Cancer Science
Japanese Cancer Association JCA
Open Access

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

Key words

Cancer, cancer registry, conditional survival, period analysis, survival

Correspondence

Yuri Ito, Department of Cancer Epidemiology and Prevention, Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3 Nakamichi 1-Chome, Higashinari-ku, Osaka 537-8511, Japan.
Tel: +81-6-6972-1181 (ext. 2310), +81-6-6972-7561 (direct);
Fax: +81-6-6972-7581;
E-mail: itou-yu2@mc.pref.osaka.jp

Funding information

Ministry of Health, Labour and Welfare of Japan

Received June 18, 2014; Revised August 17, 2014; Accepted August 24, 2014

Cancer Sci **105** (2014) 1480–1486

doi: 10.1111/cas.12525

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.

Usually, 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

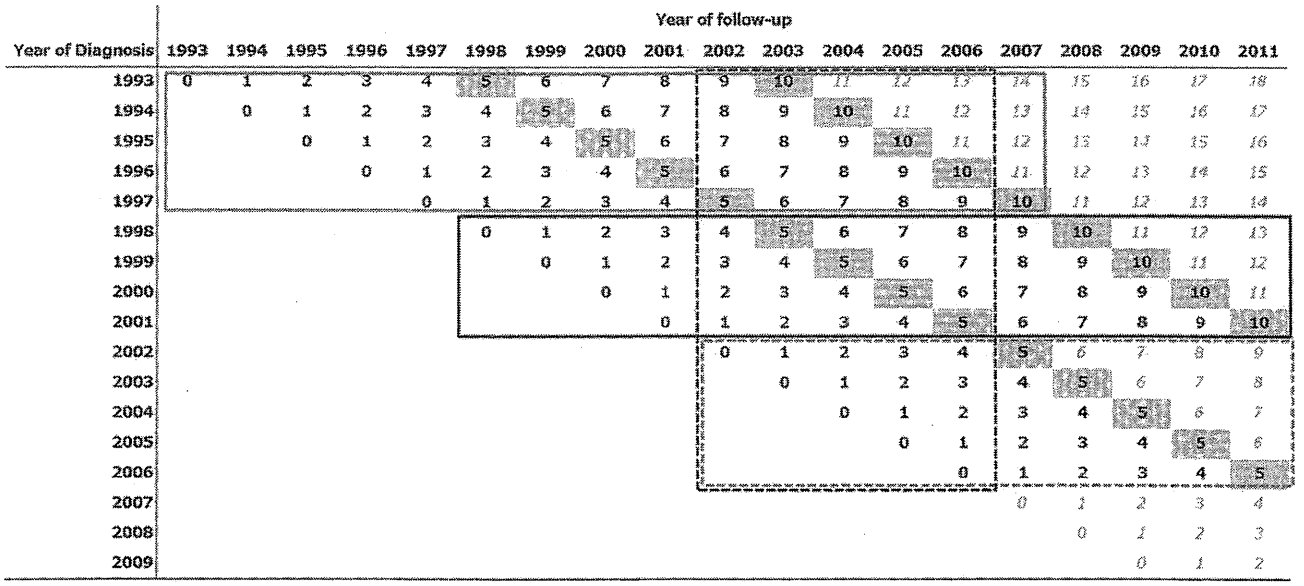

Fig. 1. Diagnosed and followed-up years of submitted patient data from six Japanese prefectural cancer registries. Bold black figures indicate data from all six prefectures; gray figures mean a limited number of registries have provided data. The solid gray line box shows the data used to calculate 10-year 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

