bile duct with the intraductal growth type, which corresponds to an intraductal papillary neoplasm of bile duct (IPNB) with invasive carcinoma according to the 2010 WHO classification of intrahepatic cholangiocarcinoma[9] (Fig. 5A). Biliary intraepithelial neoplasia (BilIN)-2 (high grade dysplasia)/3 (carcinoma *in situ*) lesions[9] spread from the medial hepatic bile ducts to the hilar bile duct and the common bile duct, including their intramural glands (Figs. 5B and 5C). Chronic bile duct injury was shown around the carcinoma and BilIN lesions (Figs. 5B and 5D). No significant reactive changes of the hepatocytes were noted. Lymphatic, venous and perineural invasion, and lymph node metastasis were absent. Postoperatively, the patient was treated with radiation for the hepatic hilum (total 50 Gy), and thereafter has been receiving adjuvant chemotherapy (gemcitabine). The patient is doing well 30 months after the operation without recurrence.

Discussion

From an anatomical point of view, CC is classified as intrahepatic or extrahepatic, with the latter form being further divided into proximal or perihilar (Klatskin tumor) and distal, depending on the location of the cancer within the extrahepatic biliary system[1]. In our case, the cancer cells were spread widely from the intrahepatic bile duct to the right hepatic duct and common bile duct, which would be broadly classified as Type IV according to the Bismuth-Corlette classification of Klatskin tumors[10], but a curative operation was performed using an extended left hepatectomy with resection of the extrahepatic bile duct. Recent histological and molecular characterizations have highlighted the heterogeneity of CC, which may emerge in different sites of the biliary tree and with different macroscopic or morphologic features[11]. Moreover, histologically, flat-type "BilIN" and papillary-type "IPNB" were previously proposed to be precursors of invasive, perihilar intrahepatic CC[9]. These findings correspond with the different macroscopic appearance and histologic findings in our case. We suggested that our patient had experienced chronic bile duct injury due to an unknown cause, which might have induced the wide-spread BilIN lesions and IPNB with invasive carcinoma[11].

There are several established risk factors for CC, including parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis, and toxins[2-5]. Other less-established potential risk factors include inflammatory bowel disease, hepatitis C virus infection, hepatitis B virus infection, cirrhosis, diabetes, obesity, alcohol, smoking, and host genetic polymorphisms[2,3,6]. In our case, a preoperative diagnosis of CC would have been difficult without cytology because the patient did not have any of the risk factors described above and was relatively young (39 years old). The typical age at presentation of CC is in the seventh decade of life[7,8]. In our case, the findings from cholangiography appeared to correspond to those of primary or secondary sclerosing cholangitis (pruned tree sign, multifocal stricture, and shaggy sign)[12], especially in the right intrahepatic bile duct where CC was absent. This suggests that CC might have been induced by secondary sclerosing cholangitis. However, our patient also did not have any of the risk factors for this disease, which include ascending cholangitis, oriental cholangiohepatitis, acquired immunodeficiency syndrome-related cholangitis, chemotherapy-induced cholangitis, ischemic cholangitis after liver transplantation, eosinophilic cholangitis, and metastasis[12].

In Japan, an epidemic of CC at the printing plant at which our patient worked was reported in a news release in May 2012. An investigation by the Ministry of Health, Labor and Welfare showed that 14 patients who worked in the factory had developed CC since 1996, and that seven had died of CC. Moreover, the mean age of the patients who died of CC was less than 40 years. Exposure to

suspected carcinogenic chemicals, including 1,2-dichloropropane, in the factory may have been one of the factors responsible for the carcinogenesis[13,14]. Currently, we cannot be certain that the CC in our patient was induced by carcinogenic chemicals, but the findings from cholangiography and the histological findings indicated possible chronic inflammation of the bile duct. Further epidemiological and environmental investigations are needed to establish risk factors for CC.

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Case Study

Changes in Laboratory Test Results and Diagnostic Imaging Presentation before the Detection of Occupational Cholangiocarcinoma

Shoji Kubo[1], Shigekazu Takemura[1], Chikaharu Sakata[1], Yorihisa Urata[1],
Takayoshi Nishioka[1], Akinori Nozawa[1], Masahiko Kinoshita[1], Genya Hamano[1],
Yasuni Nakanuma[2] and Ginji Endo[3]

[1]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Japan, [2]Department of Human Pathology, Kanazawa University Graduate School of Medicine, Japan and [3]Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, Japan

Abstract: Changes in Laboratory Test Results and Diagnostic Imaging Presentation before the Detection of Occupational Cholangiocarcinoma: Shoji Kubo, *et al.* Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine—Objectives: A cholangiocarcinoma outbreak among workers of an offset color proof-printing department in a printing company was recently reported. It is important to understand the clinical course leading to occupational cholangiocarcinoma development for investigation of the carcinogenesis process and for surveillance and early detection. We evaluated the changes in laboratory test results and diagnostic imaging presentation before the detection of cholangiocarcinoma. **Methods:** We investigated the changes in laboratory test results and diagnostic imaging presentation before the detection of cholangiocarcinoma in 2 patients because the data were available. **Results:** The clinical courses observed in the 2 participating patients showed persistent elevation of serum γ-glutamyl transpeptidase levels with or without elevated serum levels of alanine aminotransferase and/or aspartate aminotransferase before cholangiocarcinoma detection. Dilatation of the bile ducts without tumor-induced stenosis was observed several years before cholangiocarcinoma detection and progressed gradually in both patients. The serum concentration of carbohydrate 19-9 also increased prior to cholangiocarcinoma detection in both patients. Eventually, observation of stenosis of the bile duct and a space-occupying lesion strongly suggested cholangiocarcinoma. Pathological examina-
tion of the resected specimens showed chronic bile duct injury and neoplastic lesions, such as "biliary intraepithelial neoplasia" and "intraductal papillary neoplasm of the bile duct" in various sites of the bile ducts, particularly in the dilated bile ducts. **Conclusions:** The changes in laboratory test results and diagnostic imaging might be related to the development of cholangiocarcinoma. It is important to monitor diagnostic imaging presentation and laboratory test results in workers with extended exposure to organic solvents.
(J Occup Health 2014; 56: 317–322)

Key words: Carbohydrate 19-9, Dilated bile ducts, γ-Glutamyl transpeptidase, Occupational cholangiocarcinoma, Organic solvent

Recently, a cholangiocarcinoma outbreak among former and current workers of an offset color proof-printing department of a printing company was reported in Japan[1, 2]. The disease was diagnosed in relatively young workers from 25 to 45 years old with a mean age of 36 years, and the observed incidence was unusually high in the abovementioned department (17 of 111 workers diagnosed)[2]. In that department, various chemicals including organic solvents, such as 1,1,1-trichloroethane, dichloromethane, and 1,2-dichloromethane (DCP), were used to clean ink residues. An experimental reconstruction of the working environment conducted by the Japanese National Institute of Occupational Safety and Health suggested that these workers were exposed to high concentrations of organic solvents[3]. Dichloromethane is classified as group 2B (possibly carcinogenic to humans) according to the International Agency for Research on Cancer[4]. The Japanese Ministry of Health, Labour and Welfare reported that biliary tract cancer was most probably

caused by long-term exposure to high DCP concentrations and that this type of cholangiocarcinoma was recently classified as an occupational disease[5].

It is important to understand the clinical course leading to the development of such an occupational cholangiocarcinoma for investigation of the carcinogenesis process and to optimize clinical surveillance for early detection. Of the 17 patients with occupational cholangiocarcinoma in the previously mentioned printing company, complete information describing the changes in laboratory test results and diagnostic imaging presentation before cholangiocarcinoma detection was available for 2 patients. In the present report, we described these changes to understand the clinical characteristics of these 2 patients. This study was approved by the ethics committee of Osaka City University, and both patients provided written informed consent.

