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Original Article

Long-term Trends in Incidence and Mortality of Intrahepatic and Extrahepatic Bile Duct Cancer in Japan

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ABSTRACT

Background: A report of multiple cases of bile duct cancer at a Japanese printing company raised concern about such cancers. We examined long-term trends in bile duct cancer in Japan.

Methods: Data from 4 population-based cancer registries were used to calculate incidence between 1985 and 2007, and vital statistics were used to estimate mortality between 1985 and 2011. Age-standardized rates were calculated and analyzed using a joinpoint regression model.

Results: Among men, the incidence rate of intrahepatic bile duct cancer increased throughout the observation period; among women, it increased until 1996–1998 and remained stable thereafter. The incidence rate of extrahepatic bile duct cancer was stable in men and decreased from 1993–1995 in women. In people aged 30 to 49 years, the incidence rates of intra- and extrahepatic bile duct cancer remained stable or decreased. The mortality rate of intrahepatic bile duct cancer increased in both sexes and in all age groups since 1996, while that of extrahepatic bile duct cancer decreased since 1992. In people aged 30 to 49 years, the mortality rates of intra- and extrahepatic bile duct cancer remained stable and decreased, respectively.

Conclusions: The incidence and mortality rates of intrahepatic bile duct cancer remained stable or increased throughout the observation period. The incidence rate of extrahepatic bile duct cancer remained stable or decreased, and the mortality rate decreased since 1992. In people aged 30 to 49 years, the incidence and mortality rates of intra- and extrahepatic bile cancer remained stable or decreased.

Key words: intrahepatic bile duct cancer; extrahepatic bile duct cancer; incidence; mortality

INTRODUCTION

In 2012, Kumagai et al reported that a high percentage of workers at a printing company in Osaka had developed and died from intrahepatic bile duct (IHBD) or extrahepatic bile duct (EHBD) cancer.[1] In March 2013, the Ministry of Health, Labour, and Welfare reported that, among 70 men who had worked in the offset color proof-printing section of the printing company, 16 men had developed IHBD or EHBD cancer and 7 had died from these cancers.[2] Their ages at diagnosis and death were 25 to 45 years (mean, 36 years) and 27 to 46 years (mean, 37 years), respectively. The incidence and mortality rates of IHBD and EHBD in people younger than 50 years are extremely low in Japan.[3] Thus, occupational chemical exposure was suspected to be the cause of the high incidence and mortality rates of IHBD and EHBD cancer.[1]

Trends in the incidence and mortality of IHBD and EHBD cancer must be monitored to determine their respective risks. However, in the International Classification of Disease (ICD), IHBD and EHBD cancer are categorized as "liver and intrahepatic bile ducts" and "gallbladder and extrahepatic bile ducts," respectively. Therefore, individual trends in these cancers cannot be observed.

We investigated long-term trends in IHBD and EHBD cancer incidence and mortality by age group in Japan.

METHODS

Data sources

We selected 4 prefectures in Japan: Miyagi, Yamagata, Fukui, and Nagasaki. These 4 prefectures had population-based cancer registries with long-term (ie, >20 years), high-quality

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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

