cancer mortality rates have increased since 1995.[16] The observed marked increases in IHBD cancer mortality since 1995 are consistent with the present results.

We calculated provisional ASRs of mortality from "liver and intrahepatic bile ducts" (ICD-9, 155; ICD-10, C22) and "gallbladder and extrahepatic bile ducts" (ICD-9, 156; ICD-10, C23–24). The former increased steeply in 1995, while the latter changed moderately (Figure 2). Thus, our finding of a marked increase only in the ASR of IHBD cancer mortality is reasonable.

Table 2. Results of joinpoint regression analysis of trends in age-standardized incidence (1985–2007) and mortality (1985–2011) rates of IHBD and EHBD cancer

	ASR	Line segment 1					Line segment 2					Line segment 3				
		Years		PC[a]	95% CI		Years		PC[a]	95% CI		Years		PC[a]	95% CI	
		Start	End		Lower	Upper	Start	End		Lower	Upper	Start	End		Lower	Upper
Incidence																
IHBD																
Men	all	1985–1986	2005–2007	9.1*	5.5	12.8										
	30–49[b]	1987–1989	2005–2007	4.5	−6.2	16.5										
	≥50	1985–1986	2005–2007	8.6*	4.9	12.5										
Women	all	1985–1986	1996–1998	12.9*	6.2	20.0	1996–1998	2005–2007	1.7	−7.7	12					
	30–49	1985–1986	2005–2007	−1.9	−14.7	12.9										
	≥50	1985–1986	1996–1998	17.9*	12.0	24.0	1996–1998	2005–2007	−1.0	−8.6	7.3					
EHBD																
Men	all	1985–1986	2005–2007	0.4	−2.1	3.0										
	30–49	1985–1986	2005–2007	−10.5	−20.3	0.6										
	50–	1985–1986	2005–2007	1.9	−1.3	5.2										
Women	all	1985–1986	1993–1995	5.6	−3.0	15.0	1993–1995	2005–2007	−6.3*	−11.3	−1.1					
	30–49	1985–1986	2005–2007	−18.3*	−26.6	−9.0										
	50–	1985–1986	1995–1998	4.0	−2.9	11.4	1995–1998	2005–2007	−7.8	−17.3	2.8					
Mortality																
IHBD																
Men	all	1985	1993	4.3*	2.0	6.7	1993	1996	60.2*	30.3	97.0	1996	2011	1.8*	0.9	2.7
	30–49	1985	1993	3.1	−2.7	9.1	1993	1996	54.7	−8.6	161.8	1996	2011	0.0	−2.2	2.2
	50–	1985	1993	4.4*	1.9	7.0	1993	1996	60.7*	28.4	101.1	1996	2011	1.9*	0.9	2.9
Women	all	1985	1993	2.7*	0.7	4.8	1993	1996	57.6*	31.2	89.1	1996	2011	1.2*	0.4	2.0
	30–49	1985	1994	−2.6	−7.6	2.6	1994	1997	57.0	−11.8	179.5	1997	2011	0.0	−2.7	2.7
	50–	1985	1993	3.4*	1.4	5.5	1993	1996	57.9*	31.7	89.3	1996	2011	1.2*	0.4	2.0
EHBD																
Men	all	1985	1992	4.1*	3.4	4.8	1992	2011	−0.9*	−1.1	−0.8					
	30–49	1985	2011	−2.8*	−3.3	−2.2										
	50–	1985	1992	4.3*	3.6	5.0	1992	2011	−0.8*	−1.0	−0.7					
Women	all	1985	1992	3.1*	2.1	4.2	1992	2011	−1.9*	−2.1	−1.6					
	30–49	1985	2011	−4.4*	−5.2	−3.5										
	50–	1985	1992	3.4*	2.4	4.5	1992	2011	−1.8*	−2	−1.5					

*Percentage change (PC) significantly different from zero.
[a]Percentage change between 2- or 3-year period for incidence, and annual percentage change for mortality.
[b]Incidence rate was 0 in 1985–86 and was excluded from the analysis.

IHBD and EHBD cancer incidence rates have increased in the United States.[17–19] In England and Wales, incidence rates have increased and decreased, respectively.[20,21] Meanwhile, worldwide IHBD and EHBD cancer mortality rates were reported to have increased and decreased, respectively.[18,22–24] Thus, the tendencies observed in Japan in the present study conform to global trends.

However, ASRs reported in the present study differ from those in other countries. Although ASRs of IHBD cancer incidence and mortality in Japan are similar to those in other countries, the ASRs of EHBD cancer in Japan are substantially higher than in other countries. ASRs of IHBD cancer incidence in Japan during 1999–2001 were 1.25 (men) and 0.77 (women), as compared with ASRs of 1.33 (men) and 1.06 (women) in England and Wales.[21] Furthermore, the ASRs of EHBD cancer incidence in Japan were 6.69 (men) and 2.98 (women), as compared with 0.42 (men) and 0.36 (women) in England and Wales.[21] It is not clear why the ASR of EHBD cancer incidence is higher in Japan. A US study reported that the ASRs of EHBD cancer differed by ethnicity.[19] Therefore, genetic and other risk factors may explain the relatively high ASRs in Japan. Future studies should investigate factors related to IHBD and EHBD cancer incidence, to better explain these trends in Japan.

The increasing incidence of IHBD cancer might be due in part to the introduction of advanced imaging modalities such as computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP), although there is no definitive evidence of this.[21] Another explanation is diagnostic misclassification. Although hilar cholangiocarcinoma (ie, Klatskin tumors) is a cancer of the EHBD, the ICD-O cross-references it with topography codes for either IHBD or EHBD cancer, particularly the ICD-O Second Revision (ICD-O-2). Therefore, hilar cholangiocarcinoma may be mistakenly classified as IHBD cancer,[25,26] which may contribute in part to the respective increase and decrease in IHBD and EHBD cancer incidences in England, Wales, and the United States.[27,28] However, a previous study concluded that misclassification was not the only cause of increased IHBD cancer incidence.[28]

The changes in trends might be due in part to changes in risk factors. IHBD and EHBD cancer share many risk factors, such as choledochal cysts, cholangitis, inflammatory bowel disease, biliary cirrhosis, cholelithiasis, alcoholic liver disease, nonspecific cirrhosis, diabetes, thyrotoxicosis, chronic pancreatitis, and gallstones.[29–32] However, some risk factors are more strongly associated with IHBD than with EHBD cancer, such as obesity, chronic nonalcoholic liver disease, smoking, and hepatitis C virus (HCV) infection.[29,33] In