Case Presentation

Case 1

Cholangiocarcinoma was diagnosed when the patient was 39 years old. He was not a habitual alcohol consumer and did not receive prior treatment. The diagnosis was made 13 years and 3 months after he started working at the printing company, where he was exposed to DCP for 7 years and 4 months. He received treatment for acute hepatitis 1 month after starting at the company (data not available). At 9 years and 4 months before cholangiocarcinoma detection, his laboratory test results were within the reference range (Fig. 1A). However, at 8 years and 4 months prior to cholangiocarcinoma detection, an elevated level of serum γ-glutamyl transpeptidase (γ-GTP, 101 U/*l*; reference value ≤86 U/*l*) was first noted, and it continued to increase gradually. At 3 years and 9 months before diagnosis, his serum levels of aspartate aminotransferase (AST, 50 U/*l*; reference value ≤38 U/*l*) and alanine aminotransferase (ALT, 62 U/*l*; reference value ≤43 U/*l*) were elevated. Magnetic resonance cholangiopancreatography (MRCP) taken at 2 years before diagnosis showed multiple localized dilatations of the peripheral bile ducts without tumor-induced stenosis of the bile ducts in the posterior segment (Fig. 1B). The patient was suspected to have primary sclerosing cholangitis (PSC).
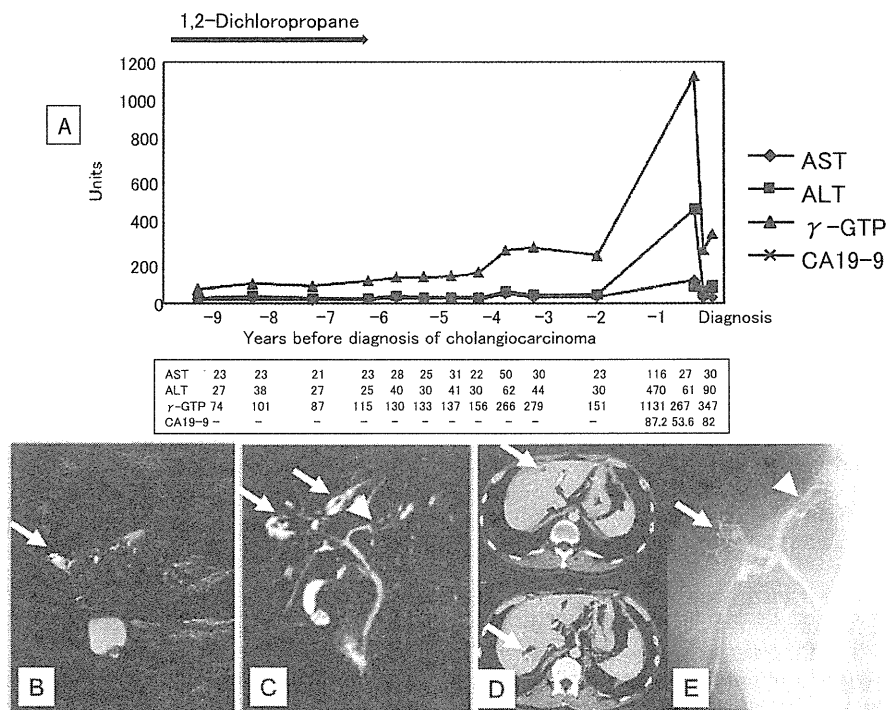
Fig. 1. Changes in laboratory test results and diagnostic imaging presentation before the diagnosis of cholangiocarcinoma in case 1. (A) Laboratory test results. (B) Magnetic resonance cholangiopancreatography (MRCP) 2 years before cholangiocarcinoma diagnosis. (C) MRCP 4 months before detection[2]. (D) Computed tomography (CT) at the time of cholangiocarcinoma diagnosis. (E) Endoscopic retrograde cholangiopancreatography (ERCP) at the time of cholangiocarcinoma diagnosis. Arrows show localized dilatation of the bile ducts. Arrowheads show stenosis of the bile duct (B2).

At 4 months before the cholangiocarcinoma diagnosis, he visited a hospital for abdominal pain, jaundice and acholic stool. His serum levels of γ-GTP, ALT and aspartate aminotransferase (AST) were elevated due to acute cholangitis. MRCP showed that the previously noted localized dilatation of the bile ducts was progressing, and a stenosis of the bile duct (B2) was suspected (Fig. 1C). His serum level of carbohydrate 19-9 (CA 19-9, reference value, ≤37 U/ml) was first measured and elevated (87.2 U/ml) 4 months before the diagnosis of cholangiocarcinoma. Ultrasonography showed the dilated bile ducts in the posterior segment (B7) and high echoic change of the bile duct walls in the lateral segment. Dynamic computed tomography (CT) showed dilatation of the bile ducts in various parts of the liver (Fig. 1D). Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis of the bile duct (B2) and dilatation of the bile ducts in the posterior segment (Fig. 1E). Brushing cytology of bile obtained from the stenotic site suggested adenocarcinoma, and cholangiocarcinoma was eventually diagnosed. At admission, laboratory test results showed elevated serum levels of ALT (57 U/l; reference value, ≤33 U/l), γ-GTP (347 U/l; reference value, ≤60 U/l), and CA19-9 (105 U/ml; reference value, ≤37 U/ml). The liver functional reserve was normal. The results of hepatitis B surface antigen and hepatitis C virus antibody titer tests were negative. His body mass index at admission was 24.3.

During surgery, intraoperative ultrasonography showed dilatation of the bile ducts (B7) with papillary tumors inside the bile ducts. Therefore, left lobectomy and segmentectomy (segment 7) were performed. Pathological examination of the resected specimens was performed. Precancerous or early-staged cancer lesions such as biliary intraepithelial neoplasia (BilIN)-2/3 and intraductal papillary neoplasm of the bile ducts (IPNB) were evaluated[6, 7]. Pathological examination showed chronic bile duct injury including sclerosis of large and medium-sized bile ducts (Fig. 2A) and intraepithelial neoplastic changes corresponding to BilIN-2/3 lesions at the various sites of the dilated and non-dilated bile ducts (Fig. 2B) and in the peribiliary glands. Focally, papillary lesions corresponding to IPNB were observed in the dilated intrahepatic bile ducts (Fig. 2C), and some parts of the IPNB showed cancer cell infiltration into the portal tract and perineural invasion (invasive IPNB or intraductal growth type of intrahepatic cholangiocarcinoma, Fig. 2D). The pathological examination of segment 7 showed such papillary changes in the dilated bile ducts (Fig. 2E), and some of them showed considerable mucin secretion with infiltration into the surrounding tissue and focal rupture. Pathological examination of the background liver showed nonspecific reactive changes such as mild portal inflammatory cell infiltration and fibrosis.

Case 2

Cholangiocarcinoma was diagnosed when the patient was 31 years old. He was not a habitual alcohol consumer and did not receive prior treatment. The diagnosis was made 12 years and 6 months after he started working at the printing company, where he was exposed to DCP for 6 years and 6 months. He retired from this position because extremely elevated levels of serum γ-GTP (1,182 U/l), AST (84 U/l), and ALT (144 U/l) were noted (although accurate reference values were unclear, the results were abnormally high) 6 years before the diagnosis of cholangiocarcinoma. His serum levels of γ-GTP, AST and ALT gradually decreased after his retirement (Fig. 3A). He started to receive ursodeoxycholic acid (600 mg/day) for liver dysfunction 3 years and 6 months before the diagnosis of cholangiocarcinoma. A CT scan performed at 5 years before cholangiocarcinoma diagnosis showed localized dilatation of the bile ducts in the posterior segment without tumor-induced stenosis of the bile duct (Fig. 3B). MRCP at 3 years and 6 months and at 8 months before cholangiocarcinoma diagnosis indicated that the number of localized bile duct dilatations and the degree of dilatation were increasing (Fig. 3C, 3D). Further, a protruded lesion was discovered in the hepatic duct (Fig. 3D, 3E). The patient's serum level of CA19-9 was first measured at 4 years and 10 months before cholangiocarcinoma diagnosis. Although his serum level of CA 19-9 increased at 4 years and 7 months (40 U/l, reference value, ≤37 U/ml) and at 3 years and 7 months (70 U/ml) before diagnosis, his serum level then decreased to the reference range. The serum level of CA19-9 started increasing again at 1 year and 5 months (43 U/l) before diagnosis (Fig. 3A). He started to receive ursodeoxycholic acid (600 mg/day) for liver dysfunction 3 years and 6 months before the diagnosis of cholangiocarcinoma. At admission, laboratory test results showed elevated serum levels of γ-GTP (75 U/l; reference value, ≤60 U/l), and CA19-9 (501 U/ml; reference value, ≤37 U/ml). A space-occupying lesion then appeared in the posterior segment of the liver (Fig. 3F). ERCP showed obstruction of the bile ducts in the posterior segment and a protruding lesion in the hepatic duct (Fig. 3G). The patient was diagnosed with a mass-forming type of intrahepatic cholangiocarcinoma and papillary type of extrahepatic cholangiocarcinoma at the hepatic duct. The results of hepatitis B surface antigen and hepatitis C virus antibody titer tests were negative. The patient's body mass index at admission was 16.2. He underwent right lobectomy and resection of the common hepatic and bile
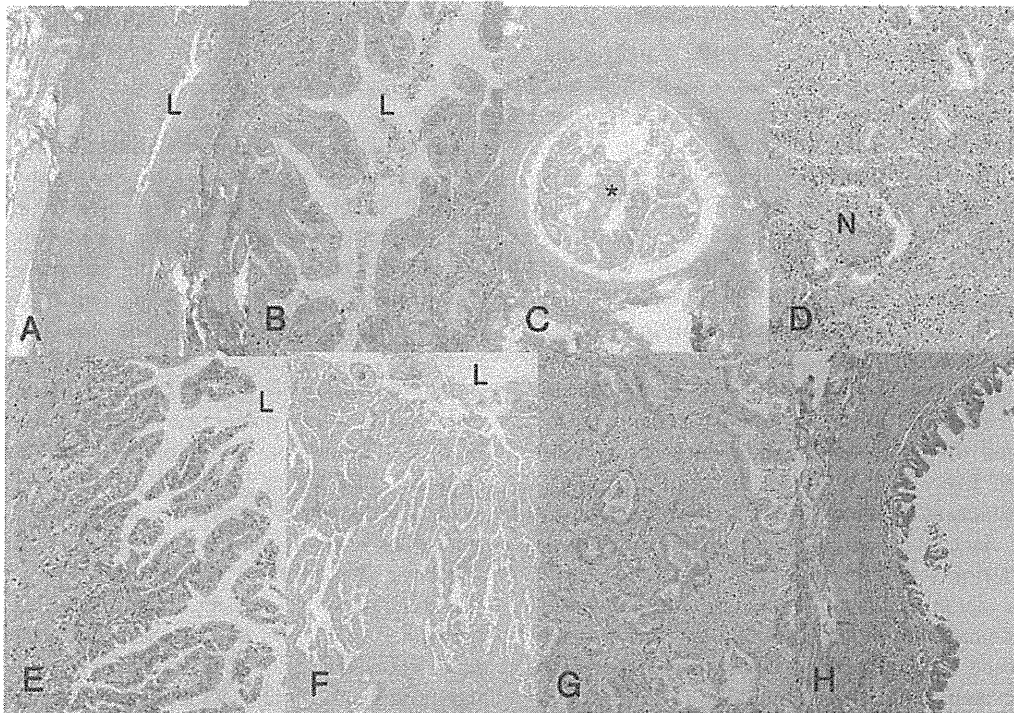
Fig. 2. Pathological findings of the resected specimens.