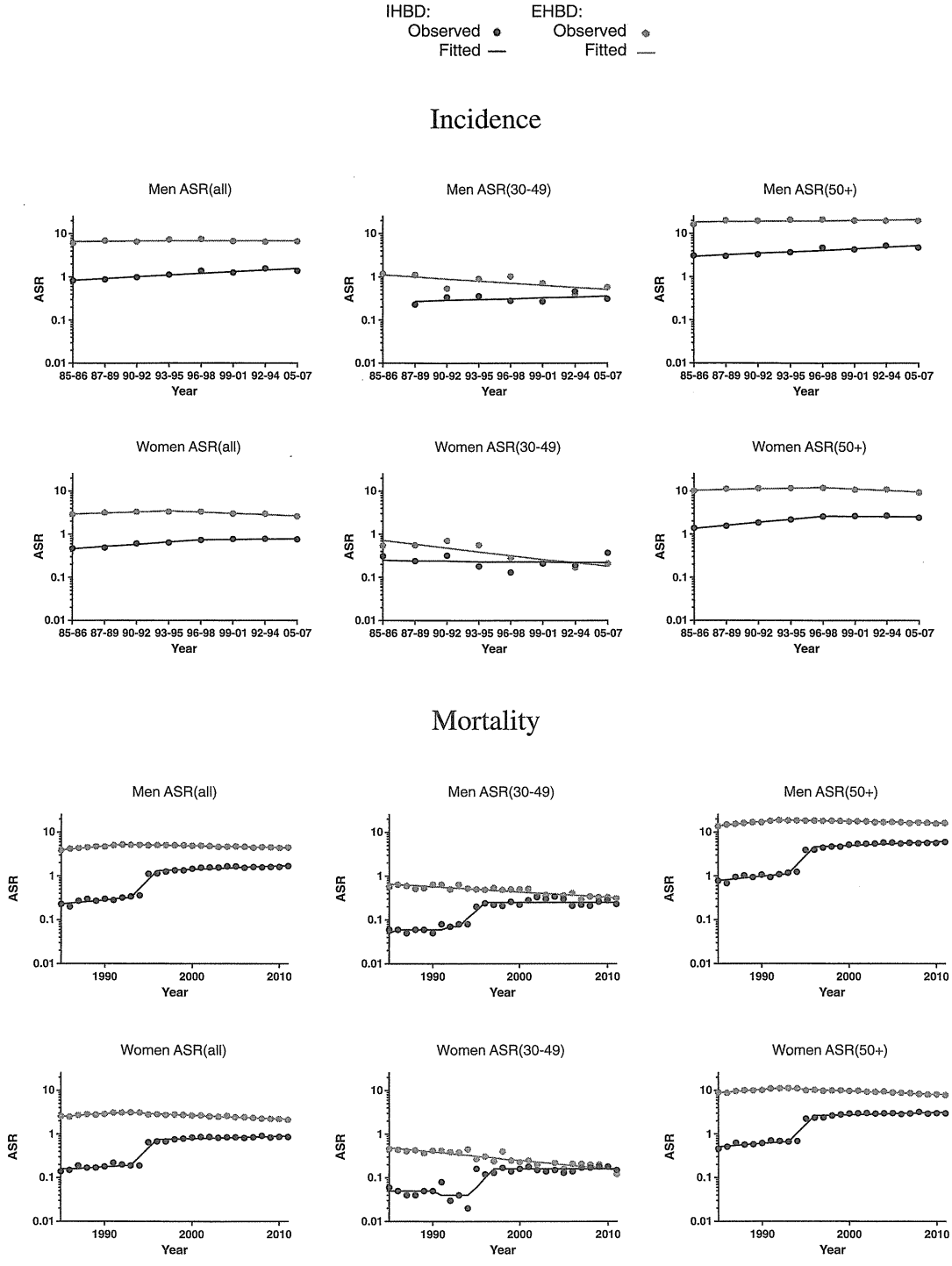

Figure 1. Trends in age-standardized IHBD and EHBD cancer incidence and mortality rates.

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.

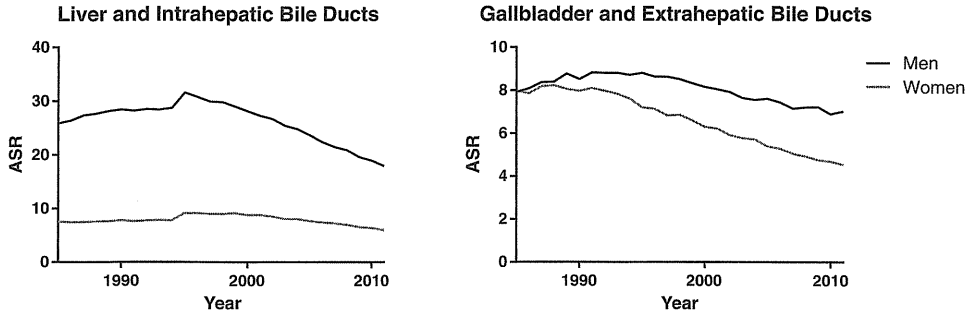

Figure 2. Trends in age-standardized mortality rates.

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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Conflicts of interest: None declared.

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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.
(J Occup Health 2013; 55: 511–515)

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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事　例

校正印刷事業場における作業環境改善状況について

Improvement of the Work Environment in a Proofreading Printing Plant

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はじめに

2012年5月に，大阪市内の校正印刷会社で複数従業員に胆管がんが集中して発症していることが報告された[1]ことを端緒として，印刷業において有機溶剤を用いて洗浄作業を行う労働者の健康被害の問題が大きくクローズアップされた[2]．

この事案は，厚生労働省においても重大なものと受け止め，全国の洗浄作業を行う印刷業に対する現地一斉点検を実施し，その結果，有機溶剤中毒予防規則（有機則）の違反等の多くの問題点が浮かび上がった[3–5]．

当該事業場での事例を含め，校正印刷作業者に多発した胆管がんの発症には，1,2-ジクロロプロパン，ジクロロメタンなどの有機塩素系溶剤が疑われているもの[6]の，当該事業場における発生の詳細やこれまでの作業状況等については調査中であり，業務と発症との因果関係については不明な事柄もあり，全貌の早期解明が待たれる状況にある．