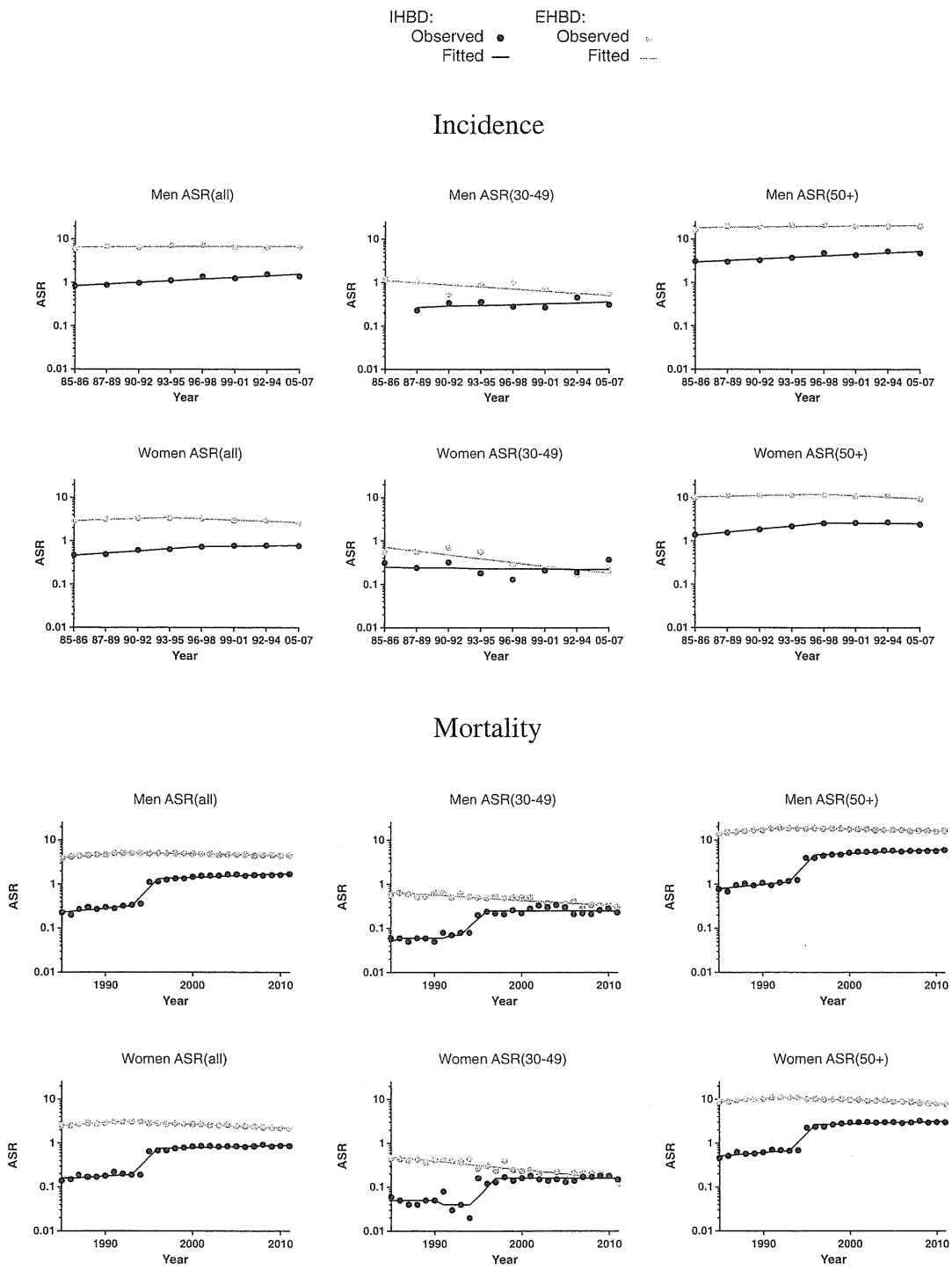

Figure 1. Trends in age-standardized IHBD and EHBD cancer incidence and mortality rates.

particular, HCV-related cirrhosis is a major risk factor for bile duct cancer, especially IHBD cancer.[34,35] The prevalence rate of HCV is reported to be high in Japanese born around 1935 (ie, people aged 73–82 years in 2013) and lower in younger Japanese.[36] This older age group also has a high incidence rate of IHBD cancer. Therefore, the increased rate of IHBD cancer incidence observed in the present study might be affected by both the high rate of HCV infection and older age. If this hypothesis is correct, however, the incidence rate of IHBD cancer should have begun to decrease from the 1990s, along with the incidence rate of liver cancer.[36] Thus, other risk factors are probably related to the increased incidence of IHBD cancer.

IHBD and EHBD cancers are not well understood, due to confusion regarding their classification and their relative rarity, poor prognosis,[26] and insufficiently understood risk factors. Therefore, additional studies of the causes of these cancers are required.

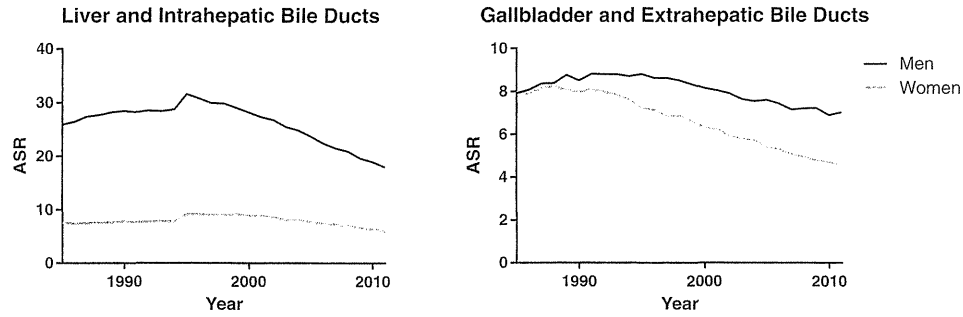

Figure 2. Trends in age-standardized mortality rates.

Finally, it is important to mention that incidence rates in this study were estimated using data from 4 selected prefectures. There are no data from a nationwide population-based cancer registry in Japan at this time, so the use of tentative data was unavoidable. However, a previous study confirmed the representativeness and homogeneity of these 4 prefectures for all-cancer incidence and mortality.[4] However, site-specific representativeness and homogeneity were not clear and were not verified for IHBD and EHBD cancer.

In conclusion, since 1992 IHBD cancer incidence and mortality rates overall and among people aged 50 years or older remained stable or increased in Japan, while the EHBD cancer incidence rate remained stable or decreased and the EHBD cancer mortality rate decreased. The incidence and mortality rates of both these cancers remained stable or decreased among people aged 30 to 49 years. These long-term trends in IHBD and EHBD cancer are comparable to those for specific groups, such as workers at printing companies, and are useful for estimating risks of incidence and mortality.

ONLINE ONLY MATERIALS

Abstract in Japanese.

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Brief Report

Prevalence of Bile Duct Cancer among Printing Industry Workers in Comparison with Other Industries

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Abstract: Prevalence of Bile Duct Cancer among Printing Industry Workers in Comparison with Other Industries: Etsuji OKAMOTO, *et al.* National Institute of Public Health, Department of Health and Welfare Service Research—Objectives: The aim of this study was to assess the risk of developing bile duct cancer among workers in the other printing industry in comparison with workers in all industries in general. **Methods:** Prevalence of bile duct cancer was compared between workers in the printing industry and age-standardized controls in all other industries using the claims database of the Japan Health Insurance Association, which insures workers of small-medium sized employers of all industries. **Results:** Young (aged 30–49) male workers in the printing industry showed an elevated but insignificant standardized prevalence rate ratio (SPRR) for bile duct cancer in comparison with workers in all other industries (SPRR: 1.78; 95%CI: 0.63–5.00). The risk was higher for intrahepatic bile duct cancer but remained insignificant (SPRR: 3.03; 95%CI: 0.52–17.56). **Conclusions:** The sharply elevated risk of bile duct cancer observed among proof-printing workers of a printing factory in Osaka may not be generalizable to workers in the printing industry nationwide.
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Key words: Administrative data, Bile duct cancer, Health insurance claims, Occupational exposure, Printing industry

There have been growing interest and concern about the elevated risk of developing bile duct cancer among proof-printing industry workers since Kumagai reported about five cases of it in a printing factory in Osaka in May 2012[1]. Subsequently, Kumagai surveyed 52 male proof-printing workers from the factory and identified 11 bile duct cancer patients, concluding that chemicals (1,2-dichloropropane, dichloromethane) were the most likely causes[2]. Also, in response to the 64 claims for workers compensation benefits made by the workers in the printing industry nationwide (as of February 28, 2013, of which 17 claims were made by workers of the factory in Osaka and 39 claims were by family members of workers who had died of bile duct cancer, with 7 claims overlapping[3]), the Ministry of Health, Labour and Welfare (MHLW) organized a committee to investigate the causes of bile duct cancer by investigating cases in workers from the factory in Osaka. The committee surveyed 70 male proof-printing workers from the factory and identified 16 bile duct cancer patients concluding that 1,2-dichloropropane was the most likely cause[4] (the discrepancy between Kumagai's report and the committee's report may be due to the different time windows: Kumagai surveyed workers who worked for at least one year between 1991 and 2006, but the committee surveyed workers between April 1991 and December 2012).

Kumagai encountered 11 cholangiocarcinoma (bile duct cancer) patients among 62 male workers employed at a printing company in Osaka. This unquestionably high SMR alerted many workers in the printing industry in general: a person would naturally be concerned about being subjected to a high risk of cancer. To address such concerns, it is necessary to compare the risk of cancer between the printing industry and other industries in general. The authors attempted to compare the prevalence of bile duct cancer between printing industry workers and workers in all other industries using claims data of the Japan Health Insurance Association (JHIA), which covers most employers in small-medium sized industries.