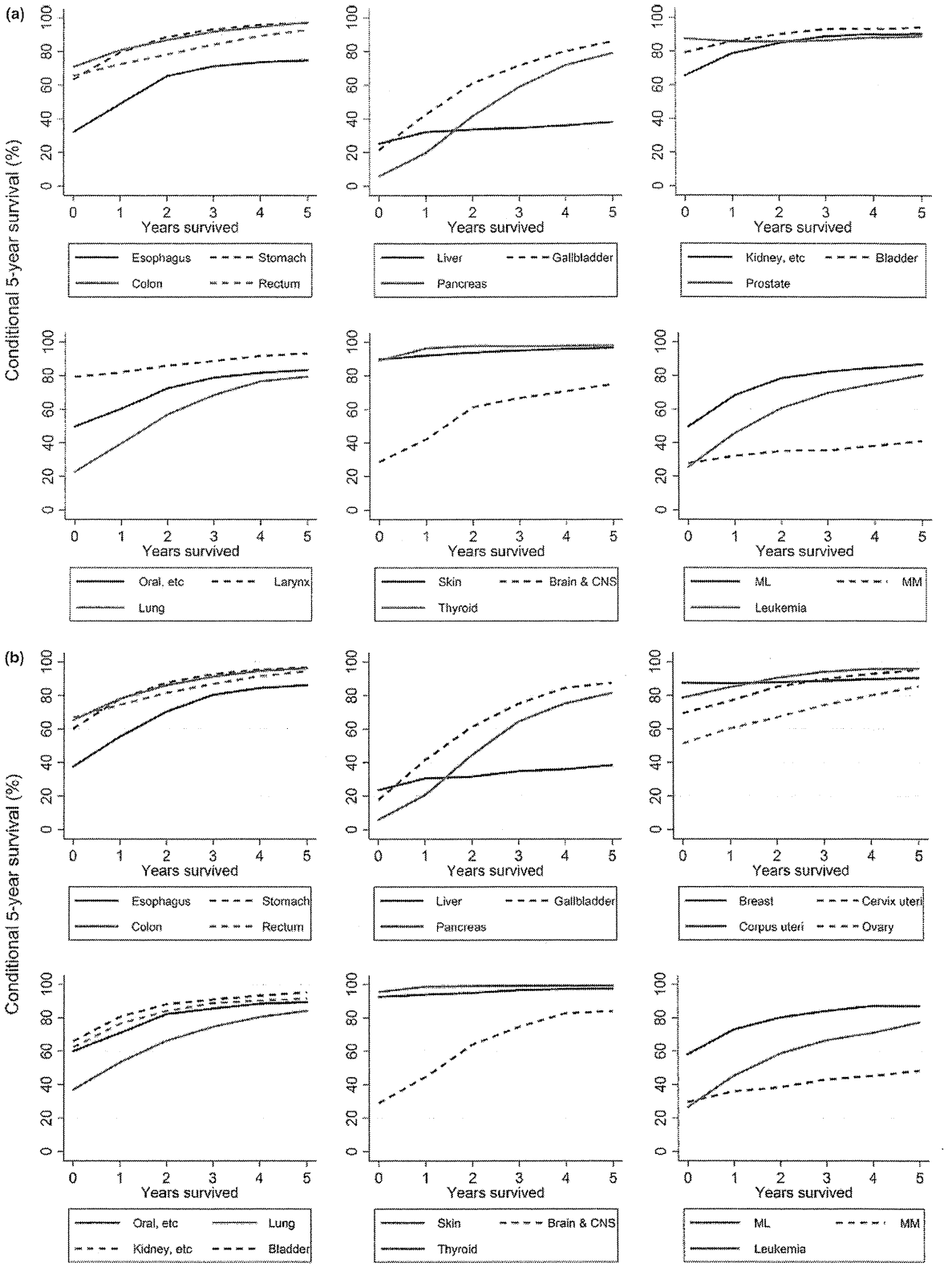

Fig. 2. Conditional 5-year survival for male (a) and female (b) cancer patients in Japan followed-up in 2002–2006. (c) Conditional 5-year survival for childhood and adolescent and young adult (AYA) cancer patients followed-up in 2002–2006. ALL, acute lymphoblastic leukemia; CNS, central nervous system;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

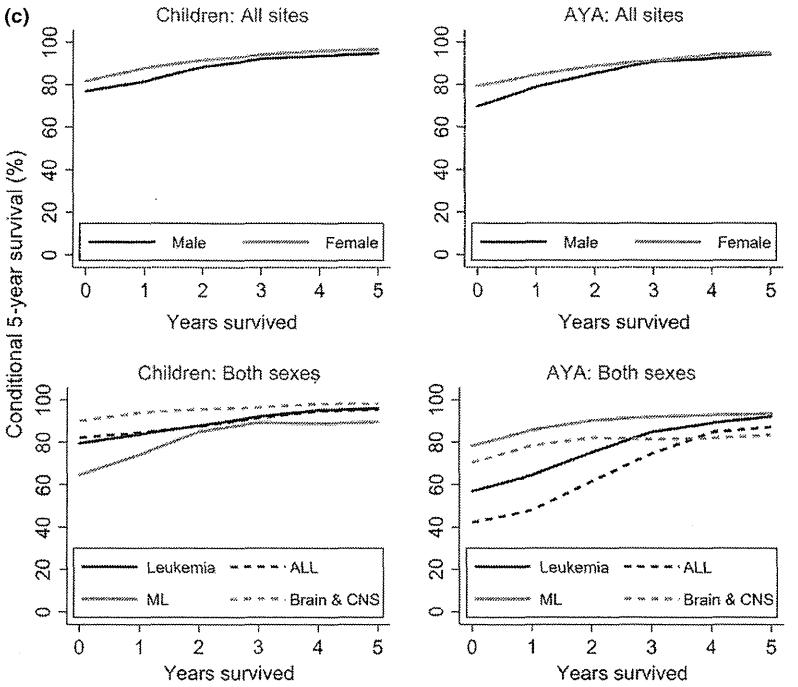

Fig. 2. *(Continued).*

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

We thank the Yamagata, Miyagi, Fukui, Niigata, Osaka, and Nagasaki Cancer Registries for understanding our research concept and providing data and all medical institutes that cooperated by submitting data to population-based cancer registries. We also extend appreciation to Drs Akira Oshima, Nobuhiro Saruki, Tomotaka Sobue, Hideo Tanaka, Midori Soda, and Akiko Ikeda who gave us relevant suggestions on how to present the results, and Drs Hiroji Iwata, Masahiko Yano, and Fumiaki Imamura who commented on the work from a clinical viewpoint. This work was supported by the Ministry of Health, Labour and Welfare of Japan through a Health and Labour Sciences Research Grant for the Third Term Comprehensive Control Research for Cancer, No. H25-008 (for Young Researchers) to Y.I., H.I., T.M. and A.I.

Disclosure Statement

The authors have no conflict of interest.