とはいうものの，今後同種の事案を発生させないためには，業務と発症の因果関係の解明を待つまでもなく，速やかに現在存在する種々の問題点を改善することが重要である．中でも作業環境の改善は重要であるが，その方法を模索している事業場も多く，改善が遅れている面があると思われる．

問題の発端となった事業場は，この問題が発生した後，作業環境等の改善を実施しているが，改善にあたって筆者らも多少のかかわりを持った．上記のような趣旨から，ここでは当該事業場における作業環境改善の概況についてのみ報告することとする．印刷業における有機溶剤発散源対策について悩んでいる事業場も多いと思われるが，本報が参考になれば幸いである．

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1. 事業場の概要

当該事業場は，大阪市内に本社を持つ校正印刷会社の本社工場で，現在の概要は次のとおりである．

従業員数は60名，うち校正印刷従事者数は21名である．建物は，地上6階地下1階，うち地下1階から地上4階までが事業場として使用している．校正印刷作業場は，地下1階で間口は7.7 m，奥行きは21.1 m，天井の高さは2 mで，5台の校正印刷機，既設ダクト，柱の出っ張りを除くと有効気積は，387 m^3となる．労働安全衛生総合研究所（安衛研）[7]では室内容量は370 m^3としており，ほぼ一致している．

2. 校正印刷作業の概要

校正印刷機の外観はFig. 1のとおり．

校正印刷作業は次の手順で行われる[7]．

① ローラーにインキを塗り，ローラーから版にインキを付着させる．
② インキの付着した版からブランケットに転写する．
③ ブランケットから紙等の印刷媒体に印刷する．

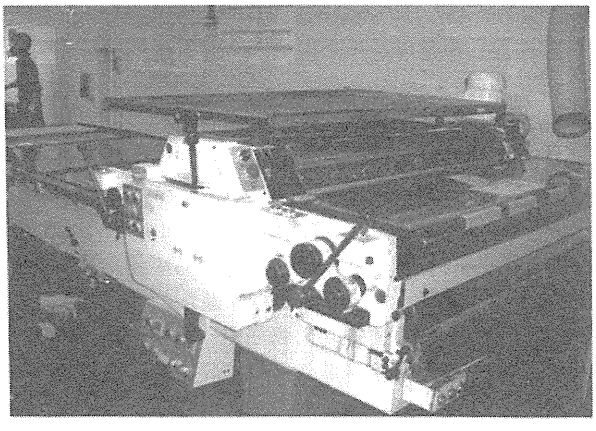


Fig. 1. An offset printing machine.

④次の版をブランケットに転写するためにブランケットを洗浄する.
⑤次の版をブランケットに転写する.
⑥ブランケットから紙等に印刷する.
⑦色を変えるときは，ローラーも洗浄する.

作業者の能力によって時間の長短はあるが，以前は1版の印刷に15–20分を要し，1時間に3–4回の洗浄作業を行っていた．現在は品質追求のため作業効率が悪くなり1版あたり25分程の作業時間を要しており，1時間に約2回の洗浄作業になっている.

3. 洗浄作業に使用する溶剤

現在，塩素系有機溶剤ならびに有機則の適用のある溶剤は使用していない．現在，ブランケットの洗浄の際は，①シクロヘキサン50–60%，プロピレングリコールモノメチルエーテル20–30%，エタノール10–20%，残り炭化水素10%のものを使っている．ローラー洗浄の際は，②キシレン1.3重量%含有の灯油，③グリコールエーテル系85–95%，ヘキシレングリコール0–10%のもの，④灯油35–45%，鉱油1–10%，活性剤1–10%，水45–75%のもの，を油性インキ，UVインキの場合に使い分けている.

4. 作業環境改善の状況

1）作業環境改善前の換気設備の概況

2012年7月現在における地下作業場の換気設備は，床面の4ヶ所と床上の1ヶ所から吸引排気する非循環系の排気設備と，作業室の片側壁上方に横列に配置された吹出し口から空調空気が吹出され，反対側に設置された吸い込み口から吸引される全体循環系の設備があった.

安衛研[7]によれば，UV排気系を作動させたときのネット換気量は約2,900 m^3/時余であり，これを室内容積で除した見かけの換気回数は7.8回/時である.