Subjects and Methods

JHIA insures workers of small-medium sized

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employers (approximately 20 million beneficiaries) as well as their dependent family members (15 million). To the authors' knowledge, the printing factory in Osaka is not insured by the JHIA (it is insured by a health insurance society), and hence workers and ex-workers of the factory are NOT counted in this study. Workers who quit their jobs may continue to enroll in the JHIA for a maximum of two years (voluntarily continuing beneficiaries). Enrollment is capped at the age of 74 because elderly individuals aged 75 years or older must enroll in a separate insurance system (the Health Care System for the Old-old).

The JHIA maintains a claims database and provides aggregate data as csv files for public use. The public use data contain the number of claims, number of days and amount of charges aggregated by calendar month, prefecture, status of beneficiaries (workers or family members), sex, ten-year age group, type of practice (inpatient, outpatient and dental) and the 119 classification of diagnoses[5]. Although it is not personally identifiable data, it is detailed enough for health economics research[6].

The JHIA database contains 776,720,246 medical and dental claims (including inpatient and DPC claims) covering April 2009 thru March 2012 and includes all elements of health insurance claims data (diagnostic codes linkable to ICD10 coding, dates of diagnosis, distinction between definite and rule-out diagnoses, distinction between primary and secondary diagnoses, provider information and, detailed treatment information such as medication and clinical procedures). The database is personally identifiable and linkable to industrial classification of workplaces. The industrial classification consists of 42 categories including "printing and related industry".

The database has been available since April 2009. We used the medical claims data for three years (April 2009–March 2012) because media coverage on the issue intensified beginning in May 2012, potentially biasing the utilization pattern of patients and the diagnosis patterns of doctors.

Numerator

The number of unique patients with medical claims containing diagnoses C22.1 (intrahepatic bile duct cancer) and C24.0 (extrahepatic bile duct cancer) treated between April 2009 and March 2012 was used for numerator. Diagnoses include both primary and secondary diagnoses but excluded rule-out diagnoses. Exclusion of rule-out diagnoses is effective in reducing the false-positive rate particularly because the diagnostic category of cancer contains the highest percentage of rule-out diagnoses[7]. Age at diagnosis was determined by the date at initial diagnosis.

Cases include all beneficiaries enrolled in the JHIA at any time of the three year observation period. Beneficiaries who were once enrolled in the JHIA and were diagnosed as bile duct cancer after quitting the JHIA cannot be counted. This loss to the follow-up is a limitation of this study but such loss to the follow up will not bias the inter-industry comparison because such loss will occur in all industries equally.

Denominator

The number of beneficiaries as of September 2010 was used for denominator. Each beneficiary was classified into 42 industrial categories. Voluntarily continuing beneficiaries were classified by the industrial classification of their previous workplaces.

Analysis

Prevalence was calculated using the above numerators and denominators. Age standardization was conducted using the beneficiaries in all other industries as a reference population. The expected prevalence was calculated for the printing industry by applying the sex- and age-specific prevalence of all other industries to the sex- and age-specific number of beneficiaries in the printing industry.

Ethics approval

This study was approved by the Ethics Committee of Osaka City University.

Results

Of approximately 35 million JHIA beneficiaries, there were a total of 201,937 workers and 168,420 dependent family members in the printing and related industry category as of September 2009, constituting approximately one percent of the JHIA's total enrollment. There were a total of 8,855 patients who were diagnosed as bile duct cancer at any time between April 2009 and March 2012, of whom 107 were in the printing and related industry category.

Expected number of patients for the printing and related industry category was calculated by applying the sex- and age-specific prevalence in all other industries to the sex- and age-specific number of beneficiaries in the printing and related industry category. Standardized prevalence rate ratio (SPRR) was calculated by applying the expected number of patients to the actually observed number of patients. The 95% confidence interval was calculated using Fisher's exact test (Table 1). Since concern was focused on the high incidence of bile duct cancer among young male workers, a separate table was created for the age group of 30–49 years old (Table 2).

There were five intrahepatic and five extrahepatic bile duct cancer patients observed among young male workers in the printing and related industry category,

Table 1. Prevalence of bile duct cancer among printing industry workers and family members (all ages)

	Workers			Family members			Total
	M	F	MF	M	F	MF	
Observed number of patients							
C22 (intrahepatic)	24	3	27	2	5	7	34
C24 (extrahepatic)	42	7	49	7	17	24	73
Total	66	10	76	9	22	31	107
Expected number of patients							
C22 (intrahepatic)	13.40	2.80	15.91	1.24	5.71	7.14	23.02
C24 (extrahepatic)	37.08	7.14	43.62	4.29	14.48	19.31	62.96
Total	50.48	9.94	59.53	5.53	20.18	26.45	85.99
Standardized prevalence rate ratio (observed/expected)							
Upper limit of 95% CI	3.49	5.45	3.15	15.19	2.91	2.78	2.51
C22 (intrahepatic)	1.79	1.07	1.70	1.62	0.88	0.98	1.48
Lower limit of 95% CI	0.92	0.21	0.91	0.17	0.26	0.35	0.87
Upper limit of 95% CI	1.76	2.78	1.69	5.43	2.37	2.26	1.62
C24 (extrahepatic)	1.13	0.98	1.12	1.63	1.17	1.24	1.16
Lower limit of 95% CI	0.73	0.35	0.75	0.49	0.58	0.68	0.83
Upper limit of 95% CI	1.89	2.42	1.79	4.70	1.99	1.97	1.65
Total	1.31	1.01	1.28	1.63	1.09	1.17	1.24
Lower limit of 95% CI	0.91	0.42	0.91	0.56	0.60	0.70	0.94

Table 2. Prevalence of bile duct cancer among printing industry workers and family members (30–49 years old)

	Workers			Family members			Total
	M	F	MF	M	F	MF	
Observed number of patients							
C22 (intrahepatic)	5	1	6				6
C24 (extrahepatic)	5	1	6	1	2	3	9
Total	10	2	12	1	2	3	15
Expected number of patients							
C22 (intrahepatic)	1.65	0.37	1.92	0.06	0.52	0.63	2.55
C24 (extrahepatic)	3.97	0.94	4.68	0.11	1.13	1.30	6.02
Total	5.62	1.31	6.60	0.17	1.65	1.93	8.56
Standardized prevalence rate ratio (observed/expected)							
Upper limit of 95% CI	17.56	115.79	15.87				10.20
C22 (intrahepatic)	3.03	2.69	3.12				2.35
Lower limit of 95% CI	0.52	0.06	0.62				0.54
Upper limit of 95% CI	4.71	17.79	4.30	4,560.87	17.83	18.00	4.20
C24 (extrahepatic)	1.26	1.06	1.28	9.07	1.77	2.30	1.50
Lower limit of 95% CI	0.34	0.06	0.38	0.02	0.18	0.29	0.53
Upper limit of 95% CI	5.00	13.79	4.70	932.89	9.50	9.50	4.05
Total	1.78	1.52	1.82	5.74	1.21	1.56	1.75
Lower limit of 95% CI	0.63	0.17	0.70	0.04	0.15	0.25	0.76

representing 3.03 times (95%CI: 0.52–17.56) and 1.26 times (95%CI: 0.34–4.71) more than the expected number of patients. Overall, young male workers in the printing industry showed an elevated but insignificant SPRR for bile duct cancer in comparison with all other industries (SPRR, 1.78; 95%CI: 0.63–5.00). However, none of them reached statistical significance due to the small sample size.

The SPRR for both sexes combined among young workers in Table 2 showed a larger ratio than the ratio for each sex (the SPRR of bile duct for both sexes was 1.82, while that for males was 1.78 and that for females was 1.52). This seemingly odd phenomenon is due to the sex imbalance in the number of workers in the printing industry. When the age-specific prevalence for all other industries was applied to the printing industry, which showed a disproportionately higher SPRR for male workers, the sex imbalance caused the expected number of bile duct cancer in the printing industry to be smaller than the sum of the expected number of each sex (the expected number of both sexes: 6.60, smaller than the sum of male: 5.62 and female: 1.31).