References

1 Allemani C, Minicozzi P, Berrino F *et al.* Predictions of survival up to 10 years after diagnosis for European women with breast cancer in 2000–2002. *Int J Cancer* 2013; **132**: 2404–12.
2 Talback M, Dickman PW. Predicting the survival of cancer patients recently diagnosed in Sweden and an evaluation of predictions published in 2004. *Acta Oncol* 2012; **51**: 17–27.
3 Lee JY, Jung KW, Park S *et al.* Long-term survival of cancer patients in Korea, 1993–2007: National Cancer Registry Study. *Asian Pac J Cancer Prev* 2010; **11**: 1459–64.
4 Arndt V, Kaatsch P, Steliarova-Foucher E, Peris-Bonet R, Brenner H. Up-to-date monitoring of childhood cancer long-term survival in Europe: central nervous system tumours. *Ann Oncol* 2007; **18**: 1734–42.
5 Zuccolo L, Dama E, Maule MM, Pastore G, Merletti F, Magnani C. Updating long-term childhood cancer survival trend with period and mixed analysis: good news from population-based estimates in Italy. *Eur J Cancer* 2006; **42**: 1135–42.
6 Ito Y, Nakayama T, Miyashiro I, Ioka A, Tsukuma H. Conditional survival for longer-term survivors from 2000–2004 using population-based cancer registry data in Osaka, Japan. *BMC Cancer* 2013; **13**: 304.
7 Yu XQ, Baade PD, O'Connell DL. Conditional survival of cancer patients: an Australian perspective. *BMC Cancer* 2012; **12**: 460.
8 Ellison LF, Bryant H, Lockwood G, Shack L. Conditional survival analyses across cancer sites. *Health Rep* 2011; **22**: 21–5.
9 Merrill RM, Hunter BD. Conditional survival among cancer patients in the United States. *Oncologist* 2010; **15**: 873–82.
10 Ministry of Health, Labour and Welfare. *Abridged Life Tables in Japan for 1962–2011*. Tokyo, Japan: Center for Cancer Control and Information Services, National Cancer Center, 2011.
11 Esteve J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. *Stat Med* 1990; **9**: 529–38.
12 Cancer Research UK Cancer Survival Group, London School of Hygiene and Tropical Medicine. Strel computer program version 1.2.7 for cancer survival analysis. 2009. [Cited 11 Jun 2014.] Available from URL: http://www.lshtm.ac.uk/ncdeu/cancersurvival/tools/index.htm
13 Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. *J Clin Epidemiol* 1997; **50**: 211–6.
14 Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. *Eur J Cancer* 2004; **40**: 326–35.
15 Brenner H, Hakulinen T. Up-to-date long-term survival curves of patients with cancer by period analysis. *J Clin Oncol* 2002; **20**: 826–32.
16 Brenner H, Soderman B, Hakulinen T. Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370,000 cancer patients in Finland. *Int J Epidemiol* 2002; **31**: 456–62.
17 StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP, 2013.
18 Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. *Int J Cancer* 2013; **132**: 401–10.
19 Ward E, Desantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 2014; **64**: 83–103.
20 Coleman MP, Forman D, Bryant H *et al.* Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2011; **377**: 127–38.
21 London School of Hygiene and Tropical Medicine. CONCORD programme. Global surveillance of cancer survival. [Cited 11 Jun 2014.] Available from URL: http://www.lshtm.ac.uk/eph/ncde/cancersurvival/research/concord/index.html

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.

J Occup Health 2014; 56: 332–338

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 operation. **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)

Key words: 1,2-dichloropropane, Cholangiocarcinoma, Dichloromethane, Environment, Printer

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

Received Apr 2, 2014; Accepted May 8, 2014
Published online in J-STAGE Jul 25, 2014
Correspondence to: G. Endo, Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine, Osaka, Japan (e-mail: endog@med.osaka-cu.ac.jp)

occupational agents or factors were responsible for cancer development in these workers. Consequently, identification of the chemicals used during work and estimation of levels of exposure to these chemicals are important. However, the levels of exposure are not directly measurable due to substitution of the chemicals at the plants and closing or relocation of plants. Accordingly, this study aimed to identify the chemicals and estimate the levels of chemical exposure in these workers using mathematical models.

Subjects and Methods

Subjects

The subjects were six printing workers employed at Plants I (Miyagi), II (Fukuoka) and III (Hokkaido), all of which were small-scale plants with fewer than 50 employees. All subjects had cholangiocarcinoma. Subjects A and B were acknowledged by the Ministry to have developed an occupational disease as of June 13, 2013. This was also the case for Subjects C and D as of October 1, 2013, Subject E as of August 1, 2013, and Subject F as of January 31, 2014.

Collection of information regarding working conditions and chemicals used

To identify the chemicals used and estimate chemical exposure concentrations, the following information was obtained from the Ministry: volume and ventilation rate of the printing rooms, type of printing machines operated by the subjects, components of chemicals used to remove ink from the ink transcription roll (blanket) and ink roll, and duration of the ink removal operation. Information on the usage amounts for 1,2-DCP and dichloromethane (DCM) was also obtained from the Ministry.

Estimation of working environment and exposure concentrations

To estimate working environment concentrations of 1,2-DCP and DCM in the printing rooms, we used the following formula derived for a steady state from a well-mixed model[8, 9]:

$$C_{En}=\frac{1{,}000\ G_T}{Q}\times\frac{24.47}{M},$$

where C_{En} is the working environment concentration (ppm), G_T is the generation rate of the chemical in the entire printing room (g/h), Q is the total ventilation rate (m^3/h), and M is the molecular weight of the chemical. Assuming that the entire amounts of 1,2-DCP and DCM were vaporized, the G_T value was calculated by dividing the daily amount of the chemical (g) by the working hours (h).

To estimate exposure concentrations of 1,2-DCP and DCM during the ink removal operation, we used the following formula derived for a steady state from a near-field and far-field model[8, 9], where the near field was assumed to be a sphere, and the radius (r (m)) was determined based on the distance between the generation source and the breathing zone of the worker in the ink removal operation.

$$C_{Ex}=\left(\frac{1{,}000\ G_{Re}}{Q}+\frac{1{,}000\ G_{Re}}{\beta}\right)\times\frac{24.47}{M},$$

where C_{Ex} (ppm) is the exposure concentration during the ink removal operation. G_{Re} (g/h) is the generation rate of the chemical during the removal operation, and its value was calculated by dividing the amount of chemical (g) by the duration of the removal operation (h). β (m^3/h) is the air exchange rate between the near field and far field, and its value was calculated using the following formula, based on the assumption that airflow passed through the surface of the near field at 0.1 m/sec:

$$\beta=0.1\times3{,}600\times2\pi r^2$$

Because the windows of the printing room were closed and air blown from the air conditioners did not directly strike the near field, the airflow rate might have been less than 0.1 m/sec. Accordingly, the airflow rate of air passing through the surface of the near field was assumed to be 0.1 m/sec.

Shift time-weighted averages (TWAs) of exposure concentrations of 1,2-DCP and DCM were calculated based on the assumption that the exposure concentrations during tasks other than the ink removal operation were equal to the working environment concentrations in the printing room.