改善前に事業場が作業環境測定機関に依頼して実施したシクロヘキサン及びプロピレングリコールモノメチルエーテル混合溶剤蒸気についての作業環境測定結果は，Table 1に示す通りである．シクロヘキサン及びプロピレングリコールモノメチルエーテルはいずれも管理濃度は設定されていないが，ACGIHのTWAは，いずれも100 ppmであることから，これらの値を管理濃度相当とみなすと，測定結果から評価したこの作業場の管理区分は，第2管理区分であった.

ちなみに，この作業場について安衛研が1,2-ジクロロプロパンとジクロロメタンを用いて行った曝露再現実験の結果[7]は，還流率は56%，換気回数は3.8回/時と算定されている.

Table 1. The result of working environment measurement before improvement

Measuring point	Cyclohexane (E_1=100)	Propylene glycol mono methyl ether (E_2=100)	$\Sigma C_i/E_i$
	C_1 (ppm)	C_2 (pm)	
A-measurement: The measurement is performed to estimate the average concentration of the workplace			
1	21	2	0.23
2	27	3	0.30
3	120	15	1.35
4	85	12	0.97
5	77	10	0.87
6	44	5	0.49
Geometric mean			0.58
Geometric standard deviation			2.63
B-measurement: The measurement in the place considered that the exposure of the worker is biggest			
1	87	14	1.01
2	25	3	0.28

Administrative classification 2: Improvement of the work environment is considered.

2）作業環境改善の検討

現在，当該事業場においては有機則で規定する有機溶剤は使用しておらず，発散源の密閉設備，局所排気装置またはプッシュプル型換気装置の設置の義務は課せられていない．しかし，報道で換気装置の能力不足が記載されて社員の不安が膨らんだことと，行政当局の指導もあって設備の改善を行うこととなった.

しかし，改善の具体的方法について行政機関等に問い合わせるも，的確な回答が得られないまま，大阪産業保健推進センターを紹介され，2012年7月4日に，相談員のもとを訪れることになった.

相談員は作業場における換気，発散源，作業態様等の状況からみて，密閉設備や局所排気装置の設置は極めて困難と判断し，Fig. 2のような開放式プッシュプル型換気装置の設置を提案し，これら設備の設置に実績のある2社を紹介した.

事業場は，そのうちプッシュプル型換気装置専門の設計施工会社を選び，改善の見積もりを依頼した．施工会社からはFig. 3に示すように洗浄作業者の頭上に下降流方式の一様吹出し装置を設置し，既設の床吸込み口を改善して吸込む方式とする案が提案されたので，事業場は施工会社とともに再び産業保健推進センターを訪ねた．意見交換の結果，設置業者の推すFig. 3の方式による設備の設置を採用することに決定した.

3）改善設備の内容

施工業者から事業者に提出された設備改善計画の概

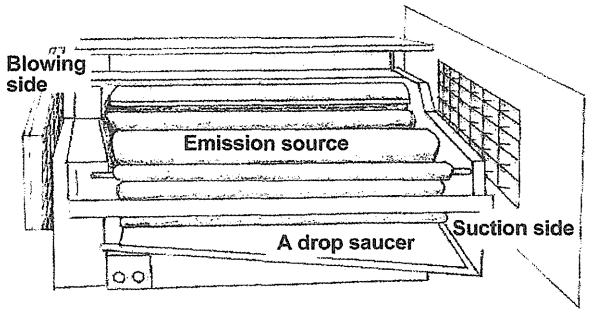
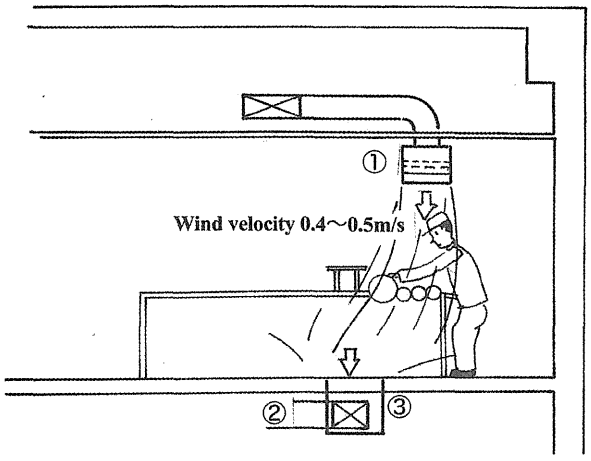


Fig. 2. A push-pull open type ventilation system.



①A blowing unit providing uniform air flow
②A suction unit
③ An existing underground duct

Fig. 3. Setting a blowing unit providing uniform air flow.