Discussion

There has been intensive public interest and concern regarding the suspected risk of bile duct cancer among printing industry workers since the first case-series were reported with regard to a printing factory in Osaka in May 2012. Although the report was about proof-printing workers at a certain factory, the public was alerted that the same phenomena might be happening among workers in the same industry nationwide. The MHLW quickly conducted a questionnaire survey among a total of 18,131 printing factories nationwide and announced that they received reports of 22 cases of bile duct cancer (including 12 deaths) from 14,267 factories (response rate: 78.7%)[8]. However, it is difficult ascertain the causality because 20 of the cases were in individuals over 50 years old.

Internationally, there have been sporadic reports concerning the occupational risks of the printing industry. A British researcher, prompted by an anecdotal report of a cluster of cases of bladder cancer in a newspaper factory in Manchester, conducted a cohort study among workers of a printing factory. Although the results did not support the occupational risk of bladder cancer, they did demonstrate elevated all-cause mortality among them[9]. Danish researchers following a cohort of printing workers demonstrated elevated risks of lung, bladder, renal pelvis and primary liver cancers among printing workers[10]. French researchers also demonstrated elevated risks of lung and esophageal cancer among workers of an offset printing plant[11].

However, none of the previous reports from around the world demonstrated an elevated risk of bile duct cancer among printing workers in particular. So far, the evidence has been confined to a case-series from a single factory in Osaka. To demonstrate if any elevated risk of bile duct cancer exists in the printing industry in Japan in general, it is necessary to compare age-standardized prevalence of the disease between the target industry and other industries, which is difficult to achieve because one has to cover workers in all industries. A large-scale administrative database would provide unbiased and reliable estimates that could be used to perform these comparisons. The JHIA is a single large health insurer insuring workers of small-medium sized employers of all industries and therefore appears to be most appropriate data source for comparison of the prevalence of specific diseases among different industries.

Since the JHIA database is an administrative database not intended for epidemiological studies, it has limitations. First, diagnoses contained in health insurance claims are not definitive diagnoses confirmed by doctors. The authors avoided overdiagnosis by excluding diagnoses with rule-out modifiers, but concerns about the validity of diagnoses remain. Second, not all workers working at workplaces classified into the printing and related industry category are exposed to hazardous environments. They include clerical workers of a printing company thereby diluting the effects of occupational exposures.

The results showed a slightly elevated prevalence of intrahepatic bile duct cancer among male workers in the printing industry (SPRR, 1.79; 95%CI: 0.92–3.49). If limited to younger age (30–49), the SPRR was higher but remained insignificant (SPRR, 3.03; 95%CI: 0.62–17.56).

Our results demonstrated that the elevated risk of bile duct cancer observed in the proof-printing workers of the Osaka factory may not be generalizable to all workers in the printing industry. The relation between work and bile duct cancer should be evaluated in the future by estimation of occupational exposure of causative chemicals on an individual basis.

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Descriptive Epidemiology of Bile Duct Carcinoma in Osaka

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Objective: An outbreak of bile duct carcinoma has been reported among workers in a certain printing company in Osaka, Japan, where there was no descriptive epidemiological study. We conducted descriptive studies of bile duct carcinoma in Osaka.
Methods: Based on the data from the Osaka Cancer Registry, the incidence and survival rate of intrahepatic and extrahepatic bile duct carcinomas, gallbladder carcinomas and hepatocellular carcinomas were analyzed. The study period was between 1975 and 2007, and total 108 407 incidents were retrieved from the Osaka Cancer Registry. Age- and sex-specific incidence rates and age-standardized incidence rates were calculated. Standardized incidence ratios were evaluated for each municipality in Osaka prefecture. Relative 5-year survival rates were also calculated for the cases diagnosed between 1993 and 2005.
Results: Age-standardized incidence rates of bile duct carcinomas increased distinctly from the middle of the 1970s to the early 1980s in males and the 1990s in females. However, no distinct increase in the incidence rates was observed in 2000. Standardized incidence ratios of those did not exceed the unity significantly in males between 1992 and 2007. In females, standardized incidence ratios exceeded the unity significantly in a few regions without any relation to the location of the printing company where the outbreak was reported. The relative 5-year survival rate is generally poor; however, patients who were diagnosed with localized disease at the age of 25–49 years showed a better survival.
Conclusion: Neither change in trend nor regional accumulation of bile duct carcinoma was confirmed in Osaka, corresponding to the outbreak reported in the printing company.

Key words: bile duct carcinoma – incidence – relative survival rate – cancer registry

INTRODUCTION

An outbreak of bile duct carcinoma has been reported among workers in a certain printing company in Osaka (1). There have been neither descriptive epidemiological studies nor reports of relative survival of patients with intrahepatic and/or extrahepatic bile duct carcinomas in Osaka, Japan. This study describes characteristics of bile duct carcinoma in Osaka, Japan, and examined whether any change in the time trend and disproportional geographical distribution was recognized in relation to the outbreak.

PATIENTS AND METHODS

The analysis was made using the data from the Osaka Cancer Registry between 1975 and 2007. Totally, 108 407 incidence data were retrieved; coded ICD-10 C22.1 (Intrahepatic bile duct carcinoma), C23 (malignant neoplasm of gallbladder), C24.0 (extrahepatic bile duct carcinoma) and C22.0 (hepatocellular carcinoma). Among those 108 407 cases, newly reported cases were 78 762. C22.9 (Malignant neoplasm of liver, unspecified) were 1.1% of C22 (malignant neoplasm of liver and intrahepatic bile ducts), while C24.1 (malignant

Table 1. Outlines of the newly reported cases with hepatocellular, intrahepatic, gallbladder and extrahepatic bile duct carcinomas, Osaka 1975–2007