A, The large bile duct shows fibrous thichening of the duct wall and periductal tissue and erosion of the linig epithelia. L, bile duct lumen. HE. B, BilIN-2 lesion. L, Bile duct lumen. HE. C, The dilated bile duct contains neoplastic lining epithelia and a papillary neoplastic lesion corresponding to IPNB (*). HE. D, Cancer cell infiltrations and perineural invasion are evident in the portal tract. N, Nerve fiber. HE. E, Large bile ducts in the S7 shows papillary projection with atypical features, corresponding to IPNB with severe atypia in the lumen (L). HE. F, The large bile ducts contains a papillary neoplasm in the dilated bile ducts and this neoplasm shows infiltration into the surrounding tissue. L, Bile duct lumen. HE. G, The infiltrated part shows papillotubular adenocarcinoma. HE. H, The lining epithelium shows micropapillary features and stratification of nuclei, corresponding to BilIN-3. HE.

ducts with anastomosis of the left hepatic duct and the jejunum (Roux-en-Y procedure). Pathological examination of the resected specimens showed luminal dilatation, and papillary carcinoma was observed in the ductal lumen (Fig. 2F). This well-differentiated carcinoma infiltrated into the periductal tissue (Fig. 2G), forming a mass (mass-forming type of intrahepatic cholangiocarcinoma). In the dilated bile ducts, BilIN 2/3 lesions were observed (Fig. 2H). The medium and large-sized bile ducts showed chronic bile duct injury including nonspecific degenerative epithelial lesions and fibrosis, and the background liver showed nonspecific reactive changes similar to case 1.

The clinical courses of both patients showed persistent elevation of serum levels of γ-GTP with or without elevated serum levels of AST and/or ALT. Dilatation of the bile ducts without tumor-induced stenosis was detected several years before the diagnosis of cholangiocarcinoma in both patients. The serum level of CA19-9 also increased before cholangiocarcinoma diagnosis in both patients. Eventually, the stenosis of the bile duct, space-occupying lesion and protruding lesion in the bile duct strongly suggested cholangiocarcinoma. Pathological examination showed chronic bile duct injury and neoplastic lesions, such as BilIN and IPNB, in the various sites of the bile ducts, particularly in the dilated bile ducts.

Discussion

Among former and current workers of the offset color proof-printing department of a Japanese printing company, cholangiocarcinoma developed at an extremely high incidence[1,2]. These workers were exposed to high concentrations of chlorinated organic solvents for a prolonged period. Thus, exposure to chlorinated organic solvents, including DCP, is thought to be a highly probable cause of cholangiocarcinoma development. In the 2 patients described here, liver
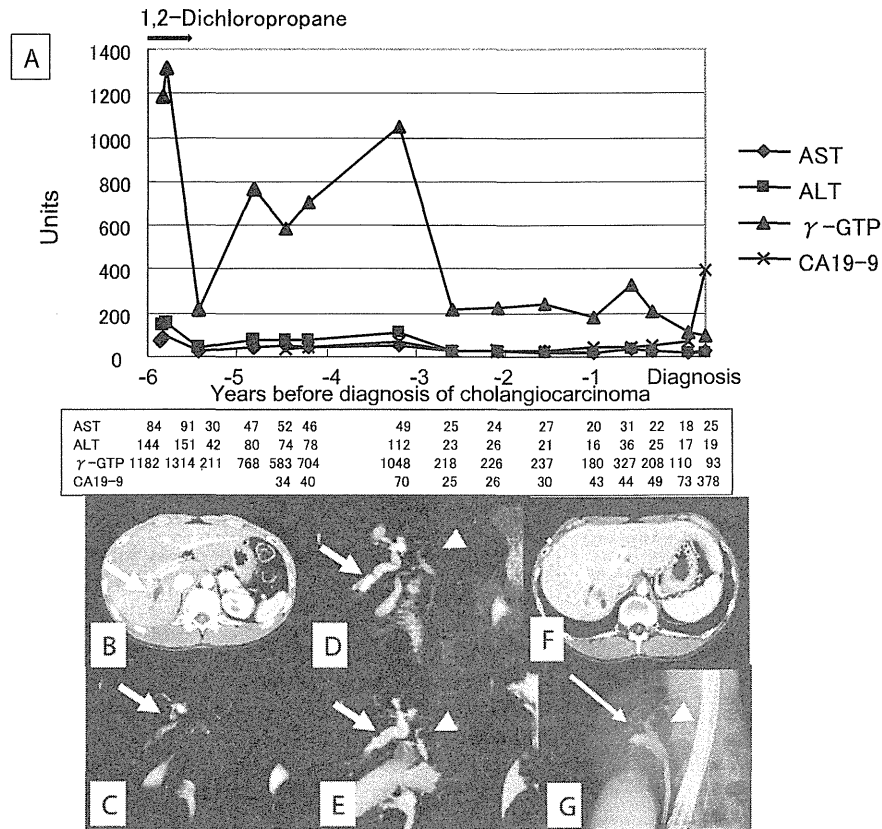
Fig. 3. Changes in laboratory test results and diagnostic imaging presentation before the diagnosis of cholangiocarcinoma in case 2. (A) Laboratory test results. (B) CT at 5 years before diagnosis. (C) MRCP at 3 years and 6 months before diagnosis. (D) MRCP at 8 months before diagnosis. (E) MRCP at 3 months before diagnosis. (F) CT at the time of cholangiocarcinoma diagnosis[2]. (G) ERCP at the time of diagnosis. Short arrows show localized dilatation of the bile ducts. Long arrow shows obstruction of the bile ducts in the posterior segment. The dotted arrow shows a mass-forming cholangiocarcinoma. Arrowheads show the protruded lesion in the hepatic duct.

dysfunction, including an elevated serum level of γ-GTP, was detected during a regular health examination performed several years before the diagnosis of cholangiocarcinoma. The serum levels of γ-GTP, AST, and ALT increased gradually during employment at the company in patient 1. On the other hand, the levels gradually decreased after the second patient's retirement from the company. International chemical safety cards[8] indicate that DCP may affect the liver. These findings suggest that the observed liver dysfunction might be related to DCP exposure.

Pathological examination of the 2 patients showed chronic bile duct injury, including bile duct sclerosis, and neoplastic lesions, such as BilIN 2/3 and IPNB, in various sites of the bile ducts in the noncancerous hepatic tissues of both patients. In a study including all 17 patients with occupational cholangiocarcinoma, the serum levels of γ-GTP were elevated in all

patients, and chronic bile duct injury was observed in all 8 patients for which pathological examination could be performed[2]. These findings indicate that an elevated serum level of γ-GTP might be related to chronic bile duct injury resulting from exposure to DCP. Therefore, at regular health examinations for workers exposed to organic solvents, it is important to monitor the serum levels of γ-GTP, AST and ALT, which may indicate chronic bile duct injury.

Conversely, localized dilatation of the bile ducts without tumor-induced stenosis was an important characteristic observed in the diagnostic imaging of the 2 patients. Similar findings were observed in other patients with occupational cholangiocarcinoma[2]. Pathological examination showed that the dilated bile ducts were related to chronic bile duct injury and neoplastic lesions, such as BilIN and IPNB. These imaging findings, especially of MRCP, in the

2 patients were similar to those observed in PSC[9], including multifocal, intrahepatic bile duct strictures alternating with normal-caliber ducts, which sometimes produce a beaded appearance. It is important to distinguish changes in the bile ducts induced by an organic solvent from PSC. In the 2 patients in this study, diagnostic imaging, including CT and magnetic resonance imaging, eventually showed bile duct stenosis, space-occupying lesions and a protruding lesion in the bile duct. A previous study indicated that occupational cholangiocarcinoma might result from chronic bile duct injuries progressing into precancerous or early cancerous lesions (BilIN and/or IPNB) at various sites of the bile ducts and eventually developing into invasive cholangiocarcinoma[2], which is similar to cholangiocarcinoma in patients with hepatolithiasis, PSC or liver flukes[10-12]. Thus, it is important to monitor changes in the shape of the bile ducts. With regard to imaging analyses, the progression of localized dilatations of the bile ducts should be closely monitored because they probably have malignant potential or malignancy. Further, both mass lesions with or without dilatation of the peripheral bile duct and dilatation and/or stenosis of the bile ducts are important findings for detecting cholangiocarcinoma.

Early cholangiocarcinoma detection is essential because surgery is the only potential curative treatment[13, 14]. Therefore, it is necessary to monitor diagnostic imaging and laboratory test results, including the levels of γ-GTP, AST and ALT and the serum level of CA19-9, for workers with extended exposure to high concentrations of organic solvents.