Results

Plant I

Subject A was a male born in 1969 who had been engaged in offset printing at Plant I from 1988 to 2011 and had been diagnosed with cholangiocarcinoma in 2011. Subject B was a male born in 1974 who had been engaged in offset printing and relief printing at Plant I from 1992 to 2011 and had been diagnosed with cholangiocarcinoma in 2011. Neither of these subjects had any other working history.

Table 1 shows basic information for estimating exposure concentrations of 1,2-DCP and DCM. The plant had two printing rooms. The volume and ventilation rate of Room 1 were 1,260 m^3 and 3,690 m^3/h, respectively, and those of Room 2 were 570 m^3 and 1960 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Removal of ink from the blanket was performed using 1,1,1-trichloroethane (1,1,1-TCE) until 1994, and 1,2-DCP and DCM were used thereafter. Mineral spirit and naphtha were used to remove ink from the

ink roll. The amounts used in the printing rooms were 320–710 g/h for 1,2-DCP and less than 1 g/h for DCM. The amounts used during the ink removal operation were 630–1,800 g/h for 1,2-DCP and less than 4 g/h for DCM.

Considering the distance between the generation source and the breathing zone of the subjects during the ink removal operation, the radius of the near field was determined to be 0.5 m for all machines, except for the rotary relief printing machine. Given the larger working space of the rotary relief printing machine, the radius was determined to be 0.85 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. Working environment concentrations in the printing room were estimated to be 35–42 ppm for 1,2-DCP and less than 1 ppm for DCM. Exposure concentrations during the ink removal operation were estimated to be 280–490 ppm for 1,2-DCP and less than 3 ppm for DCM in Subject A and 310–490 ppm for 1,2-DCP and less than 3 ppm for DCM in Subject B. The shift time-weighted averages (10-h TWAs) of the exposure concentrations were estimated to be 100–170 ppm for 1,2-DCP and less than 1 ppm for DCM in Subject A and 80–120 ppm for 1,2-DCP and less than 1 ppm for DCM in Subject B. These subjects did not use any respiratory protection.

Plant II

Subject C was a male born in 1950 who had been engaged in offset proof printing at Plant II from around 1970 to 1973 and then from 1975 to 1998 and had been diagnosed with cholangiocarcinoma in 1998. Subject D was a male born in 1965 who had been engaged in offset proof printing at Plant II from 1992 to 2008 and had been diagnosed with cholangiocarcinoma in 2008. Although both subjects had worked at other companies, their work at those companies had not involved the use of chemicals.

Table 1 shows basic information. Plant II had two printing rooms. The volume and ventilation rate of Room 3 were 170 m^3 and 3,020 or 1,790 m^3/h, respectively, and those of Room 4 were 180 m^3 and 1,100 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Gasoline was used to remove ink from the blanket until 1985, and the cleaning solvents used thereafter included 1,2-DCP (1986–2008), DCM (1986–1998), 1,1-dichloro-1-fluoroethane (DCFE) (1996–1999), and mineral spirit (1993–1998). Kerosene and mineral oil were used to remove ink from the ink roll. The amounts used in the printing rooms were 230–580 g/h for 1,2-DCP and 0–310 g/h for DCM, while those used during the ink removal operation were 330–1,200 g/h for 1,2-DCP and 0–830 g/h for DCM. The radius of the near field was determined to be 0.5 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. The working environment concentrations in the printing room were estimated to be 17–92 ppm for 1,2-DCP and 0–50 ppm for DCM. The exposure concentrations during the ink removal operation were estimated to be 150–620 ppm for 1,2-DCP and 110–560 ppm for DCM in Subject C, and 170–420 ppm for 1,2-DCP and 0–340 ppm for DCM in Subject D. The shift TWAs (9-h TWAs) of the exposure concentrations were estimated to be 62–170 ppm for 1,2-DCP and 29–150 ppm for DCM in Subject C, and 75–200 ppm for 1,2-DCP and 0–150 ppm for DCM in Subject D. Subjects did not use any respiratory protection.

Plant III

Subject E was a male born in 1946 who had been engaged in offset proof printing at Plant III from 1980 to 1995 and had been diagnosed with cholangiocarcinoma in 2003. Subject F was a male born in 1955 who had been engaged in offset proof printing at Plant III from 1980 to 1995 and had been diagnosed with cholangiocarcinoma in 2013. Subject E had worked at seven other printing plants. Of these, five had used gasoline for the ink removal operation; DCM (0.15 kg/day), *iso*-propyl alcohol, mineral spirit, mineral oil, and polyoxyethylene nonylphenyl ether had been used at another plant, and unspecified chemicals other than 1,2-DCP and DCM had been used at the remaining plant; Subject F had worked at another printing plant, that had not used 1,2-DCP or DCM.

Table 1 shows basic information. Plant III had three printing rooms. The volume and ventilation rate of Room 5 were 150 m^3 and 480 m^3/h, respectively, those of Room 6 were 750 m^3 and 2,400 m^3/h, respectively, and those of Room 7 were 340 m^3 and 1,090 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Gasoline had been used to remove ink from the blanket until 1984, and the cleaning solvents used thereafter included 1,2-DCP and DCM (1985–1995), 1,1,1-TCE (1985–1992), and mineral spirit (1993–1995). Kerosene was used to remove ink from the ink roll. The amounts used in the printing rooms were 320–390 g/h for 1,2-DCP and 160–370 g/h for DCM, while those used during the ink removal operation were 280–350 g/h for 1,2-DCP and 140–320 g/h for DCM. The radius of the near-field was determined to be 0.5 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. The working environment concentrations in the printing room were estimated to be 35–180 ppm for 1,2-DCP and 20–98 ppm for DCM. The exposure concentrations during the ink removal operation were estimated to be 160–290 ppm

Table 1. Basic information for estimating exposure concentration of 1,2-dichloropropane and dichloromethane