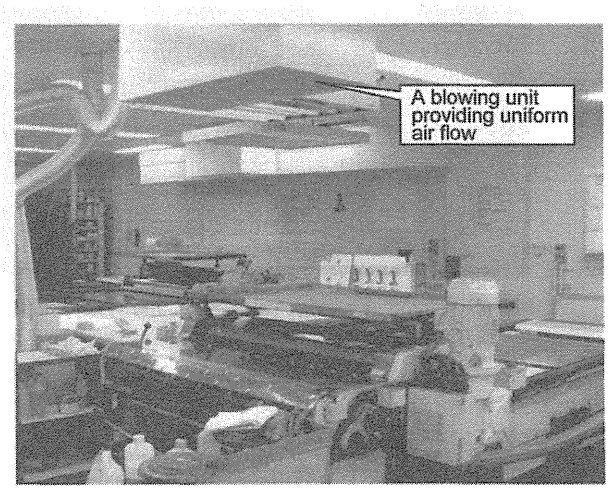


Fig. 4. A blowing unit providing uniform air flow.

要は次の通りである．

①従来の循環式空調システムを取り止め，オール外気を取り入れ，オール排気のシステムとする．
外気取り入れ量は100 m^3/min，排気量は150 m^3/minで設計する．

②作業者が洗浄作業を行うとき，作業者の呼吸域が有機溶剤蒸気に曝露されないよう，作業エリアに空気の一様吹出しユニット5基を設置する．
一様流吹出しユニットは，校正作業場の5台の校正印刷機それぞれに洗浄を行うロールの上方に設けたもので，吹出し面1,000 mm × 500 mm，吹出し面風速0.5 m/s（風量15 m^3/min）である（Fig. 3参照）．

③上記②のほかに，校正作業場内の全体換気用として，吹出し面250 mm × 250 mm，吹出し風速1.5 m/s（風量5 m^3/min）の新鮮空気吹き出し口を，一様吹出しユニットの気流に影響を与えないように作業場の壁付近に分散して5基設置する．

④印刷機械の下床面にある既設吸込みダクトを利用して，吸込み面400 mm × 600 mm，周囲350 mm，吸込み面風速0.5 m/s（風量18 m^3/min）を5基設置．

⑤上記④のほかに，作業室内用吸い込みグリルとして，吸込み面350 mm × 350 mm，吸込み面風速1.5 m/s（風量11 m^3/min）を3基設置．

⑥機械室に加湿器を新規に設置し，また，天井埋め込みタイプの空調機を設置し，これらにより温室度をコントロールする．

4）改善後の状況

改善状況をFig. 4およびFig. 5に示す．

Figure 4は，新設された一様吹出しユニットの写真である．

Figure 5は，床吸込み口の改善前後の写真である．

これらの結果，作業環境は，次のように改善された．

(1) 外気100％の導入により，汚染空気は循環されなくなった．

改善後の2013年2月に施工会社が実施した換気設備稼働状況調査結果によれば，

① 排気ファンの排出風量は124 m^3/min（このうち洗い場の局排フード風量23 m^3/min，地下作業場の排風量101 m^3/min）であった（Fig. 6）．

②機械室吸込みグリルからの外気吸込み量は99.8 m^3/minであった．

以上から，地下作業室の給・排気はバランスよく順調に作動していることが確認できた．

(2)換気回数が大幅に増加した．

新鮮空気の換気量100 m^3/minが確保されたことから，

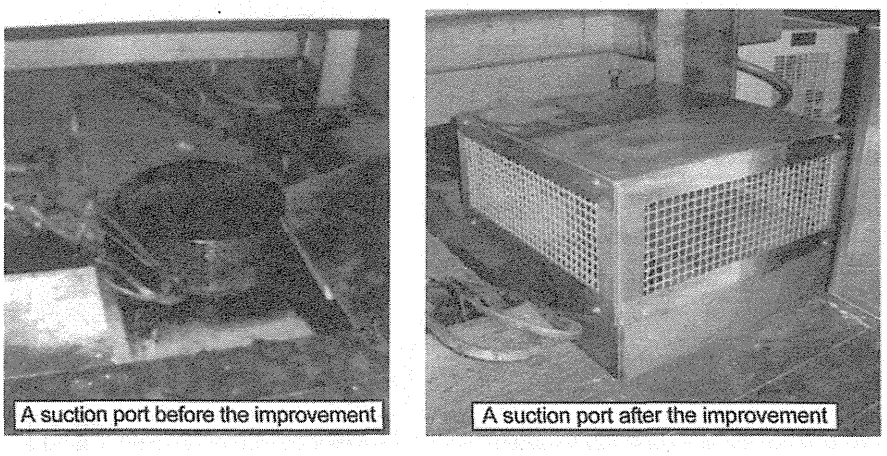


Fig. 5. A suction port on the floor.