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Case Study

Severe acute hepatitis in a printing company worker: A case study

Shoji Kubo[1], Koichi Matsuzaki[2], Toshihito Seki[2], Masahiko Ohsawa[3], Shinji Kumagai[4] and Ginji Endo[5]

[1]Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Japan, [2]Department of Gastroenterology and Hepatology, Kansai Medical University, Japan, [3]Department of Diagnostic Pathology, Osaka City University Graduate School of Medicine, Japan, [4]Department of Management of Occupational Safety and Health, University of Occupational and Environmental Health, Japan and [5]Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, Japan

Abstract: Severe acute hepatitis in a printing company worker: A case study: Shoji Kubo, et al. Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine—Objectives: It has been reported that chlorinated organic solvent is a cause of hepatitis. **Methods:** we investigate clinical and pathological findings of a patient with severe acute hepatitis who was exposed to chlorinated organic solvents. **Results:** A 34-year-old man who was exposed to chlorinated organic solvents including dichloromethane, 1,2-dichloropropane, and trichloroethylene, presented with general fatigue, vomiting, and diarrhea. At admission, his laboratory test results showed extremely elevated aspartate aminotransferase (4,872 IU/l), alanine aminotransferase (3,000 IU/l), and lactate dehydrogenase (11,600 IU/l) levels and a prothrombin level below normal (41%). No encephalopathy was noted. These findings were indicative of severe acute hepatitis. Viral hepatitis, autoimmune hepatitis, alcoholic disease, bile duct disease, and viral infection were excluded as causes of hepatitis by clinical, laboratory, and imaging findings. After diagnosis, the patient was administered fresh frozen plasma and glucagon-insulin therapy. Liver function recovered within a few weeks, and a liver biopsy performed 25 days after admission showed the recovery phase after acute liver damage. **Conclusions:** These clinical and pathological findings indicate that exposure to chlorinated organic solvents may have induced severe acute hepatitis in this patient.
(J Occup Health 2015; 57: 87–90)

The toxicities of various chemicals, including organic solvents, have been reported, and methods for protection and occupational exposure limits have been established. Most organic solvents are mainly absorbed into the body via inhalation, ingestion, and the skin, and they often directly affect the eyes, skin, and respiratory tract. Absorbed organic solvents are toxic to the nervous system, liver, kidney, and heart[1, 2]. Hepatic damage after exposure to certain organic solvents has been described[3–9]. Here, we report a case of severe acute hepatitis in a printing company worker who was exposed to various chemicals, including organic solvents such as 1,2-dichloropropane (DCP), dichloromethane (DCM), and trichloroethylene (TCE). This study was performed according to the Declaration of Helsinki (2008), and the patient provided written informed consent.

Case Report

The patient started work in an offset color proof-printing department of a company in 1986. The present building was constructed in 1991. The printing room was located in the first basement floor of the building, with a front room adjacent to the printing room. The ventilation rates of these rooms were very low because of the basement location and the low capacity of the installed ventilation equipment. The patient made printing plates in the front room. In the process, he used high-purity TCE to remove stains from glass plates for about one year just before developing severe acute hepatitis. The amount of TCE he used per day was estimated to be 1-2 l based on his memory. Because no respiratory protection was

provided, he have been exposed to high levels of TCE.

In the printing room, proof-printing workers used large amount of organic solvent cleaner to remove ink residue from a rubber transcription roller. The cleaners was a mixture of gasoline (50% by weight) and 1,1,1-trichloroethane (50%) before 1989; it was a mixture of DCP (50–60%), DCM (15–25%), and 1,1,1-trichloroethane (15–25%) from approximately 1985 to 1992-1993; and it was a mixture of DCP (40–50%), DCM (40–50%) and petroleum hydrocarbons (1–10%) from 1992–1993 to March 1996; and it was nearly pure DCP solvent (98%) from April 1996 to October 2006. Airborne solvent concentrations in the printing room were estimated to be extremely high, which was confirmed in an experiment conducted by the Japanese National Institute of Occupational Safety and Health[10].

Furthermore, because the contaminated air of the printing room flowed into the front room due to positive pressure in the printing room, the airborne solvent concentrations were also estimated to have been high in the front room. Consequently, the patient was also exposed to these chemicals when working in the front room. In addition to making printing plates, he also supervised the progress of printing mainly in the front room but frequently went into the printing room to provide guidance and occasionally to conduct proof-printing. When working in the printing room, he was exposed to high levels of the abovementioned chlorinated organic solvents. Other chemicals such as kerosene and inks were also used in the department.

The patient (at 34 years of age) experienced general fatigue, vomiting, and diarrhea and visited a hospital in December 1996. According to the period of solvent use, he had been exposed to DCP and TCE just before the onset of symptoms and to DCM within 1 year before onset. He had drank 350 ml of beer per day during previous 10 years (<80 g of ethanol daily, which is the lower limit for alcoholic liver disease[11]) and smoked 20 cigarettes/day during the previous 14 years. He had no history of blood transfusion, sometimes took vitamins and aspirin for headaches, and had a body mass index of 18.3.

At admission, the patient was lucid with no abnormal neurological system or respiratory tract findings. The liver was palpable in the right infracostal region at a two finger widths. No dermatitis was noted. The laboratory test results at admission are shown in Table 1. The aspartate aminotransferase (AST, 4,872 IU/l), alanine aminotransferase (ALT, 3,000 IU/l); and lactate dehydrogenase (LDH, 11,160 IU/l) levels were markedly elevated, and the prothrombin test value was 41%. The concentrations of total bilirubin and direct bilirubin were 1.2 mg/dl and 0.2 mg/dl, respectively.

Table 1. Laboratory test results at admission

Red blood cell (×10⁴/mm³)	448
Hemoglobin (g/dl)	13.6
White blood cell (/mm³)	6,800
Prothrombin test (%)	41
Aspartate aminotransferase (U/l)	4,872
Alanine aminotransferase (U/l)	3,000
Alkaline phosphatase (U/l)	140
Total bilirubin (mg/dl)	1.2
Direct bilirubin (mg/dl)	0.2
Lactate dehydrogenase (U/l)	11,160
γ-Glutamyl transpeptidase[a] (U/l)	45
BUN[a] (mg/dl)	18
Creatine[a] (mg/dl)	0.6
Na[a] (mEq/ml)	137
K[a] (mEq/ml)	3.6
Cl[a] (mEq/ml)	105
CRP (mg/dl)	1.9

[a]Tests performed the day after admission.

The serum alkaline phosphatase and γ-glutamyl transpeptidase (γ-GTP) levels were within the reference range. Eosinophilia was not detected. The results for hepatitis viral markers (IgM-HA antibody, hepatitis B e antigen and antibody, hepatitis B surface antigen and antibody, hepatitis B core antibody, hepatitis B virus DNA polymerase, hepatitis C virus [HCV] antibody, HCV RNA, hepatitis D virus antibody, and GBV-C RNA) were negative. The patient was positive for cytomegalovirus IgG and Epstein-Barr (EB) virus IgG antibody, but negative for cytomegalovirus IgM antibody and EB virus IgM antibody, indicating previous infections with cytomegalovirus and EB virus. Serum anti-nuclear antibody and lupus erythematosus (LE) test results were negative. Serum complement (CH50; 50% hemolytic unit of complement), carcinoembryonic antigen, and carbohydrate antigen 19–9 levels were within the reference ranges. Ultrasonography and computed tomography showed mild hepatomegaly but no abnormal findings in the biliary system. From these findings, severe acute hepatitis was diagnosed, and the patient was treated with fresh frozen plasma and glucagon-insulin therapy. Liver function recovered within a few weeks (Fig. 1). A liver biopsy performed 25 days after admission showed size inequality of hepatocytes and multinuclear hepatocytes (Fig. 2). Many phagocytes were present in the hepatic lobules, and mild lymphocytes infiltration and fatty droplets in a few hepatocytes were seen. Fibrous expansion of portal areas and cholestasis were not observed. These findings are indicative of the recovery phase after acute liver damage. The
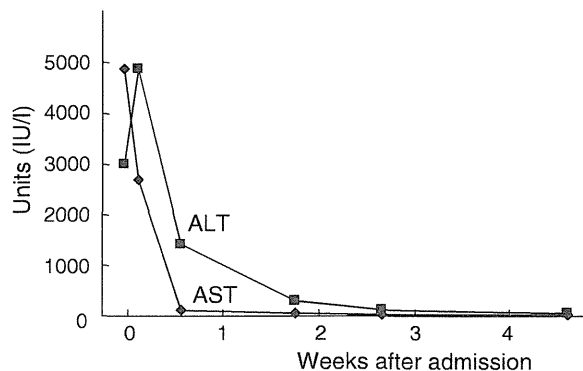
Fig. 1. Changes in alanine and aspartate aminotransferase levels after admission.

Fig. 2. Pathological findings of liver biopsy (hematoxylin and eosin, 20×, and inset, 40×).

clinical course and pathological findings indicate that the patient's severe acute hepatitis was not caused by viral hepatitis, autoimmune hepatitis, alcoholic disease, bile duct disease, or viral infection (cytomegalovirus and EB virus) but instead was caused by exposure to chlorinated organic solvents.

Use of TCE was stopped at the printing company after this event. Since his discharge from the hospital, he has not been exposed to high concentrations of chlorinated organic solvents. The patient is now in good health.

Discussion

Severe acute hepatitis developed in a worker in an offset color proof-printing department of a company. The three criteria for the diagnosis of toxic hepatitis include the following: (1) liver damage after occupational exposure to a substance, considering the patient's work history and current workplace; (2) elevated liver enzyme activity to at least double the upper limit of the reference range; and (3) exclusion of tertiary conditions such as other causes of liver damage[12, 13]. The patient in this study was exposed to various solvents, including DCP, DCM, and TCE. His serum AST, ALT and LDH levels were remarkably elevated at the time of admission to the hospital and improved rapidly after admission (stopping exposure) and treatment. The patient did not have any known cause of severe acute hepatitis, such as viral hepatitis, autoimmune hepatitis, alcoholic liver disease, viral infection (adenovirus, cytomegalovirus, or EB virus), or biliary tract disease.