		Hepatocellular n = 61315				Intrahepatic bile duct n = 3095				Gallbladder n= 7836				Extrahepatic bile duct n = 6516			
		Male		Female		Male		Female		Male		Female		Male		Female	
		n = 45898		n = 15417		n = 1797		n = 1298		n = 2801		n = 5035		n = 3638		n = 2878	
Age	Mean ± SE	63.7 ± 0.05		68.9 ± 0.08		66.5 ± 0.21		68.0 ± 0.34		69.2 ± 0.21		70.9 ± 0.16		68.9 ± 0.19		72.0 ± 0.22	
			%		%		%		%		%		%		%		%
	0–24	38	0.1	23	0.1	0	0.0	2	0.2	1	0.04	1	0.02	1	0.03	7	0.2
	25–29	38	0.1	14	0.1	1	0.1	3	0.2	5	0.2	4	0.1	4	0.1	1	0.0
	30–34	102	0.2	25	0.2	5	0.3	7	0.5	6	0.2	6	0.1	8	0.2	5	0.2
	35–39	315	0.7	53	0.3	16	0.9	10	0.8	20	0.7	23	0.5	19	0.5	9	0.3
	40–44	826	1.8	149	1.0	37	2.1	24	1.8	40	1.4	53	1.1	44	1.2	33	1.1
	45–49	2148	4.7	296	1.9	78	4.3	47	3.6	77	2.7	137	2.7	98	2.7	71	2.5
	50–54	4591	10.0	618	4.0	155	8.6	91	7.0	140	5.0	244	4.8	200	5.5	128	4.4
	55–59	7277	15.9	1314	8.5	225	12.5	125	9.6	246	8.8	354	7.0	342	9.4	193	6.7
	60–64	8630	18.8	2210	14.3	259	14.4	156	12.0	329	11.7	535	10.6	512	14.1	253	8.8
	65–69	8772	19.1	3082	20.0	339	18.9	203	15.6	466	16.6	745	14.8	588	16.2	406	14.1
	70–74	6789	14.8	3114	20.2	309	17.2	217	16.7	519	18.5	855	17.0	615	16.9	441	15.3
	75–79	3905	8.5	2359	15.3	222	12.4	190	14.6	459	16.4	873	17.3	537	14.8	496	17.2
	80–84	1736	3.8	1338	8.7	99	5.5	122	9.4	295	10.5	663	13.2	419	11.5	430	14.9
	85 +	1462	3.2	822	5.3	52	2.9	101	7.8	198	7.1	542	10.8	251	6.9	405	14.1
Year of diagnosis	1975–1991	18548	40.4	5116	33.2	443	24.7	352	27.1	1048	37.4	2073	41.2	1164	32.0	933	32.4
	1992–2007	27350	59.6	10301	66.8	1354	75.3	946	72.9	1753	62.6	2962	58.8	2474	68.0	1945	67.6
Age 25–45	Total	1565	3.4	285	1.8	74	4.1	49	3.8	78	2.8	103	2.0	94	2.6	53	1.8
Year of diagnosis	1975–1991	979	(5.3)	169	(3.3)	39	(8.8)	23	(6.5)	47	(4.5)	60	(2.9)	55	(4.7)	28	(3.0)
	1992–2007	586	(2.1)	116	(1.1)	35	(2.6)	26	(2.7)	31	(1.8)	43	(2.1)	39	(1.6)	25	(1.3)
Extent of disease																	
Stage	Localized	21578	47.0	7655	49.7	441	24.5	312	24.0	403	14.4	691	13.7	699	19.2	490	17.0
	Regional	6420	14.0	1938	12.6	602	33.5	434	33.4	1220	43.6	2183	43.4	1487	40.9	1175	40.8
	Distant	5779	12.6	1635	10.6	448	24.9	326	25.1	801	28.6	1531	30.4	595	16.4	528	18.3
	Unknown	12121	26.4	4189	27.2	306	17.0	226	17.4	377	13.5	630	12.5	857	23.6	685	23.8
Surgery	Yes	7522	16.4	1953	12.7	624	34.7	439	33.8	1158	41.3	2077	41.3	1477	40.6	954	33.1
	No	35494	77.3	12405	80.5	1099	61.2	805	62.0	1525	54.4	2776	55.1	2004	55.1	1804	62.7
	Unknown	2882	6.3	1059	6.9	74	4.1	54	4.2	118	4.2	182	3.6	157	4.3	120	4.2

neoplasm of ampulla of Vater), C24.8 (malignant neoplasm of overlapping lesion of biliary tract) and C24.9 (malignant neoplasm of biliary tract, unspecified) were 16.8, 0.1 and 5.8% of C24 (malignant neoplasm of other and unspecified parts of biliary tract), respectively.

The age of diagnosis was grouped by 5-year range for those who were between 25 and 84 and those data were obtained every 3-year interval. The age-standardized incidence rates (ASRs) were calculated by using Japanese 1985 model population as a standard. Standardized incidence rates (SIRs) of each municipality in Osaka were calculated using the age-specific incidence rates of Osaka as unity, and tested whether statistically significant differences existed with a 0.05 significance level, on Poisson's distribution.

Relative 5-year survival time and median survival time (MST) were calculated for each group (25–49, 50–74 and 75–99), and the extent of disease (localized, regional and distant) (2) for the cases was diagnosed between 1993 and 2005, who were followed up for at least 5 years after the diagnosis.

RESULTS

Outlines of the Study Subjects

Outlines of the newly reported cases are shown in Table 1. The proportion of the cases between 25 and 45 years, the same age range at which workers in the printing company in Osaka were diagnosed with bile duct carcinomas, was 3.0% for hepatocellular carcinoma (males 3.4%, females 1.8%), 4.0% for intrahepatic bile duct carcinoma (males 4.1%, females 3.8%), 2.3% for gallbladder carcinoma (males 2.8%, females 2.0%) and 2.3% for extrahepatic bile duct carcinoma (males 2.6% females 1.8%). The female-to-male ratios were 0.34, 0.72, 1.80 and 0.79, respectively.

Trends of ASRs and Age-specific Incidence Rates

ASRs of the intrahepatic bile duct carcinoma in both males and females rapidly increased from the year 1975 to the 1990s, and turned to decrease in the beginning of 2000 (Figure 1). ASRs of the extrahepatic bile duct carcinoma increased remarkably until the early 1980s, and then has become almost plateau from the beginning of 1990s in males. In females, the ASR increased until the early 1980s, and plateaued or decreased slightly thereafter (Figure 1). For the gallbladder carcinoma, ASRs had increased since 1975, plateaued in the 1980s and then decreased later. Age-specific incidence rates of both the intrahepatic and extrahepatic bile duct carcinomas have never increased since around 2000 (Figure 2). Incidence rates of intrahepatic and extrahepatic bile duct carcinomas were higher in males than in females (Figure 2).

SIR of Each Municipality in Osaka

SIRs of the bile duct carcinomas combined with intrahepatic and extrahepatic bile duct carcinomas did not exceed the unity significantly in males between 1992 and 2007 (Figure 3). SIRs

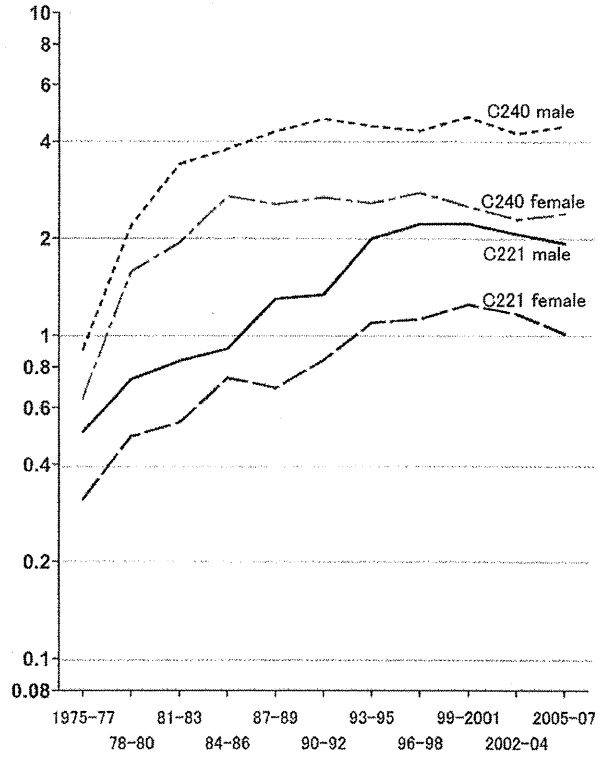

Figure 1. Age-standardized incidence rates (ASRs per 100 000 Japanese 1985 model population) of intrahepatic and extrahepatic bile duct carcinomas in Osaka, 1975–2007.

in females were significantly higher than the unity in Higashi-yodogawa-ku (ward) and Suminoe-ku. In Chuo-ku, where that printing company is located, SIRs of the bile duct carcinoma were 1.11 (95%CI 0.79–1.44) in males and 1.10 (95%CI 0.75–1.44) in females. Any SIR (not shown) never exceeded significantly than the unity.

Relative 5-year Survival and MST

Relative 5-year survival is generally poor among patients who are diagnosed with bile duct carcinoma in Osaka between 1993 and 2005. Some patients who were 25–49 years old with localized disease showed a better survival: 52.7% for the intrahepatic bile duct carcinoma and 76.4% for the gallbladder carcinoma, although they show a poor survival: 26.9% for the extrahepatic bile duct carcinoma. The difference in the relative survival of patients with localized disease between the age groups 25–49 and 50–74 was getting smaller, in the order of intrahepatic bile duct carcinoma, gallbladder carcinoma and extrahepatic bile duct carcinoma. There was no remarkable difference in relative survival among the age groups for regional and distant diseases, except regional cases of the extrahepatic bile duct carcinoma. In the age group of 25–49, the MST of the patients with intrahepatic bile duct carcinoma was 8.0 months for the regional and 6.0 months for the distant, while the MST of the patients with extrahepatic bile duct carcinoma was 16.4 months for the regional and 6.0 months for the distant (Figure 4).