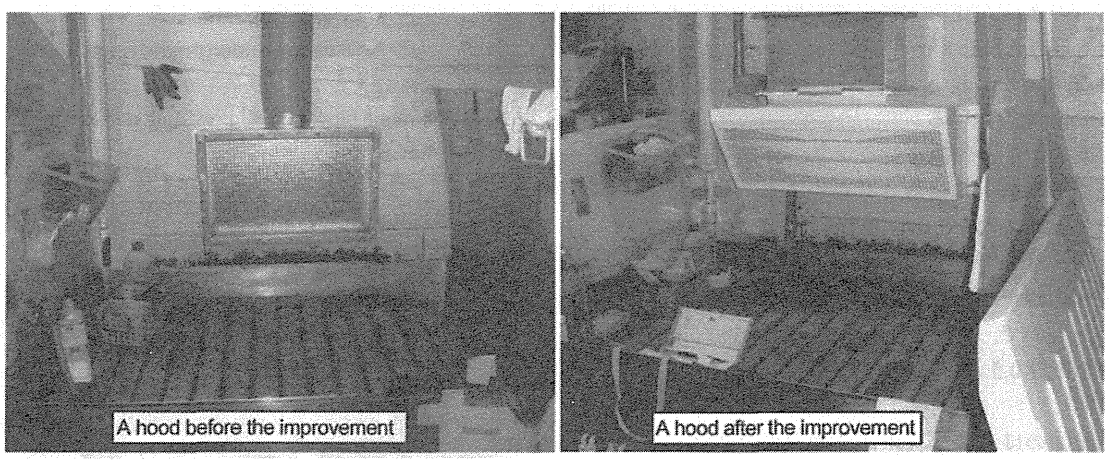


Fig. 6. A hood of local exhaust ventilation system in the washing space.

換気回数は15.5回/時と大幅に改善された.

(3)作業者に新鮮空気が直接給気されるようになった.

一様吹出しユニットから吹出される新鮮空気は, Fig. 7に示すように, 緩やかに真下に降下し, 作業者の呼吸域を包み込んだ後, ローラー位置付近で水平に分かれ, 床下から排出されることを確認した.

(4)作業環境測定結果に基づく環境レベルが改善された.

改善後に実施した作業環境測定結果, Table 2のとおりであり, その結果に基づく環境評価結果は第1管理区分に改善された.

5. 今後の留意点

改善された作業環境を維持するためには, 今後次の点に留意することが重要である.

① 作業中はもちろん, 作業の前後もしばらく換気装置を稼働すること.

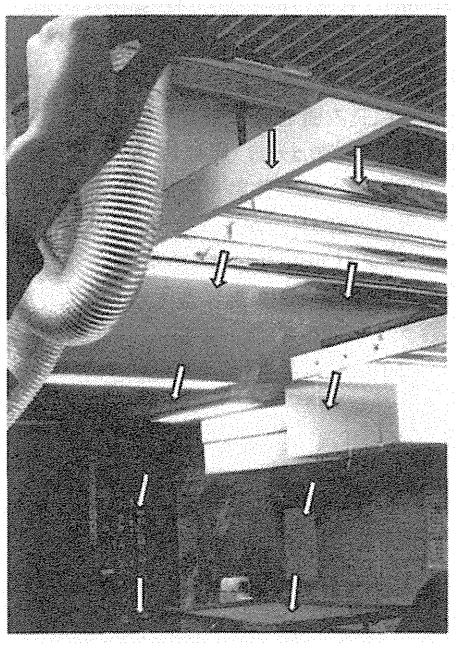


Fig. 7. Flow of blowing air.

Table 2. The result of working environment measurement after improvement

Measuring point	Cyclohexane (E_1=100)	Propylene glycol mono methyl ether (E_2=100)	$\Sigma C_i/E_i$
	C_1 (ppm)	C_2 (ppm)	
A-measurement: The measurement is performed to estimate the average concentration of the workplace.			
1	21	3	0.24
2	28	5	0.33
3	8	2	0.10
4	17	2	0.19
5	5	1	0.06
6	11	1	0.12
Geometric mean			0.15
Geometric standard deviation			2.49
B-measurement: The measurement in the place considered that the exposure of the worker is biggest			
1	14	1	0.15
2	36	3	0.39

Administrative classification 1: The state is judged to be appropriate.