Acute toxicity cause by DCP, DCM and TCE has been reported by several investigators[3-9]. The International Chemical Safety Cards produced of the International Labour Organization[2] warn that long-term or repeated exposure to DCM or DCP may affect the liver and kidneys. Repeated or prolonged contact of skin with TCE may cause dermatitis. This
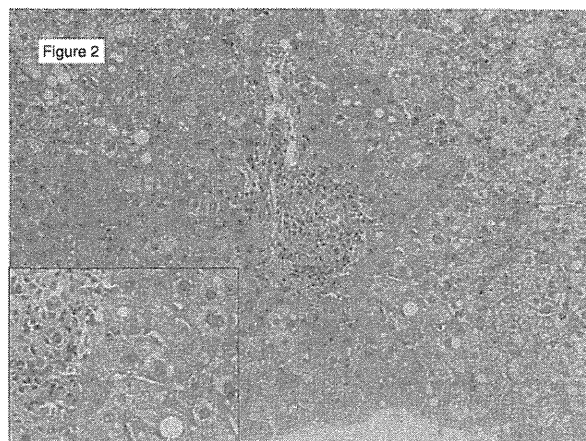
solvent may affect the central nervous system, liver, and kidneys. Recently, Chang et al.[14] reported that exposure to both lead and organic solvents is dangerous, even if exposure to each of the individual components is within the respective permissible limit. In the present case, the patient developed symptoms during exposure to DCP and TCE and within 1 year of exposure to DCM. There were few workers exposed to both DCP and TCE. Therefore, DCP and TCE were suspected to be the causative agents of the severe acute hepatitis in the patient. DCM also might have contributed to the development of hepatitis. In addition, mixed exposure to such organic solvents might synergize towards the development of the hepatitis.

Toxic hepatitis after exposure to chemicals can be divided into three types: hepatocellular, cholestatic, and mixed type[15]. Laboratory test results in this patient showed elevated AST, ALT, and LDH levels and a decreased prothrombin value, whereas the serum alkaline phosphatase and γ-GTP levels were within the reference ranges. These results indicate that the hepatitis in this patient should be classified into as a hepatocellular type. Recently, an outbreak of cholangiocarcinoma occurred in this same company, and chlorinated organic solvents, particularly DCM and DCP, were suspected to play a causative role[16, 17]. In patients with occupational cholangiocarcinoma, laboratory test results showed elevated γ-GTP levels (with or without elevated AST and/or ALT levels), and pathological findings demonstrated chronic bile duct injury and non-injured hepatocytes[17]. In addition, the patients with occupational cholangiocarcinoma were not exposed to TCE. Therefore, the mechanism causing severe acute hepatitis in the present patient seemed to be different from that causing occupational cholangiocarcinoma.

Although this patient's liver function improved rapidly after restricting further exposure and administering fresh frozen plasma and glucagon-insulin therapy, death due to acute liver failure was reported in a patient with suspected TCE exposure[9]. Thus, regular assessment of liver function in workers exposed to such chlorinated organic solvents is important because excessive exposure may induce lethal acute hepatitis.

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Long-term survival and conditional survival of cancer patients in Japan using population-based cancer registry data

Yuri Ito,[1] Isao Miyashiro,[1] Hidemi Ito,[2] Satoyo Hosono,[2] Dai Chihara,[2] Kayo Nakata-Yamada,[1] Masashi Nakayama,[3] Masashi Matsuzaka,[4] Masakazu Hattori,[5] Hiromi Sugiyama,[6] Isao Oze,[2] Rina Tanaka,[4] Etsuko Nomura,[1] Yoshikazu Nishino,[7] Tomohiro Matsuda,[8] Akiko Ioka,[1] Hideaki Tsukuma,[1] Tomio Nakayama[1] and the J-CANSIS Research Group

[1]Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; [2]Division of Epidemiology and Prevention, Aichi Cancer Research Institute, Nagoya; [3]Department of Urology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; [4]Department of Cancer Epidemiology and Community Health, Hirosaki University Graduate School of Medicine, Hirosaki; [5]Department of Cancer Therapy Center, Fukui Prefectural Hospital, Fukui; [6]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima; [7]Division of Epidemiology, Miyagi Cancer Center, Research Institute, Natori; [8]Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

Although we usually report 5-year cancer survival using population-based cancer registry data, nowadays many cancer patients survive longer and need to be followed-up for more than 5 years. Long-term cancer survival figures are scarce in Japan. Here we report 10-year cancer survival and conditional survival using an established statistical approach. We received data on 1 387 489 cancer cases from six prefectural population-based cancer registries in Japan, diagnosed between 1993 and 2009 and followed-up for at least 5 years. We estimated the 10-year relative survival of patients who were followed-up between 2002 and 2006 using period analysis. Using this 10-year survival, we also calculated the conditional 5-year survival for cancer survivors who lived for some years after diagnosis. We reported 10-year survival and conditional survival of 23 types of cancer for 15–99-year-old patients and four types of cancer for children (0–14 years old) and adolescent and young adults (15–29 years old) patients by sex. Variation in 10-year cancer survival by site was wide, from 5% for pancreatic cancer to 95% for female thyroid cancer. Approximately 70–80% of children and adolescent and young adult cancer patients survived for more than 10 years. Conditional 5-year survival for most cancer sites increased according to years, whereas those for liver cancer and multiple myeloma did not increase. We reported 10-year cancer survival and conditional survival using population-based cancer registries in Japan. It is important for patients and clinicians to report these relevant figures using population-based data.

U sually, population-based cancer registries report 5-year relative survival of cancer patients. Nowadays, however, many patients with a variety of cancers can live more than 5 years and thus need more information about their long-term prognosis. Clinicians and medical staff also need information about how long they should follow up their cancer patients and when they can assume patients are cured of cancer. This type of data, based on nationwide databases, was scarce in Japan. Using conventional methods (cohort approach) to calculate cancer survival, we need to follow-up for a certain period (e.g. 5 or 10 years) after diagnosis. Ten-year survival using conventional methods is based on the data of patients who were diagnosed more than 10 years ago; both patients and clinicians need information that is more up-to-date. To solve the problem, an alternative method (period approach) has recently been applied to estimate more up-to-date long-term survival in other countries.[1–5]

Using 10-year survival, we can also report the conditional 5-year survival, as this is known to be a useful statistic for cancer patients, especially for long-term cancer survivors.

Conditional survival is a survival estimate based on data of patients who have survived 1 or more years. As they provide more relevant information for cancer patients, their families, and clinicians, some countries have started to report these figures.[6–9]

Our research project (J-CANSIS, the Japanese CANcer Survival Information for Society), supported by Grant-In-Aid from the Ministry of Health, Labor and Welfare of Japan in the financial year 2013, aimed to analyze recent trends in cancer survival and report long-term survival based on population-based cancer registry data in Japan.

In this study, we aimed to report the latest 10-year survival of cancer patients applying established statistical methods, and demonstrate conditional survival as relevant information for cancer survivors.

Methods

Study design. A total of 1 387 489 cancer cases were provided by the population-based cancer registries of six

prefectures (Yamagata, Miyagi, Fukui, Niigata, Osaka, and Nagasaki) in Japan. These prefectural cancer registries have cancer records with high data quality (% of death certificate only = 3.9–17.7, Table S1.1) and have been used to estimate national statistics for cancer survival in Japan for a long time. This study was approved by the ethical committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) in September 2013, and use of the data was approved by the six prefectural cancer registries.

Data excluded. We excluded data that were registered by death certificate only and in situ cases from the analysis. Numbers of submitted and excluded cases from analysis are shown in Table S1.1. We analyzed 789 600 cases with first, primary, and invasive malignant tumor in a total of six prefectural cancer registries (Table S1.2).

Follow-up of patients. In our research project, we used data of cancer patients who were followed-up for at least 5 years post-diagnosis. Follow-up methods, years of diagnosis, and follow-up for each registry are shown in Table S2. All cancer registries adopted linkage to the death certificate database in the prefecture to confirm the vital status of patients. Patients without linkage to the prefecture death certificate database are considered as alive based on this method. This assumption will be biased and cause overestimation of survival, because if patients die in a prefecture other than that in which they were diagnosed, their death will not be noted. Registries of Yamagata, Fukui, Osaka (for the whole period), and Nagasaki (partial period) additionally confirm the vital status of patients who were considered as alive 5 (and 10) years after diagnosis using linkage to the residential database from the death certificate. This method can complement data on patients who moved outside the prefecture where they were registered. In total, the percentage of lost to follow-up was <4%. We used a subset of the study period in which all prefectures had covered years of diagnosis and follow-up, shown in Figure 1.

We calculated relative survival by sex and cancer site: 23 types for 15–99-year-old patients and four types for childhood and adolescent and young adult (AYA) cancer.

Statistical analysis. In the original research project, we analyzed all the data in Figure 1 to examine trends in cancer survival. Using conventional approaches, we calculated 10-year survival for patients diagnosed between 1993 and 1997 (Fig. 1, solid gray line box) and between 1998 and 2001 (Fig. 1, solid black line box), 5-year survival for patients diagnosed between 2002 and 2006 (Fig. 1, dashed gray line box). In addition, we estimated the 10-year survival for patients followed-up between 2002 and 2006 using the period approach (dashed black line box). In this paper, we report the 10-year survival for patients followed-up between 2002 and 2006 using the period approach and the conditional survival based on the 10-year survival, due to limitations of space. The whole report of this research project, which includes all statistics of 10-year survival by period, sex, and cancer site and the latest 10-year survival and conditional survival by sex, cancer site, age group, and stage at diagnosis is available on the website: http://www. mc.pref.osaka.jp/ocr/data/data2/j-cansis.html (in Japanese).