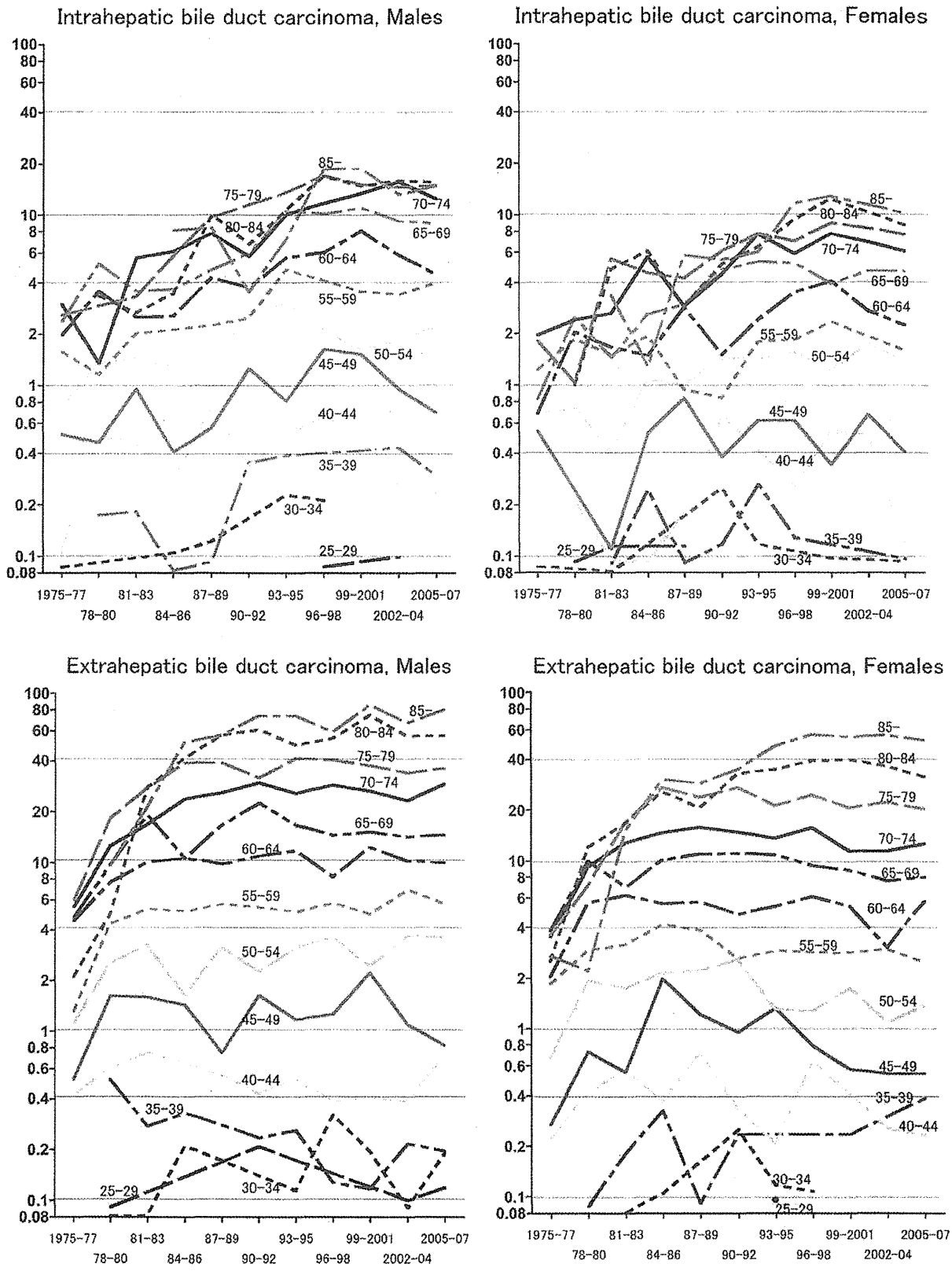

Figure 2. Age-specific incidence rates (per 100 000 population) of intrahepatic and extrahepatic bile duct carcinomas in Osaka, 1975–2007.

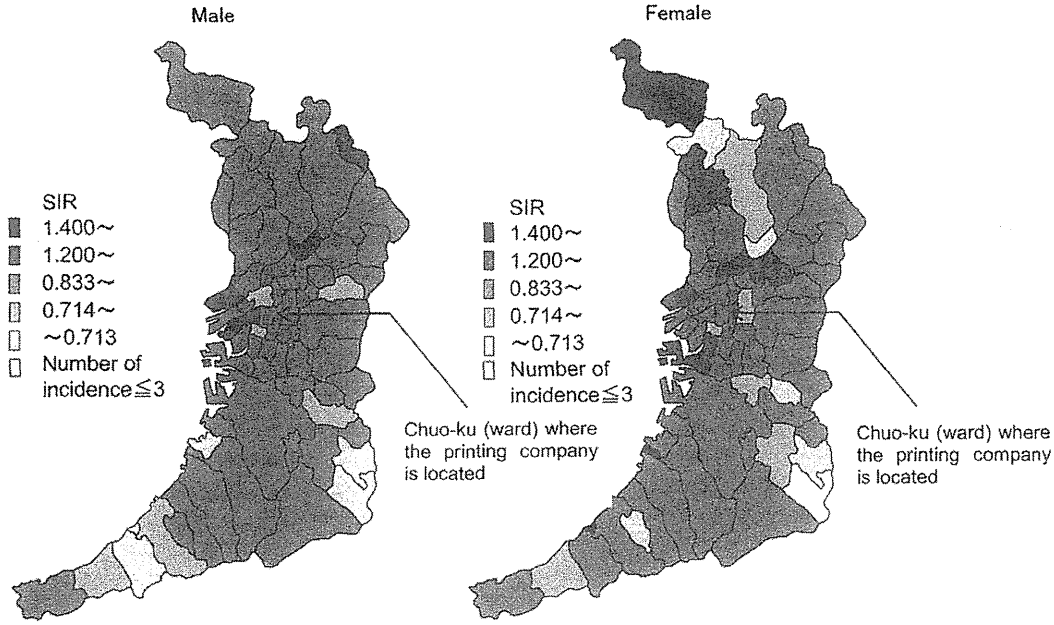

Figure 3. Standardized incidence ratios (SIRs) of bile duct carcinomas (C22.1 + C24.0) by municipality in Osaka, 1992–2007.

DISCUSSION

This study presented descriptive epidemiological profiles of bile duct carcinoma in Osaka, Japan, where the outbreak of bile duct carcinoma has been reported among workers in a printing company. Observed findings did not support any change in the time trend and disproportional geographical distribution related to the outbreak.

Advantages and Limitations of This Study

Osaka Cancer Registry has provided reliable and high-quality incidence data for a long period. This enabled us to examine incidence and survival of bile duct carcinoma in Osaka for over 30 years. Possible underreporting to the Osaka Cancer Registry may lead to lower estimation of cancer incidence and survival; however, cancers with poor survival are not caused by this bias. Therefore, we consider that our findings are reliable.

Our study did not support that any change in the time trend and disproportional geographical distribution was recognized in relation to the outbreak; however, this does not mean that such outbreak has never affected the environment. Exposure must be widely distributed and more people might have been exposed to some extent, according to the exert impact of the incidence rate. Although this study has some limitations to evaluate the effect of the outbreak, the geographical cluster analysis may be a suitable procedure to approach this problem.

Reason of the High Incidence of Bile Duct Carcinoma

ASRs of biliary tract cancer had increased since 1975, and reached peak or plateau in the 1980s to 1990s. These increases starting in 1975 were considered to be caused mainly by the improved diagnostic image techniques, such as endoscopic retrograde cholangiopancreatography (3), ultrasonography, computed tomography and magnetic resonance cholangiopancreatography (MRCP) (4,5). The detection rate for bile duct carcinoma by MRCP has been reported to be over 90% (6). In the USA, the increased incidence of the intrahepatic bile duct carcinoma between 1973 and 1997 was reported (7), and they have suggested that this might be related to increase in metabolic syndrome. However, this explanation is unlikely in Japan.