Plant	Worker	Calendar year of engagement in printing	Printing room						Ink removal operation					Chemicals used for ink removal operation	
			No.	Volume (m^3)	Ventilation rate (m^3/h)	Number of ventilation (h^{-1})	Amount of 1,2-DCP (g/h)	Amount of DCM (g/h)	Printing machine	r (m)	β (m^3/h)	Amount of 1,2-DCP (g/h)	Amount of DCM (g/h)	For removing from blanket	For removing from ink roll
I	A	1988–1994	1	NI	NI	—	—	—	Rotary offset	NI		—	—	1,1,1-TCE	MS Naphtha
		1995–1998		1,260	3,690	2.9	630	<1		0.5	570	1,100	<4	1,2-DCP, DCM	
		1999–2011					660–710	<1	Sheet-fed offset			630–900	<4		
	B	1992–1994	1	NI	NI	—	—	—	Rotary offset	NI		—	—	1,1,1-TCE	MS Naphtha
		1995		1,260	3,690	2.9	630	<1		0.5	570	1,100	<4	1,2-DCP, DCM	
		1996–2001	2	570	1,960	3.4	360	<1	Sheet-fed relief			900	<4		
		2002–2004					360	<1	Rotary relief	0.85	1,630	1,800	<4		
		2005–2011					320–360	<1	Rotary offset	0.5	570	630–700	<4		
II	C	1970–1973 1975–1985	3	NI	NI	—	—	—	Flatbed offset (proof-printing)	NI		—	—	Gasoline	Kerosene MO
		1986–1990		170	3,020	17.8	230	270		0.5	570	330	400	1,2-DCP, DCM	
		1990–1992			1,790	10.5	230	270				330	400		
		1993					230	270				330	400	1,2-DCP, DCM, MS	
		1994–1995					240–270	280–310				560–720	670–830		
		1996–1998					280–480	56				720–1,200	170	1,2-DCP, DCM, DCFE, MS	
	D	1992	3	170	1,790	10.5	230	270	Flatbed offset (proof-printing)	0.5	570	330	400	1,2-DCP, DCM	Kerosene MO
		1993–1995					230–270	270–310				330–430	400–500	1,2-DCP, DCM, MS	
		1996–1998					280–480	56				430–730	100	1,2-DCP, DCM, DCFE, MS	
		1999					470	0				700	0	1,2-DCP, DCFE	
		2000–2004					470–580	0				700–830	0	1,2-DCP	
		2005–2008	4	180	1,100	6.1	470	0				700	0		
III	E F	1980–1984	5	NI	NI	—	—	—	Flatbed offset (proof-printing)	NI		—	—	Gasoline	Kerosene
		1985–1987		150	480	3.2	390	160		0.5	570	350	140	1,2-DCP, DCM, 1.1.1-TCE	
		1988–1991	6	750	2,400	3.2	390	160				350	140		
		1991–1992	7	340	1,090	3.2	390	160				350	140		
		1993–1995					320	370				280	320	1,2-DCP, DCM, MS	

NI, no information; r, radius of near field; β, air exchange rate between the near field and far field=$0.1\times3,600\times2\pi r^2$; 1,2-DCP, 1,2-dichloropropane; DCM, dichloromethane; 1,1,1-TCE, 1,1,1-trichloroethane; DCFE, 1,1-dichloro-1-fluoroethane; MS, mineral spirit, MO, mineral oil.

Table 2. Estimated working environment concentrations of 1,2-dichloropropane and dichloromethane in printing rooms, exposure concentrations during the ink removal operation and shift time-weighted averages (TWAs)

Plant	Worker	Calendar year of engagement in printing	Printing room			Ink removal operation				Shift TWAs		
			No.	1,2-DCP (ppm)	DCM (ppm)	Printing machine	Duration (h)	1,2-DCP (ppm)	DCM (ppm)	Working hours (h)	1,2-DCP (ppm)	DCM (ppm)
I	A	1988–1994	1	—	—	Rotary offset	NI	—	—	NI	—	—
		1995–1998		37	<1		1.5	490	<3	10	100	<1
		1999–2011		39–42	<1	Sheet-fed offset	3.5	280–400	<3		120–170	<1
	B	1992–1994	1	—	—	Rotary offset	NI	—	—	NI	—	—
		1995		37	<1		1.5	490	<3	10	100	<1
		1996–2001	2	40	<1	Sheet-fed relief	2	440	<3		120	<1
		2002–2004		40	<1	Rotary relief	1	440	<3		80	<1
		2005–2011		35–40	<1	Rotary offset	2.5	310–350	<3		100–120	<1
II	C	1970–1973 1975–1985	3	—	—	Flatbed offset (proof-printing)	NI	—	—	NI	—	—
		1986–1990		17	25		3	150	240	9	62	98
		1990–1992		28	43			170	270		75	120
		1993		28	43			170	270		75	120
		1994–1995		30–32	45–50		1.8	280–360	450–560		80–99	130–150
		1996–1998		34–58	9			360–620	110		100–170	29
	D	1992		28	43		3	170	270		75	120
		1993–1995		28–32	43–50			170–220	270–340		75–94	120–150
		1996–1998		34–58	9			220–370	67		95–160	28
		1999		56	0			350	0		160	0
		2000–2004		56–70	0			350–420	0		160–190	0
		2005–2008	4	92	0			410	0		200	0
III	E F	1980–1984	5	—	—	Flatbed offset (proof-printing)	NI	—	—	NI	—	—
		1985–1987		180	98		6.5	290	160	11.5	240	130
		1988–1991	6	35	20			160	91		110	60
		1991–1992	7	78	43			200	110		150	82
		1993–1995		64	97			160	250		120	180

NI, no information; 1,2-DCP, 1,2-dichloropropane; DCM, dichloromethane.

for 1,2-DCP and 91–250 ppm for DCM in Subjects E and F. The shift TWAs (11.5-h TWAs) of the exposure concentrations were estimated to be 110–240 ppm for 1,2-DCP and 60–180 ppm for DCM in Subjects E and F. They did not use any respiratory protection.