Relative survival. Relative survival is one of the standard methods to adjust competing causes of death, which is used when we report cancer survival from population-based cancer registry data; the ratio of the observed survival (overall survival) and the expected survival estimated by background mortality (obtained from life tables). We used the complete (single-year-of-age) national population life tables by sex to derive the background mortality of cancer patients.[10] In this study, we applied the maximum likelihood method[11] to estimate relative survival using the strel command in the publicly available Stata program.[12] The concept of relative survival is explained in the Document S1.

Period approach to estimate 10-year survival. We applied the period approach[13–16] to estimate 10-year survival. Usually we

Year of follow-up

Year of Diagnosis	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
1993	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1994		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1995			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1996				0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1997					0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1998						0	1	2	3	4	5	6	7	8	9	10	11	12	13
1999							0	1	2	3	4	5	6	7	8	9	10	11	12
2000								0	1	2	3	4	5	6	7	8	9	10	11
2001									0	1	2	3	4	5	6	7	8	9	10
2002										0	1	2	3	4	5	6	7	8	9
2003											0	1	2	3	4	5	6	7	8
2004												0	1	2	3	4	5	6	7
2005													0	1	2	3	4	5	6
2006														0	1	2	3	4	5
2007															0	1	2	3	4
2008																0	1	2	3
2009																	0	1	2

Fig. 1. Diagnosed and followed-up years of submitted patient data from six Japanese prefectural cancer registries. Bold black figures indicate data from all six prefectures; gray figures mean a limited number of registries have provided data. The solid gray line box shows the data used to calculate 10-year survival for patients diagnosed between 1993 and 1997 using conventional methods (cohort approach). The solid black line box shows the data used to calculate 10-year survival for patients diagnosed between 1998 and 2001 using the cohort approach. The dashed gray line box shows the data to calculate 5-year survival for patients diagnosed between 2002 and 2006 using the cohort approach. The dashed black line box shows the data for period approach we applied in this study.

Table 1. Ten-year relative survival in Japanese cancer patients followed-up between 2002 and 2006 (period approach) and conditional 5-year survival of 5-year survivors (15–99 years old)

Site (ICD-10 code)	Male			Female		
	n	Ten-year relative survival, % (95% CI)	Conditional 5-year survival of 5-year survivors, % (95% CI)	n	Ten-year relative survival, % (95% CI)	Conditional 5-year survival of 5-year survivors, % (95% CI)
Lip, oral cavity, and pharynx (C00–C14)	4214	41.4 (39.4–43.5)	83.3 (80.4–85.9)	1857	53.6 (50.5–56.5)	89.3 (85.8–92.0)
Esophagus (C15)	8265	24.0 (22.7–25.4)	74.7 (71.5–77.6)	1540	32.4 (29.2–35.5)	86.2 (79.8–90.6)
Stomach (C16)	42 930	61.3 (60.7–62.0)	96.8 (96.2–97.3)	20 778	58.2 (57.3–59.0)	96.5 (95.8–97.1)
Colon (C18)	18 514	68.9 (67.9–70.0)	97.2 (96.3–98.0)	16 907	62.8 (61.8–63.8)	96.1 (95.3–96.8)
Rectum (C19–C20)	11 922	60.8 (59.5–62.0)	92.7 (91.5–93.8)	6866	63.2 (61.7–64.7)	94.4 (93.1–95.5)
Liver (C22)	14 230	9.6 (9.0–10.3)	38.0 (35.8–40.2)	6945	9.1 (8.2–10.0)	38.4 (35.1–41.7)
Gallbladder etc. (C23–C24)	4436	18.5 (16.9–20.1)	85.9 (80.6–89.8)	5064	15.5 (14.3–16.8)	87.6 (83.2–90.9)
Pancreas (C25)	6310	4.6 (3.9–5.4)	78.8 (70.2–85.2)	5318	4.8 (4.1–5.6)	81.6 (72.4–88.0)
Larynx (C32)†	2297	73.8 (70.8–76.6)	93.2 (90.3–95.3)	–	–	–
Lung (C33–C34)	30 537	18.1 (17.4–18.7)	79.4 (77.4–81.3)	12 525	31.2 (30.1–32.3)	84.2 (82.1–86.2)
Skin (C43–C44)	2213	86.6 (83.0–89.4)	96.5 (92.6–98.4)	2431	90.4 (87.5–92.6)	97.6 (94.7–98.9)
Breast (C50)	–	–	–	28 301	79.3 (78.6–79.9)	90.5 (90.0–91.1)
Cervix uteri (C53)	–	–	–	5106	66.1 (64.5–67.7)	95.4 (94.2–96.4)
Corpus uteri (C54)	–	–	–	4097	75.6 (73.7–77.3)	96.2 (94.6–97.3)
Ovary (C56)	–	–	–	4163	43.9 (42.0–45.7)	85.6 (83.3–87.6)
Prostate (C61)	19 519	78.0 (75.8–79.9)	89.2 (86.9–91.1)	–	–	–
Kidney, renal pelvis, ureter etc. (C64–C66, C68)	4725	59.3 (57.1–61.4)	90.5 (88.1–92.5)	2374	57.1 (54.2–59.8)	91.5 (88.4–93.9)
Bladder (C67)	5937	74.6 (72.6–76.5)	94.3 (92.4–95.8)	1928	62.8 (59.5–65.8)	95.3 (91.8–97.3)
Brain and CNS (C70–C72, C75.1–C75.3)‡	921	21.5 (18.6–24.6)	75.0 (68.1–80.6)	785	24.4 (21.1–27.8)	84.1 (77.1–89.0)
Thyroid (C73)	1077	87.1 (83.2–90.2)	97.9 (92.9–99.4)	3713	94.8 (93.5–95.9)	99.3 (98.1–99.7)
Malingant lymphoma (C81–C85, C96)	4577	43.1 (41.0–45.1)	86.9 (84.0–89.4)	3925	50.6 (48.4–52.7)	87.1 (84.4–89.4)
Multiple myeloma (C88–C90)	1153	11.4 (8.9–14.3)	41.2 (32.7–49.5)	1090	14.3 (11.6–17.2)	48.4 (40.2–56.1)
Leukemia (C91–C95)	2599	20.5 (18.6–22.5)	80.4 (75.2–84.7)	1894	20.5 (18.4–22.7)	77.4 (71.9–81.9)

†Both sexes combined. ‡Malignant cases only. –, Not applicable; CI, confidence interval; CNS, central nervous system.

use a conventional method (cohort approach) to report cancer survival. However, long-term survival using the conventional method would be outdated, because we need to wait a long time to follow-up, up to 10 years after diagnosis. The period approach was developed to solve the problem and enabled us to estimate up-to-date long-term survival using recently followed-up data (Fig. 1, dashed black line box). Using the period approach, we only used data on patients who were alive at some point during 2002–2006, and the cumulative survival was estimated as the product of interval-specific relative survival values for cohorts of patients who were diagnosed in earlier years (1993–2006). In this study, we estimated the 10-year relative survival of patients who were followed-up between 2002 and 2006.

Conditional survival: figures for cancer survivors. Using the latest 10-year survival estimates, we also calculated conditional 5-year survival, which was 5-year survival with the precondition of having already survived a certain length of time (0–5 years in this report). Conditional 5-year survival for x-year survival is calculated as follows: divide the $(x + 5)$-year cumulative survival rate by the x-year cumulative survival, or calculate $(x + 5)$-year cumulative survival, limited to the x-year survivors, in accordance with other studies.[6–9] We show how the conditional survival estimate was obtained in Document S2, together with examples.

All statistical analyses were carried out using the standard statistical package Stata version 13.1.[17]

Results

We calculated 10-year relative survival based on patients who were followed-up between 2002 and 2006 by sex and cancer site (Table 1, Fig. S1a,b, and Table S3.1–3.3 in detail). For both sexes, over 85% of patients with thyroid and skin cancer survived for more than 10 years. Ten-year survival rates of pancreas and liver cancer patients were <10%. For men, prostate cancer patients also had a good prognosis; 10-year survival was 78%. For women, 10-year survival of breast cancer patients was approximately 80%. Ten-year survival rates of lung, oral cavity, esophageal, thyroid cancer, and malignant lymphoma for women were 8–13% higher than for men. On the other hand, men with stomach, colon, gallbladder, and bladder cancer survived longer than women.

For both child and AYA patients, 10-year survival in males was lower than females. Ten-year survival of leukemia, acute lymphoblastic leukemia, and malignant lymphoma was higher among children than AYAs (Table 2, Fig. S1c,d, and Table S3.1 in detail).

Conditional survival showed different patterns according to cancer site (Fig. 2a,b, Table 1, and Table S4.1–4.3 in detail).