② 換気装置は定期的に点検・検査を行うこと．
③ 定期的に作業環境測定を行い，環境状態を確認すること．
④ 作業者に換気装置の正しい使い方等について教育すること．

おわりに

校正印刷作業場における作業環境改善事例を報告したが，類似の作業を行っている事業場における環境改善に参考となれば幸いである．

今回問題となった事案のように，大きな労働衛生上の問題が存在しているにもかかわらず，表面化せずに見過ごされている例がこの他にもないとは言い切れない．

作業環境上の問題が判明した場合には，ただちに環境改善を実施しなければならないが，適切な指導ができる体制が確立していることが重要である．

局所排気装置やプッシュプル型換気装置の理論は広く周知されているが，現場では所要の性能を有しないものが多くみられる．今後この方面における対策の一層の充実を切に望んでやまない．

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印刷会社で集団発生した胆管癌の解明と対策

Investigation and countermeasures on the outbreak of cholangiocarcinoma in a printing company

圓藤吟史
久保正二

＜要　約＞

大阪のオフセット校正印刷会社の校正印刷部門に働いていた従業員から、2012年末までに17例の胆管癌罹患と、そのうちの７例の胆管癌による死亡が確認された。大阪校正部門所属歴がある男性の標準化罹患比は1,242、標準化死亡比は644とそれぞれ大きな値を示した。17例の主腫瘍は、10例が肝内胆管癌、５例が肝外胆管癌、２例が肝内胆管癌と肝外胆管癌の併存であった。原発部位の特定が困難であった２例を除く15例の原発部位は総胆管から肝内第３次分岐部までの比較的太い胆管であり、その部位に早期がん病変を広範囲に合併している例が多く認められた。病理標本から胆管上皮細胞にグルタチオン S- 転移酵素 θ -1（GSTT1-1）の高い発現が認められた。また胆管癌細胞のDNA解析では極めて激しいDNA損傷が認められた。厚生労働省の検討会報告書では、「1,2- ジクロロプロパンまたはジクロロメタンに長期間、高濃度曝露することにより発症し得ると医学的に推定できる」とし、胆管上皮細胞で活性の高い中間代謝物が作用している可能性が考えられている。全国健康保険協会のレセプトデータからの解析では印刷業本人男性で30～49歳の年齢階級で胆管癌患者数は10人で、期待値5.62人と比較して、標準化有病率比とその95％信頼区間は1.78（0.63-5.00）であり、印刷業での広がりは限定されたものと考えられる。今後、健康管理手帳による健診が円滑に進められることが望まれる。

キーワード：胆管癌、職業癌、印刷業、1,2- ジクロロプロパン、ジクロロメタン

端緒

印刷会社元従業員で胆管癌が多発しているとの2012年５月18日のニュースは衝撃的なものであった。熊谷ら[1]によると、オフセット校正印刷会社（A 社）の校正印刷部門に1990年代および2000年代前半に１年以上在籍していた約40人の男性従業員の中から、肝内・肝外胆管癌に５

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名が罹患し、そのうち４名が死亡していたとのことである。この集団発生の全貌を明らかにし、原因を追究するために、私どもは、厚生労働科学研究として調査・研究を実施した。

１．コホート研究

その後の調査[2]でＡ社の現・元従業員326人において、2012年末までに17例の胆管癌罹患と、そのうちの７例の胆管癌による死亡が確認された。死亡を含む胆管癌罹患者はいずれも男性で、大阪の校正部門に所属歴があり、診断時25歳から45歳であった。大阪校正部門所属歴を有する者のうち、生年月日不明の者、入社年月日と退職年月日のいずれかが不明な者、入社年月日が2012年９月以降の者を除いた対象者は男性80名、女性21名であった。観察開始を1985年１月１日、観察終了を2012年12月31日とし、後ろ向きコホート研究を行った。期待罹患数の算出には、宮城、山形、福井、長崎の４県の地域がん登録データを基に全国がん罹患モニタリング集計を参考とした方法で算出した３年移動平均の全国罹患率推計値（1985-2007年）を用い、期待死亡数の算出には、人口動態統計を基に算出した全国死亡率（1985-2011年）を用いた。その結果、大阪校正部門所属歴がある男性ならびに男女合計の標準化罹患比（standardized incidence ratio; SIR）はそれぞれ1,242、1,226、男性ならびに男女合計の標準化死亡比（standardized mortality ratio; SMR）はそれぞれ644、634といずれも大きな値を示した。なお、2013年は12月末までに、新たな胆管癌発症はなく、罹患者のうちの２名が胆管癌と肝不全により死亡されたので、観察期間を2013年末までに延長すると、SIR は若干下がり、SMR は上がる。