Discussion

The well-mixed model assumes that dilution air and chemicals are quickly dispersed throughout a room so that the same chemical concentration exists at all points in the room[8, 9]. However, as chemical concentrations actually vary from point to point in the room, this assumption is not realistic. Nevertheless, due to a lack of information concerning concentration variability, we had no choice but to use this model to estimate working environment concentrations. On the other hand, the near-field and far-field model has two zones such that different concentrations can be represented in the area surrounding the generation source and a far away area[8, 9]. While the model's assumption that the chemical concentrations are the same at all points in each of the areas is erroneous, the model is

better at estimating the chemical exposure concentration for a worker near the generation source than the well-mixed model. Consequently, we used the near-field and far-field model to estimate chemical exposure concentrations during the ink removal operation. However, because the two models cannot completely express the actual exposure situation, the values reported by the present study should be interpreted as crude estimates.

In the Osaka offset proof-printing plant mentioned above, 17 workers suffered from cholangiocarcinoma, with their ages at diagnosis ranging from 25 to 45 years. All of these workers had been exposed to 1,2-DCP for 6–16 years[2]. The Japan National Institute of Occupational Safety and Health (JNIOSH) conducted an experiment to reproduce the working environment of the proof-printing room of the Osaka plant and reported that the exposure concentration of 1,2-DCP was 60–210 ppm when 1,2-DCP was used at 1,000 g/h[10]. Assuming that the exposure concentration was proportional to the amount of chemicals used (1,700–3,200 g/h) and using JNIOSH data, Kumagai *et al.* estimated the actual exposure concentrations to be 100–670 ppm for the proof-printing[3].

The current study found that two workers in each of the three small printing plants suffered from cholangiocarcinoma, and all six had also been exposed to 1,2-DCP for 10–16 years. The estimated exposure concentrations of 1,2-DCP during the ink removal operation were 150–620 ppm, and the shift TWAs were 62–240 ppm, which were similar levels of exposure to those at the Osaka printing plant. For Subject C, Kumagai previously reported the estimated working environment concentration of 1,2-DCP to be 36 ppm using the well-mixed model[11], which is nearly equal to the current estimated values (17–58 ppm, Table 2). Assuming that the exposure concentration was twice that of the working environment concentration, Kumagai also reported an estimated exposure concentration of 72 ppm[11], which is within the range of the current estimated values (62–170 ppm, Table 2).

The current study demonstrated that all six printing workers with cholangiocarcinoma were exposed to 1,2-DCP at very high levels for a long term. Based on the information obtained from the Ministry, the workers had no chemicals in common that they had been exposed to at high levels other than 1,2-DCP. The 17 workers with cholangiocarcinoma in the Osaka printing plant were also exposed to 1,2-DCP at very high levels for a long term. These findings suggest that high-level and long-term exposure to 1,2-DCP can contribute to the development of cholangiocarcinoma in humans.

Four of the six workers (Plants II and III) were also exposed to high levels of DCM (Table 2), as were 11 of the 17 workers at the Osaka printing plant[2]. An epidemiological study of workers exposed to DCM at a cellulose fiber production plant found a significantly increased mortality risk for biliary tract cancer[12]. These findings suggest that DCM might play a role in development of cholangiocarcinoma. 1,1,1-TCE was used at Plants I and III, and DCFE were used at Plant II, but we could not assess whether these chemicals contributed in any way to the development of cholangiocarcinoma. Petroleum solvents (gasoline, naphtha, mineral spirit, mineral oil, kerosene) were also used in the ink removal operation, but no reports have suggested that exposure to these petroleum solvents might cause cholangiocarcinoma.

Similar to the case of in the Osaka printing plant, the printing method was offset proof printing at Plants II and III. In offset proof printing, the levels of chemical exposure can easily reach high levels, given the high frequency of the ink removal operation and large amounts of chemicals used. In contrast, regular offset printing involves a lower frequency of ink removal and a smaller amount of chemicals used. Thus, in general, the levels of chemical exposure are not considered to be high. However, the estimated exposure concentration at Plant I was very high, due to the fact that the amounts of 1,2-DCP used here were comparable to those used at Plants II and III (Table 1), despite the fact that regular offset printing was being performed. Furthermore, Plant I also conducted relief printing, and the estimated exposure concentration was also very high. These findings demonstrate that high exposure to 1,2-DCP can occur not only in offset proof-printing workers, but also in regular offset printing workers and relief printing workers, if large amounts of 1,2-DCP are used in the ink removal operation.

Conclusion

All six printing workers with cholangiocarcinoma had long-term exposure to very high levels of 1,2-DCP. This suggests that 1,2-DCP can contribute to the development of cholangiocarcinoma in humans.

References

1) Kumagai S, Kurumatani N. Intrahepatic and extrahepatic bile duct cancers among offset proof-printing workers. Proceedings of the 85th Annual Meeting of the Japan Society for Occupational Health; 30 May to 2 June, Nagoya, 2012: 297 (in Japanese).
2) Kubo S, Nakanuma Y, Takemura S, et al. Case series of 17 patients with cholangiocarcinoma among young adult workers of a printing company in Japan. J Hepatobiliary Pancreat Sci 2014; 21: 479–88.
3) Kumagai S, Kurumatani N, Arimoto A, Ichihara G. Cholangiocarcinoma among offset color proof-