Table 2. Ten-year relative survival in Japanese cancer patients followed-up between 2002 and 2006 (period approach) and conditional 5-year survival of 5-year survivors: Children (0–14 years old) and adolescents and young adults (AYAs, 15–29 years old)

Types of cancer (ICD-10 code)	Children (0–14 years old)			AYAs (15–29 years old)		
	n	Ten-year relative survival, % (95% CI)	Conditional 5-year survival of 5-year survivors, % (95% CI)	n	Ten-year relative survival, % (95% CI)	Conditional 5-year survival of 5-year survivors, % (95% CI)
All sites (C00–C96)						
male	762	73.2 (69.8–76.3)	94.9 (92.7–96.5)	1060	66.0 (62.9–68.9)	94.5 (92.4–96.0)
female	621	79.3 (75.8–82.3)	96.8 (94.7–98.1)	1396	75.3 (72.8–77.7)	94.9 (93.2–96.2)
Leukemia (C91–C95)	470	76.5 (72.2–80.3)	96.1 (93.4–97.7)	277	52.5 (46.1–58.6)	92.3 (83.6–96.4)
ALL	310	78.6 (73.3–83.0)	96.8 (94.7–98.1)	97	36.9 (26.4–47.4)	87.4 (60.7–96.4)
Malignant lymphoma (C81–C85, C96)	125	88.6 (81.4–93.1)	89.7 (82.6–94.0)	262	73.4 (66.7–78.9)	93.6 (87.2–96.9)
Brain and CNS (C70–C72, C75)†	271	58.0 (51.3–64.2)	95.5 (90.5–97.9)	170	58.9 (50.8–66.1)	83.5 (75.2–89.3)

†Malignant cases only. ALL, acute lymphoblastic leukemia (ICD O3-M 9811-9818, 9826, 9835-9837); CI, confidence interval; CNS, central nervous system.

Most cancer sites, such as stomach, colorectum gallbladder, and kidney, showed that after surviving 2–3 years post diagnosis, the conditional 5-year survival approached 100%. Conditional survival of liver cancer and multiple myeloma patients did not increase; even 5 years post diagnosis, conditional 5-year survival was <50%. Prostate and breast cancer patients achieved high 5-year survival from the initial phase after diagnosis; however, survival among those with conditional 5-year survival did not increase. This means that a small proportion of those cancer patients continued to die after diagnosis. For thyroid and skin cancer, 5-year survival at diagnosis was approximately 90%, and conditional 5-year survival of survivors some years after diagnosis was approaching 100%. This means that patients of those cancers generally did not die from those cancers for a long time.

For both male and female childhood cancer, conditional 5-year survival increased over the years (Fig. 2c, Table 2, and Table S4.1–4.3 in detail). Conditional 5-year survival reached more than 95% 5 years after diagnosis. For AYA cancer patients, although the 5-year survival rates at diagnosis were lower than those of children, conditional 5-year survival for 5-year survivors approached 95%.

Discussion

We reported 10-year cancer survival and conditional survival using population-based cancer registry data from six prefectures with high quality and a long history within Japan. These statistics have been required by cancer patients and clinicians in order to know their prognosis for a long time. Nowadays, many patients can be cured of cancer due to improvements in cancer management (early detection and treatment). However, some sites of cancer patients need to be medically followed-up, because of the possibility of recurrence of disease. Publishing this type of statistical data is one way to support cancer patients and clinicians.

Ten-year survival. Ten-year survival rates of thyroid, skin and breast cancer were higher than 85–90%. This means that these patients have a very low possibility of death from those cancers after diagnosis. Cancer at sites that can be diagnosed earlier, such as prostate, thyroid, breast, cervix uteri, colon, rectum, stomach, and bladder, have a relatively better prognosis. In contrast, 10-year survival rates of some cancer sites that

cannot be diagnosed early or for which there is no curative treatment, such as pancreas and liver cancer and multiple myeloma, are very low.

The advantage of survival for lung, oral cavity, and esophageal cancers in females may be partly explained by the differences in smoking prevalence, which was known as a prognostic factor.[18]

Comparing Japanese data with Korean data[3] (1999–2007), 10-year survival of some cancer sites in patients from Korea and Japan was similar. For esophagus, stomach, lung, and prostate cancer, 10-year survival rates in Japan was higher than those in Korea. Long-term survival of thyroid, cervical, corpus, ovarian cancer, and leukemia was higher in Korea than in Japan. These differences may be partly related to variations in the system of early detection and cancer care in both countries.

Compared with Swedish data[2] (period approach of 2005–2009), 10-year survival for most sites of cancer in Japan were higher than in Sweden, especially esophageal, stomach, colorectal, lung, ovarian, cervical, and thyroid cancer which were much higher. However, 10-year survival of multiple myeloma in Japan was slightly lower than in Sweden.

For childhood cancer, compared with the SEER report (US data),[19] although the age range was slightly different (US, 0–19 years; Japan, 0–14 years), 10-year survival was similar for leukemia, ALL, and all sites, except for brain and central nervous system, for which survival was slightly lower in Japan.

Further research is needed to investigate the mechanisms of differences in cancer survival between countries, by comparing distribution of stage at diagnosis and treatment, based on a strictly controlled protocol, as implemented by some international collaborative studies.[20,21]

Conditional survival. We presented conditional survival using up-to-date long-term survival, which was a relatively new approach to demonstrate cancer survival figures for survivors. Using this approach, we were able to provide more relevant information than conventional survival figures. As shown in the supporting information Doc S2 (example 1: stomach cancer), conditional 5-year survival of cancer of digestive organs increased according to years survived and mostly reached 100%. This means that patients who have an unfavorable status (stage) died shortly after diagnosis, and remaining patients who survived more than 5 years have almost the same

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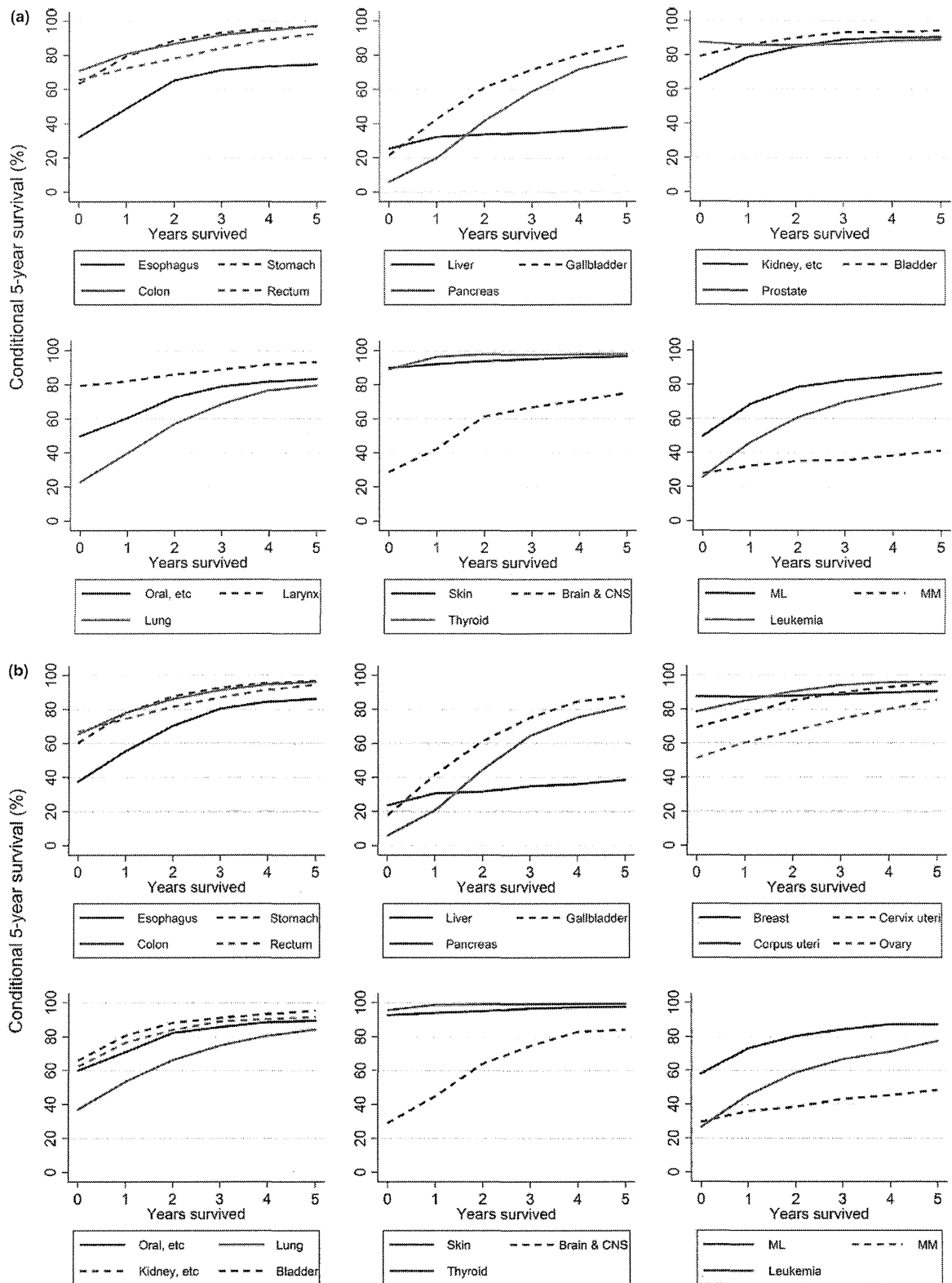
Fig. 2. Conditional 5-year survival for male (a) and female (b) cancer patients in Japan followed-up in 2002–2006. (c) Conditional 5-year survival for childhood and adolescent and young adult (AYA) cancer patients followed-up in 2002–2006. ALL, acute lymphoblastic leukemia; CNS, central nervous system; ML, malignant lymphoma; MM, multiple myeloma.
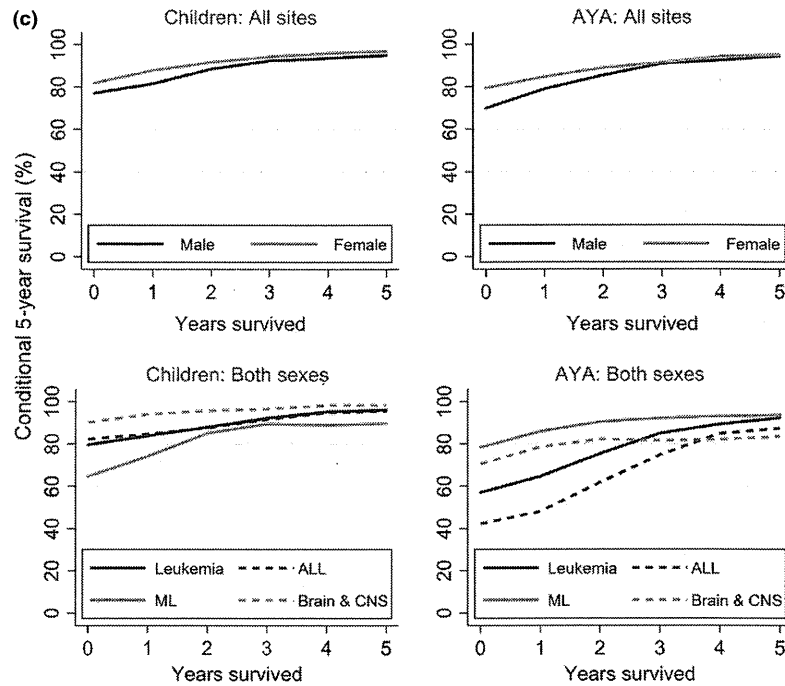
(c)