Survival of Bile Duct Carcinoma

Relative 5-year survival is generally poor among patients with bile duct carcinoma in Osaka. However, patients aged 25–49 years with localized disease showed a better survival: 52.7% for the intrahepatic bile duct carcinoma and 76.4% for the gallbladder carcinoma. The Biliary Tract Cancer Statistics Registry (8) in Japan reported that 5-year survival of extrahepatic biliary tract cancer patients with Stage I was >60% after surgical resection. These results suggest the importance of early detection and surgical resection for a better prognosis in the biliary tract cancer. To detect this cancer in the early stage, it will be necessary to build a screening system for high-risk workers by skilled clinical staffs.

Funding

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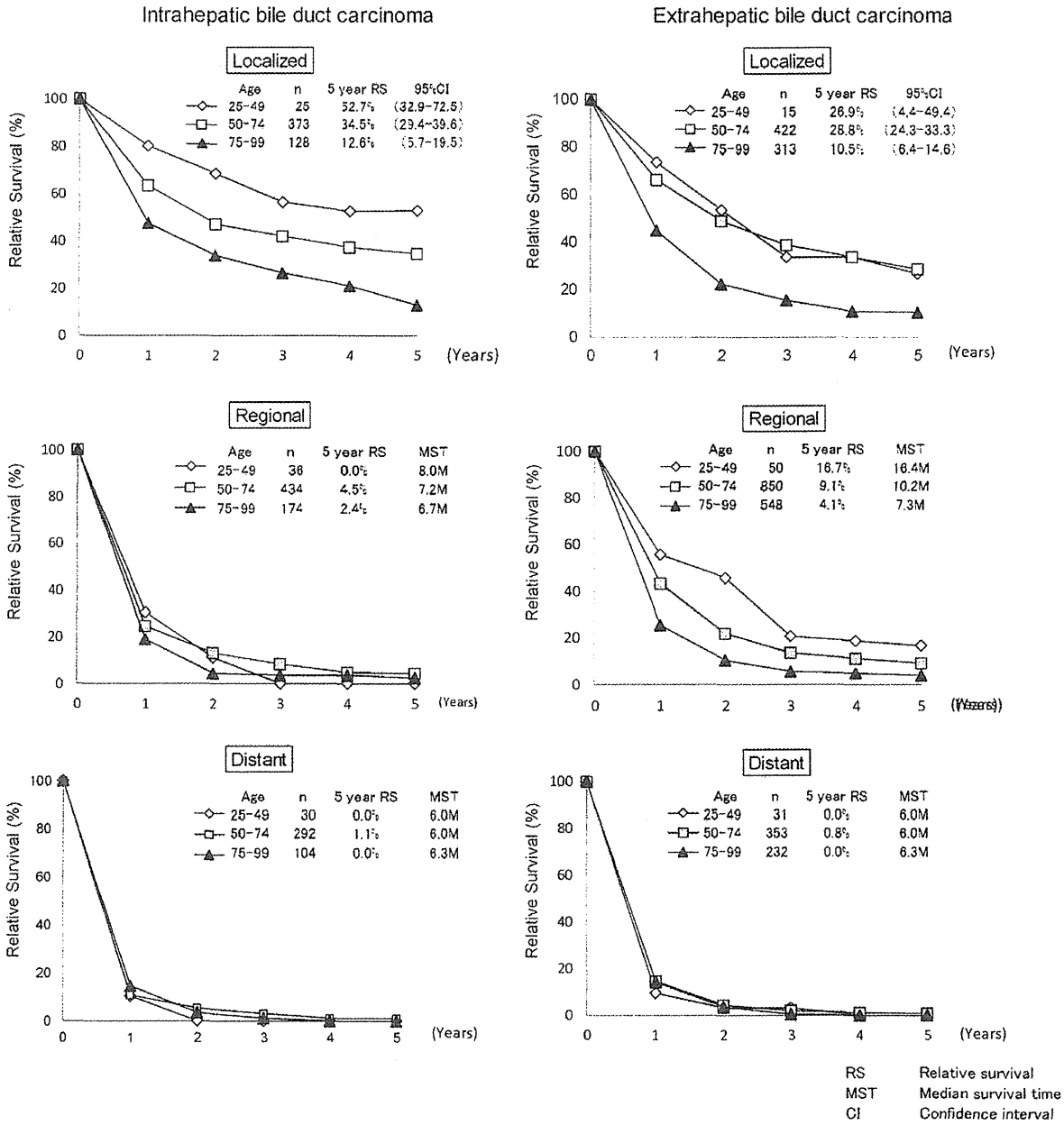

Figure 4. Relative survival of intrahepatic and extrahepatic bile duct carcinomas in Osaka, cases, 1993–2005.

Conflict of interest statement

None declared.

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Original Article

Different carcinogenic process in cholangiocarcinoma cases epidemically developing among workers of a printing company in Japan

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Abstract: Recently, cholangiocarcinoma has epidemically developed among young adult workers of a printing company in Japan. Exposure to organic solvents including 1,2-dichloropropane and/or dichloromethane is supposed to be associated with the carcinoma development. The metabolism of dichloromethane proceeds through a Theta-class glutathione S-transferase (GST) T1-1-catalyzed pathway, where its reactive intermediates have been implicated in genotoxicity and carcinogenicity. This study examined features of the carcinogenic process of the cholangiocarcinoma developed in the printing company. Surgically resected specimens of the cholangiocarcinoma cases were analyzed, where all cases were associated with precursor lesions such as biliary intraepithelial neoplasia (BilIN) and/or intraductal papillary neoplasm of the bile duct (IPNB). Immunohistochemical analysis confirmed constitutional expression of GST T1-1 in normal hepatobiliary tract. Immunostaining of γ-H2AX, a marker of DNA double strand break, showed that its expression was significantly increased in foci of BilIN, IPNB and invasive carcinoma as well as in non-neoplastic biliary epithelial cells of the printing company cases when compared to that of control groups. In the printing company cases, immunohistochemical expression of p53 was observed in non-neoplastic biliary epithelial cells and BilIN-1. Mutations of KRAS and GNAS were detected in foci of BilIN in one out of 3 cases of the printing company. These results revealed different carcinogenic process of the printing company cases, suggesting that the exposed organic solvents might act as a carcinogen for biliary epithelial cells by causing DNA damage, thereby contributing to the carcinoma development.

Keywords: Occupational cholangiocarcinoma, carcinogenesis, organic solvent, glutathione S-transferase, DNA damage

Introduction

Chronic biliary inflammation as occurs in primary sclerosing cholangitis and hepatolithiasis is a risk factor for the development of cholangiocarcinoma [1]. Biliary epithelial damage due to chronic inflammation can lead to the development of precursor lesions of cholangiocarcinoma such as biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of the bile duct (IPNB), and cholangiocarcinoma under the condition of chronic biliary inflammation often represents a multistep carcinogenesis process [2]. The patient age over 65 years is also a risk factor of cholangiocarcinoma, and it is rarely diagnosed before 40 years of age except in patients with predisposal factors such as primary sclerosing cholangitis [1, 3].