printing workers exposed to 1,2-dichloropropane and/or dichloromethane. Occup Environ Med 2013; 70: 508–10.
4) The worker compensation panel of the Ministry of Health, Labour and Welfare. Report of the worker compensation panel on cholangiocarginoma among printing workers. 2013 (in Japanese) .
5) Japan Industrial Safety and Health Association. The number of claims filed and results on biliary tract cancer cases at printing plants. [Online]. [cited 2014 Mar day]; Available from: URL: http://www.jisha.or.jp/english/pdf/Number_of_claims.pdf
6) Matsuba T, Qiu D, Kurosawa M, et al. Overview of epidemiology of bile duct and gallbladder cancer focusing on the JACC study. J Epidemiol 2005; 15: S150–6.
7) Utada M, Ohno Y, Tamaki T, Sobue T, Endo G. Long-term trends in incidence and mortality of intrahepatic and extrahepatic bile duct cancer in Japan. J Epidemiol 2014; 24: 193–9.
8) Nicas M. Estimating exposure intensity in an imperfectly mixed room, Am Ind Hyg Assoc J 1996; 57: 542–50.
9) Yamada K. Estimation of chemical exposure for risk assessment. In: Handbook for risk assessment and risk management of chemical substances and other environment factors.Vol.2. Tokyo (Japan): Japan Association for Working Environment Measurement; 2007. p. 62–108 (in Japanese).
10) National Institute of Occupational Safety and Health, Japan (JNIOSH). Disaster in a printing company in Osaka prefecture. JNIOSH Report A-2012-02, Kawasaki, Japan: JNIOSH, 2012 (in Japanese).
11) Kumagai S. Two offset printing workers with cholangiocarcinoma. J Occup Health 2014; 56: 164–8.
12) Lanes SF, Cohen A, Rothman KJ, et al. Mortality of cellulose fiber production workers. Scand J Work Environ Health 1990; 16: 247–51.

最近の話題 Recent topics

印刷労働者における胆管癌多発事例：新たな職業癌

久保 正二 竹村 茂一 坂田 親治 浦田 順久
野沢 彰紀 西岡 孝芳 木下 正彦 濱野 玄弥[1)]
田中 肖吾[2)] 菅原 寧彦[3)] 中沼 安二[4)] 圓藤 吟史[5)]

索引用語：胆管癌，印刷労働者，塩素系有機溶剤，biliary intraepithelial neoplasia（BilIN），intraductal papillary neoplasm of the bile duct（IPNB）

Key Point

- 塩素系有機溶剤に長期間，高濃度曝露を受けた印刷労働者に，胆管癌が高率に発症した．
- 胆管癌の発見には検診が重要で，その際，γ-GTP を含む肝機能検査，CA19-9 や CEA を含む腫瘍マーカー，腹部超音波検査が有用であり，可能であれば MRCP を施行することが望ましい．
- 画像診断において，腫瘤像，胆管狭窄像，主腫瘍による末梢側胆管拡張像に加えて，限局性の胆管拡張像がみられる．
- 画像所見あるいは病理学的検索から腫瘤形成型肝内胆管癌，胆管内発育型肝内胆管癌，乳頭型肝外胆管癌がみられた．
- 主腫瘍以外の広範囲の胆管に慢性胆管傷害像および biliary intraepithelial neoplasia（BilIN）や intraductal papillary neoplasm of the bile duct（IPNB）などの前癌病変がみられるが，肝硬変や進行性肝病変はみられなかった．
- 環境，臨床像や病理所見から，化学物質による多段階発癌機序を示すことが推測された．
- ジクロロメタンや 1,2-ジクロロプロパンにさらされる業務による胆管癌が，業務上疾病に分類され，新たな職業癌として認識されるようになった．

はじめに

最近，大阪の某印刷事業場のオフセット校正印刷部門の元および現従業員において，胆管癌が多発していることが報告された[1)]．2013 年 3 月に，本事例について厚生労働省による「印刷事業場で発生した胆管がんの業務上外に関する検討会」報告書である「化学物質ばく露と胆管がん発症との因果関係について～大阪の印刷事業場の症例からの検討～」[2)]が発表された．その中で，(1) 胆管癌

1）大阪市立大学大学院肝胆膵外科学 2）石切生喜病院外科 3）東京大学肝胆膵外科・人工臓器移植外科 4）金沢大学医薬保険研究域医学系形態機能病理学 5）大阪市立大学大学院産業医学
Outbreak of cholangiocarcinoma developing in printing company workers : a new type of occupational cancer
Shoji KUBO, Shigekazu TAKEMURA, Chikaharu SAKATA, Yorihisa URATA, Akinori NOZAWA, Takayoshi NISHIOKA, Masahiko KINOSHITA, Genya HAMANO[1)], Shogo TANAKA[2)], Yasuhiko SUGAWARA[3)], Yasuni NAKANUMA[4)] and Ginji ENDO[5)]
1) Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, 2) Department of Surgery, Ishikiriseiki Hospital, 3) Artificial Organ & Transplantation Division, Department of Surgery, University of Tokyo, 4) Department of Human Pathology, Kanazawa University Graduate School of Medicine, 5) Department of Preventive Medicine and Environmental Health, Osaka City University Graduate School of Medicine
Corresponding author：久保 正二（m7696493@msic.med.osaka-cu.ac.jp）

は，ジクロロメタン（dichloromethane；DCM）または1,2-ジクロロプロパン（1,2-dichloropropane；DCP）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，(2) 本件事業場で発生した胆管癌は，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ことが報告された．印刷労働者の胆管癌患者からの労災申請に対して，2013年12月末の段階で大阪の印刷事業場の17例[3]と他地域の9例が労災認定を受けている．さらに，2013年10月1日より「DCMやDCPにさらされる業務による胆管癌」が，労働安全衛生法施行令別表第1の2に掲げる業務上疾病に分類されるようになり，新たな職業癌として認識されるに至った．本事例が明らかとなって以来，著者らは，厚生労働科学研究費補助金「印刷労働者にみられる胆管癌発症の疫学的解明と原因追究」を中心として，本事例の疫学的ならびに臨床病理学的研究を進めてきた[3)~6)]．それに従い，種々の実態が明らかになるとともに，依然として不明な点が少なくないことも判明してきた．本稿では，印刷労働者に多発した胆管癌事例について，現在までの知見と今後の課題について述べる．