Fig. 2. (Continued).

probability as the general population. They could therefore be considered as cured.

On the other hand, as we show in example 2 in the supporting information Doc S2, conditional 5-year survival of liver cancer and multiple myeloma did not increase, even some years post diagnosis. This type of figure indicates that a certain number of cancer patients continue to die during follow-up years. Liver cancer patients have a high possibility of recurrence, or die from liver cirrhosis or liver failure related to the hepatitis B or C virus. There is essentially no chance of cure in patients with multiple myeloma so conditional survival remains low even after 5 years from diagnosis.

Although breast cancer showed high survival, a small proportion of survivors continue to die from the cancer, probably due to a recurrence (example 3 in the supporting information Doc S2). Similar figures were shown for prostate cancer. In total, prostate cancer patients had a favorable prognosis as most patients were diagnosed at an early stage by prostate-specific antigen testing. However, some patients who were diagnosed at an advanced stage received hormonal therapy and the treatment was effective for a few years; some patients subsequently developed resistance to the treatment and died after some years.

Limitation of the study. At the time this study was implemented, there were a limited number of prefectural cancer registries that could provide the data to estimate long-term survival using the period approach. Timeliness of registration and follow-up of patients still lagged behind North American and northern European countries. In Japan, the Cancer Registry Law was enacted in December 2013, with the aim of promoting the effective use of cancer registry data for cancer control. The law encourages improvement in the quality of

population-based cancer registry data and provision of the research results for practical use by cancer patients, their families, oncologists, and public health workers. In addition, as all prefectures established prefectural cancer registries in 2012, the quality of cancer registry will improve considerably. In the near future, we will be able to estimate more up-to-date long-term cancer survival using data from many more prefectures in Japan.

We reported 10-year cancer survival and conditional survival using six prefectural population-based cancer registries in Japan. It is important for cancer patients and clinicians to report these relevant figures in succession using unbiased population-based data.

Acknowledgments

Disclosure Statement

The authors have no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1.1. Submitted data and data excluded from analysis.

Table S1.2. Analyzed cases diagnosed between 1993 and 2006 by sex and site.

Table S2. Years of diagnosis, follow-up method, and period of submitted data from each Japanese prefectural cancer registry.

Table S3.1. One-, 3-, 5- and 10-year relative survival of cancer patients by sex and cancer sites: Six selected prefectures in Japan, followed-up in 2002–2006 (all patients: all ages, all stages).

Table S3.2. One-, 3-, 5- and 10-year relative survival of cancer patients by sex and cancer sites: Six selected prefectures in Japan, followed-up in 2002–2006 (by age group: 15–64/65–74/75–99 years or 15–44/45–64/65–99 years).

Table S3.3. One-, 3-, 5- and 10-year relative survival of cancer patients by sex and cancer sites: Six selected prefectures in Japan, followed-up in 2002–2006 (by stage: localised/regional/distant).

Table S4.1. Conditional 5-year survival (%) of 0- to 5-year survivors in Japan (six selected prefectures), patients followed-up in 2002 and 2006 (All patients: all ages, all stages). [Correction added on 7 November 2014, after first online publication: Some data under Childhood Cancer for ALL, Malignant lymphoma, and Brain and CNS have been corrected.]

Table S4.2. Conditional 5-year survival (%) of 0- to 5-year survivors in Japan (six selected prefectures), patients followed-up in 2002 and 2006 (By age group: 15–64/65–74/75–99 or 15–44/45–64/65–99).

Table S4.3. Conditional 5-year survival (%) of 0- to 5-year survivors in Japan (six selected prefectures), patients followed-up in 2002 and 2006 (By Stage).

Fig. S1a. Ten-year relative survival of patients followed-up in 2002–2006 using period analysis, based on data from six selected prefectural population-based cancer registries in Japan (men, 15–99 years old).

Fig. S1b. Ten-year relative survival of patients followed-up in 2002–2006 using period analysis, based on data from six selected prefectural population-based cancer registries in Japan (women, 15–99 years old).

Fig. S1c. Ten-year relative survival of childhood cancer patients followed-up in 2002–2006 using period analysis, based on data from six selected prefectural population-based cancer registries in Japan (both sexes, 0–14 years old).

Fig. S1d. Ten-year relative survival of cancer patients of adolescent and young adults followed-up in 2002–2006 using period analysis, based on data from six selected prefectural population-based cancer registries in Japan (both sexes, 15–29 years old).

Doc. S1. Additional explanations of relative survival (net survival): Why do we use the relative survival approach for population-based cancer registry data?

Doc. S2. Additional explanations of conditional survival: Relationship between conventional relative survival curves and conditional 5-year survival curves.

Journal of Occupational Health

Chemical Exposure Levels in Printing Workers with Cholangiocarcinoma

Kenichi Yamada[1], Shinji Kumagai[2], Toshio Nagoya[3] and Ginji Endo[4]

[1]Occupational Health Research and Development Center, Japan Industrial Safety and Health Association, Japan, [2]Department of Occupational Safety and Health Management, University of Occupational and Environmental Health, Japan, [3]Department of Resources and Environmental Engineering, Waseda University, Japan and [4]Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, Japan

Abstract: Chemical Exposure Levels in Printing Workers with Cholangiocarcinoma: Kenichi Yamada, et al. Occupational Health Research and Development Center, Japan Industrial Safety and Health Association—Objective: This study aimed to identify chemicals used by printing workers with cholangiocarcinoma, as well as the levels of exposure to the chemicals. **Methods:** Information necessary to identify chemicals used by printing workers with cholangiocarcinoma and to estimate chemical exposure concentrations was obtained from the Ministry of Health, Labour and Welfare, Japan. Working environment concentrations of the chemicals in the printing rooms were estimated using a well-mixed model, and exposure concentrations during the ink removal operation were estimated using a near-field and far-field model. Shift time-weighted averages (TWA) of exposure concentrations were also calculated. **Results:** Two workers from each of three small printing plants examined suffered from cholangiocarcinoma, and all six of these workers had been exposed to 1,2-dichloropropane (1,2-DCP) for 10–16 years. The estimated working environment concentrations of 1,2-DCP in the printing rooms were 17–180 ppm and estimated exposure concentrations during the ink removal operation were 150–620 ppm. Shift TWA values were estimated to be 62–240 ppm. Four of the six workers had also been exposed to dichloromethane (DCM) at estimated working environment concentrations of 0–98 ppm and estimated exposure concentrations during the ink removal operation of 0–560 ppm. Shift TWA values were estimated to be 0–180 ppm. Other chlorinated organic solvents (1,1,1-trichloroethane, 1,1-dichloro-1-fluoroethane) and petroleum solvents (gasoline, naphtha, mineral spirit, mineral oil, kerosene) were also used in the ink removal opera-

tion. **Conclusions:** All six printing workers with cholangiocarcinoma were exposed to very high levels of 1,2-DCP for a long term.
(J Occup Health 2014; 56: 332–338)

In May 2012, five employees (including former employees) of an offset proof-printing plant in Osaka, Japan were reported to have suffered from intrahepatic or extrahepatic bile duct cancer cholangiocarcinoma[1]. Subsequently, other workers with cholangiocarcinoma were identified among employees of the plant and the total number reached 17 by the end of 2012[2]. All workers were acknowledged to have developed an occupational disease by the Ministry of Health, Labour and Welfare ("the Ministry"). It is suspected that cancer development was due to high-level and long-term exposure to 1,2-dichloropropane (1,2-DCP)[3, 4].

After this incident became widely known through the mass media, workers with cholangiocarcinoma from other printing plants filed claims for workers' compensation, with the total number of such workers reaching 83 (including the above 17) as of February 2014[5]. With regard to these cases, there are four small printing plants accounted for multiple cases of cholangiocarcinoma (eight workers in total) in addition to the abovementioned Osaka plant. Six workers from three of the four plants were already recognized as having developed an occupational disease by the Ministry[5]. The remaining two workers are currently under review by the Ministry. The workers were in their 30 s to 50 s when they were diagnosed. Given the low prevalence of cholangiocarcinoma in these age groups among the general population[6, 7], the fact that two workers were identified with this cancer in each of the small plants strongly suggests that some