Recently, epidemical development of cholangiocarcinoma among young adult men has been reported in Japan, in which all patients were workers of a printing company [4, 5]. At least 17 men suffered from cholangiocarcinoma arising from the large bile ducts, and their mean age was 36 years (range, 25 to 45 years) [5]. In the

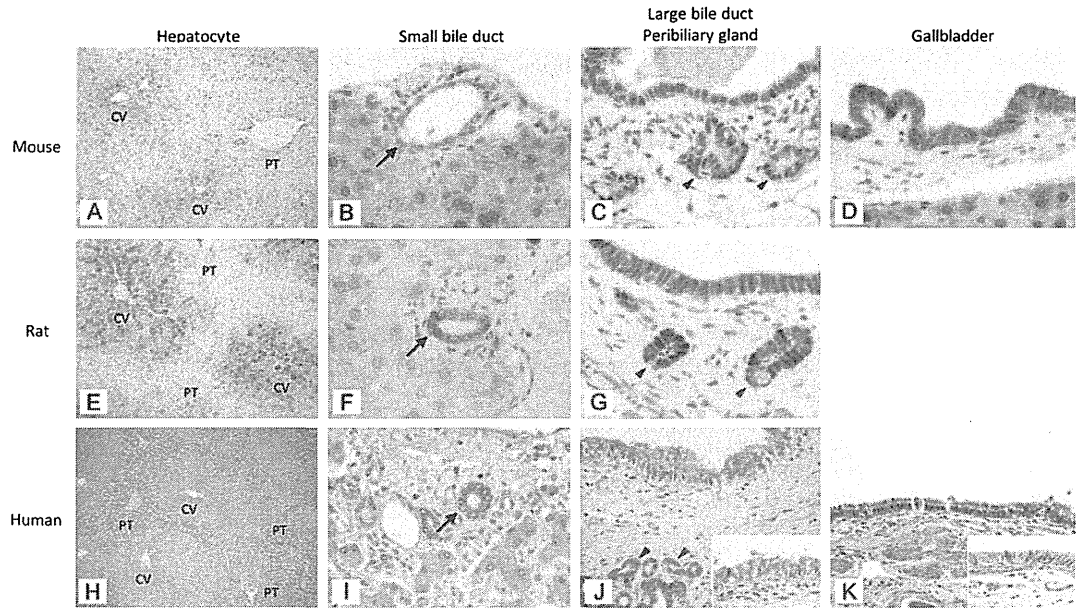

Figure 1. Distribution of GST T1-1 in normal hepatobiliary tract. Immunohistochemical expression of GST T1-1 was observed in hepatocytes and biliary epithelial cells of normal mouse, rat and human. Arrows and arrowheads indicate small bile ducts and peribiliary glands, respectively. Insets (J and K) were images taken from another part of the same case of each figure, showing heterogeneous expression of GST T1-1 in a single case. CV, central vein; PT, portal tract. Original magnifications: (A, E, H); x200: (B-D, F, G), (J) (inset), (K) (inset); x1000; (I-K); x400.

printing company, they engaged in offset color proof-printing using several organic solvents including 1,2-dichloropropane (1,2-DCP) and dichloromethane (DCM), where 1,2-DCP and DCM are classified as group 1 (carcinogenic to humans) and group 2A (probably carcinogenic to humans), respectively, according to the latest classification by the International Agency for Research on Cancer [6, 7]. In this series, DNA damage of biliary epithelial cells due to exposure to organic solvents including 1,2-DCP and/or DCM is supposed to be associated with the carcinogenic process, although the exact mechanism of the outbreak of cholangiocarcinoma remains to be determined.

In mammalian species, the metabolism of DCM proceeds through two pathways; a cytochrome P450 (CYP) 2E1 dependent oxidative pathway producing carbon monoxide, and a Theta-class glutathione S-transferase (GST) T1-1-catalyzed pathway resulting in the production of two highly reactive intermediates, formaldehyde and S-(chloromethyl) glutathione, and carbon dioxide [8]. The proportion of DCM metabolized via the GST pathway increases at higher exposures. Although CYP and GST are considered detoxification pathways for many chemicals, in the case of DCM it is the GST pathway that has been most strongly implicated in genotoxicity and carcinogenicity [9], while the involvement of the GST pathway in the metabolism of 1,2-DCP has not been fully clarified. To understand the mechanism of cholangiocarcinoma development in relation to the exposure to organic solvents, it is necessary to know the normal distribution of GST T1-1 and CYP2E1 in hepatobiliary tract. To date, however, detailed data on the distribution of the enzymes, especially GST T1-1, are lacking.

This study examined the immunohistochemical expression of GST T1-1 and CYP2E1 in normal hepatobiliary tract of mouse, rat and human. The DNA damage of biliary epithelial cells in the cholangiocarcinoma cases of the printing company was evaluated using immunohistochemistry by detecting the expression of γ-H2AX as a marker of DNA double strand break. Mutation analysis of KRAS and GNAS was also performed for the cases.

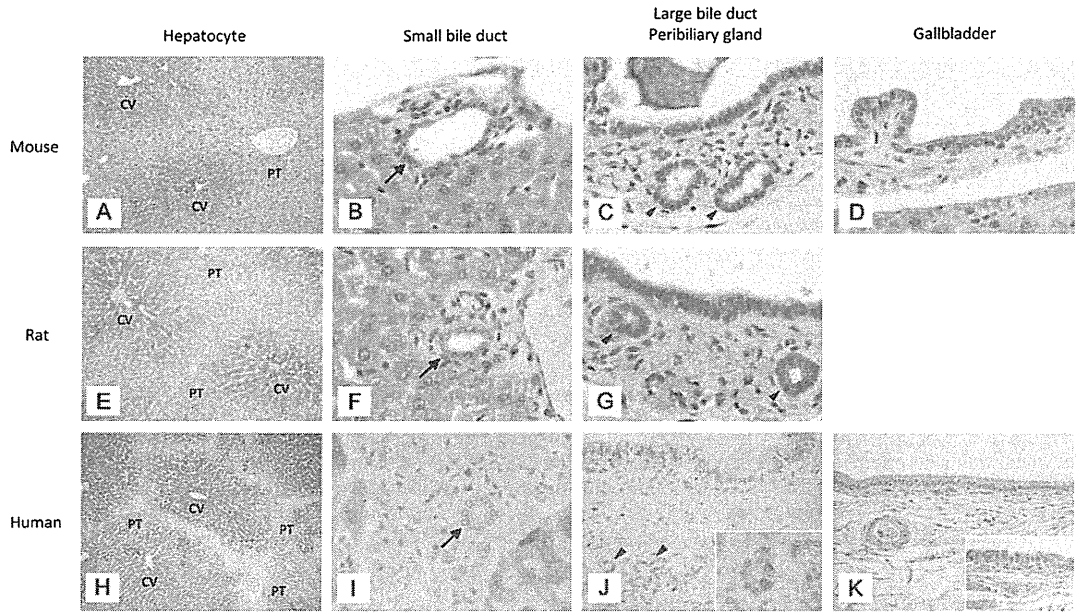

Figure 2. Distribution of CYP2E1 in normal hepatobiliary tract. Immunohistochemical expression of CYP2E1 was observed in zone 3-2 hepatocytes of normal liver of mouse, rat and human. Biliary epithelial cells typically lacked the expression of CYP2E1, but several human cases showed focal and weak immunohistochemical expression of CYP2E1 in the epithelium of peribiliary glands and gallbladder (J and K, insets). Arrows and arrowheads indicate small bile ducts and peribiliary glands, respectively. CV, central vein; PT, portal tract. Original magnifications: (A, E, H); x200: (B-D, F, G), (J) (inset), (K) (inset); x1000; (I-K); x400.

Table 1. Immunohistochemical expression of GST T1-1 and CYP2E1 in epithelial cells of normal hepatobiliary tract of mouse, rat and human

Enzyme	Species	Hepatocyte	Small bile duct	Large bile duct	Peribiliary gland	Gallbladder
GST T1-1	Mouse	+	-~+	+	+	++
	Rat	+~++	+~++	++	++	
	Human	+	+~++	+~++	+~++	+~++
CYP2E1	Mouse	+	-	-	-	-
	Rat	+	-	-	-	
	Human	+	-	-	-~+	-~+

CYP, cytochrome P450; GST, glutathione S-transferase. -, negative; +, positive (weak to moderate); ++, positive (marked).

Materials and methods

Tissue preparation

The experiments were performed in accordance with the guidelines for the care and use of laboratory animals of Kanazawa University and the World Medical Association's Declaration of Helsinki. Samples of normal liver and gallbladder were taken from 8-week-old ICR mice (n = 10), and samples of normal liver were from 8-week-old F344 rats (n = 10). Human liver samples (n = 30; mean age, 72 years) were obtained from the hilar region of the liver from autopsy files of our department. Histological examination confirmed that the human liver samples were almost normal. Human gallbladder samples (n = 15; mean age, 66 years) were obtained at the time of gastrectomy and cholecystectomy due to cholecystolithiasis, and the extent of inflammation in the gallbladder was histologically mild or minimal for all cases. The samples were formalin-fixed, and paraffin-embedded.