２．症例研究

17例の主腫瘍は、10例が肝内胆管癌、５例が肝外胆管癌で、２例が肝内胆管癌と肝外胆管癌の併存であった[3]。２例が診断時に進行がんであったため原発部位の特定は困難であったが、残り15例の原発部位は総胆管から肝内第３次分岐部までの比較的太い胆管であり、その部位に早期がん病変を広範囲に合併している例が多く認められた。肝内胆管癌がみられた12例のうち、８例は腫瘤形成型で、４例は胆管内発育型であった。肝外胆管癌がみられた７例のうち、５例が乳頭型で、２例が結節型であった。

８例について病理組織学的検討がなされ、それらの主腫瘍は低分化から高分化の腫瘤形成性胆管癌、浸潤型胆管内乳頭状腫瘍（invasive intraductal papillary neoplasm of the bile duct: invasive IPNB）で、胆管内発育型胆管癌あるいは乳頭状肝外胆管癌であった。また、広範囲の胆管に主腫瘍以外に前がん病変とみられる胆管上皮内腫瘍（biliary intraepithelial neoplasia, grades 2 and 3: BilIN-2/3）とIPNB が確認された。さらに、胆管付属腺を含めた広範囲な胆管に、炎症性細胞浸潤を伴う胆管硬化像、胆管消失を伴う胆管傷害像や非特異的な反応が認められた。しかし、肝硬変や進行性肝実質病変は認められなかった。また、胆管癌の危険因子として知られている、膵・胆管合流異常、原発性硬化性胆管炎、肝内結石を含む胆石症、肝吸虫、Ｂ型肝炎、Ｃ型肝炎は存在しなかった。

17例中５例は診断時にすでに広範囲リンパ節転移や腹膜播種を伴う進行癌で化学療法やステント挿入がなされた。12例には外科的治療がなされ、うち４例は術中病理検査において胆管断端陽性であった。外科的治療がなされた12例中10例でリンパ節廓清やサンプリングが行われ、うち４例に肝十二指腸間膜内リンパ節などに転移がみられた。８例に術後補助化学療法としてS-１やゲムシタビンが投与され、２例に放射線治療が行われた。外科的治療がなされた12例中、５例に切除断端近傍や肝内再発がみられ、１例にリンパ節再発がみられた。2013年末までに非切除５例中４例、切除後再発５例中４例が癌により死亡し、１例は切除後再発がなかったものの肝不全の進行により死亡している。

３．推定原因とその評価

原因について、Kumagai et al.[4] は、1,2-ジクロロプロパン（$CH_3CHClCH_2Cl$: 以下「DCP」と表記する。）and/or ジクロロメタン（CH_2Cl_2：以下「DCM」と表記する。）が示唆されるとした。厚生労働省の検討会報告書[5] では、「本件事業場で発生した胆管癌については、DCP に長期間、高濃度曝露したことが原因で発症した蓋然性が極めて高いと判断する。」としている。

日本産業衛生学会の許容濃度等に関する委員会は、「オフセット印刷工程」を発がん分類の第１群（ヒトに対して発がん性があると判断できる物質である。この群に分類される物質は、疫学研究からの十分な証拠がある。）とする暫定案と、DCPを許容濃度の１ppm、発がん分類の第２群Ａ（ヒトに対しておそらく発がん性があると判断できる物質である。証拠が比較的十分な物質で，疫学研究からの証拠が限定的であるが、動物実験からの証拠が十分である。）、皮膚感作性物質の第２群（人間に対しておそらく感作性があると考えられる物質）とする暫定案を2013年５月に開かれた総会に提案し、承認された。その提案理由書[6] で DCP を発がん分類第２群Ａにした根拠について「２つの動物実験は曝露経路発がん部位、動物種が異なること、ヒトで十分でないものの、発がんの可能性を示唆する報告である」と述べている。一方、オフセット印刷工程を発がん分類の第１群とした根拠について、大阪の印刷事業場での「校正印刷部門での作業のヒト胆管での発がん性は明らかであり、その原因は塩素系有機溶剤等を使用するオフセット印刷工程の中にあると考えられる」としている。

許容濃度等は化学物質や物理的要因ごとに定めることになっており、「工程」は「物質」でないので、許容濃度等としては異例である。しかし、IARCは「靴製造あるいは修理」や「ゴム産業」も評価対象としているので、世界からみれば異例ではない。

４．業務上外の検討

厚生労働省の検討会では、請求された案件について順次、検討されている。2013年11月末までに印刷業における胆管癌例が81件請求され、そのうち12月までに26件が業務上と決定されている。内訳は、発端となった大阪の事業場で17例、宮城と福岡の事業場で２例ずつ、北海道、埼玉、愛知、青森と大阪の別の事業場で１例ずつとなっている。新たな請求には北海道の事例と