胆管癌の動向と危険因子

胆管癌の罹患率は地域によって異なるが，ヨーロッパ，米国およびオーストラリアにおける肝内胆管癌の罹患率が上昇していることが報告されている[7)~9)]．一方，肝外胆管癌の罹患率はむしろ低下傾向にあると報告されている．ICD分類における肝門部胆管癌の取扱いの変更，内視鏡技術や画像診断の進歩による診断能の向上，原発性硬化性胆管炎（primary sclerosing cholangitis；PSC）やウイルス性肝炎の罹患率の増加などが，これらの原因としてあげられている．

胆管癌の危険因子として，従来よりPSC，膵・胆管合流異常，肝内結石症，肝吸虫やニトロソアミンなどの化学物質が報告されてきた[7)~10)]．PSCからの胆管癌発生率は1年当たり0.6～1.5%とされ，肝吸虫による胆管癌はタイ北西部が好発地域であり，同地区のタイ男性での胆管癌発症率は10万人当たり100人前後と極めて高率であることが報告されている．しかし，本邦においてはPSCや肝吸虫に起因する胆管癌症例数は多くない．膵・胆管合流異常では胆嚢および拡張胆管に胆管癌が発生する．肝内結石症ではその7～10%に胆管癌がみられ[11)]，胆管癌が肝内結石症の予後規定因子であると報告されている[12)]．肝内結石症における胆管癌は胆管炎を繰り返す結石存在部位に発生することが知られ，また，同部には胆管癌の前癌病変と考えられるbiliary intraepithelial neoplasia（BilIN）病変がみられることが明らかにされている[13)14)]．C型肝炎，B型肝炎，肝硬変，糖尿病，肥満，飲酒，喫煙，炎症性腸疾患が胆管癌の危険因子であることも報告されてきた[15)~17)]．さらに，International Agency for Research on Cancer（IARC）からは，アフラトキシン，経口避妊薬，プルトニウム，トロトラストが胆管癌の危険因子として報告されている[18)]．一方，IARC monographにおいて，印刷工程やcarbon blackはgroup 2A（possibly carcinogen）に分類されているが，その際に指摘されている癌腫は喉頭・咽頭癌，膀胱癌，腎癌，白血病などであり，胆管癌の報告はみられない[18)]．

印刷労働者にみられた胆管癌の疫学的検討

本件事業場のオフセット校正印刷部門におけるアルバイトを含めた元あるいは現従業員は111名（男性88名，女性23名）である．経過が確認されている101名のうち17名の男性従業員に胆管癌が確認され，9名がすでに死亡している[3)]．2012年末の時点での死亡例は7例であったため，この時点での胆管癌の標準化罹患比は1226，標準化死亡比は633と，極めて高い値であった[19)]．また，

Table 1. 本件事業場で使用されていた化学物質

1,1,1-Trichloroethane	Diethylene glycol monobutyl ether
1,2-Dichloropropane	Propylene glycol monomethyl ether
Dichloromethane	2-Methyl-2,4-pentanediol
Dichlorofluoroethane	3-Methyl-3-methoxybutanol
2-Buthanol	Solvent naphtha (coal)
2-Methylpentane	Xylene
3-Methylpentane	Kerosene
N-Hexane	Mineral oil
Cyclohexane	Hydrocarbons
Isopropyl alcohol	Aromatic hydrocarbons
Ethanol	Inks

この胆管癌17例全員が本件事業場の校正印刷部門に勤務しており，他の部門勤務者では胆管癌の発症はみられなかったことから，この胆管癌発症は業務特異性があると考えられる．一方，17例の胆管癌患者は診断時25歳から45歳と若年であり，全例男性であった．これは，オフセット校正印刷部門のほとんどの従業員が若く，長期間曝露された50歳以上の従業員数がもともと少なかったことが関連している．また，女性従業員に胆管癌発症がみられないのは，同部門で塩素系有機溶剤に高濃度，長期間曝露した女性従業員がわずかであったことが関連していると考えられる．

全国の中小企業を網羅する全国健康保険協会の2009年4月から2012年3月までのレセプトデータを用いて胆管癌受療率を検討したところ，印刷業事業所と全業態での胆管癌受療率に有意差はみられず，中小の印刷業での胆管癌の多発は認められなかった[5]．さらに，大阪府がん登録資料に基づいてICD-10のC22.1（肝内胆管がん）およびC24.0（肝外胆管がん）の地理的分布を検討したところ，大阪府および府内市町村レベル，本件事業場の5km圏，2km圏，1km圏において胆管癌に関連する罹患率の上昇や罹患リスクの上昇はみられず，地域集積性は確認されなかった[6]．

最近，北欧4カ国の職業別疾患登録による解析から，男性印刷関係労働者における胆管癌の発症率は，他の職業の約2倍であったと報告されている[20]．しかし，この印刷関係労働者にはタイピストなども含まれるなど就業内容がさまざまであることや長期間でのデータであり，同期間における胆管癌診断能などの医療状況の変化も考慮した上で，慎重な評価が必要と考えられる．

本件事業場の職場環境

本件事業場では，1,1,1-トリクロロエタン（1,1,1-trichloroethane；TCE），DCMやDCPなどの塩素系有機溶剤を含め，多くの化学物質が使用されていた（Table 1）．中でも，塩素系有機溶剤はインクの洗浄剤として多量に使用されていた．TCE，DCMおよびDCPはGlobally Harmonized System of Classification and Labelling of Chemicals[21]によると，category 2（suspected human carcinogens）に分類され，IARC[18]によるとDCMはgroup 2Bに分類されている．本件事業場での胆管癌17例全員が曝露した有機溶剤はDCPであり，17例中11例がDCMにも曝露していた[3]．また，独立行政法人労働安全衛生総合研究所の報告[22]によると，当時の空調システムを想定した模擬実験では排気量は多かったものの還流率が56%に達しており，汚染された空気が循環するため同作業室は極めて悪い換気状況にあったことが，高濃度曝露につながったと予想されている．また，模擬作業を行ったところ，個人曝露はDCM

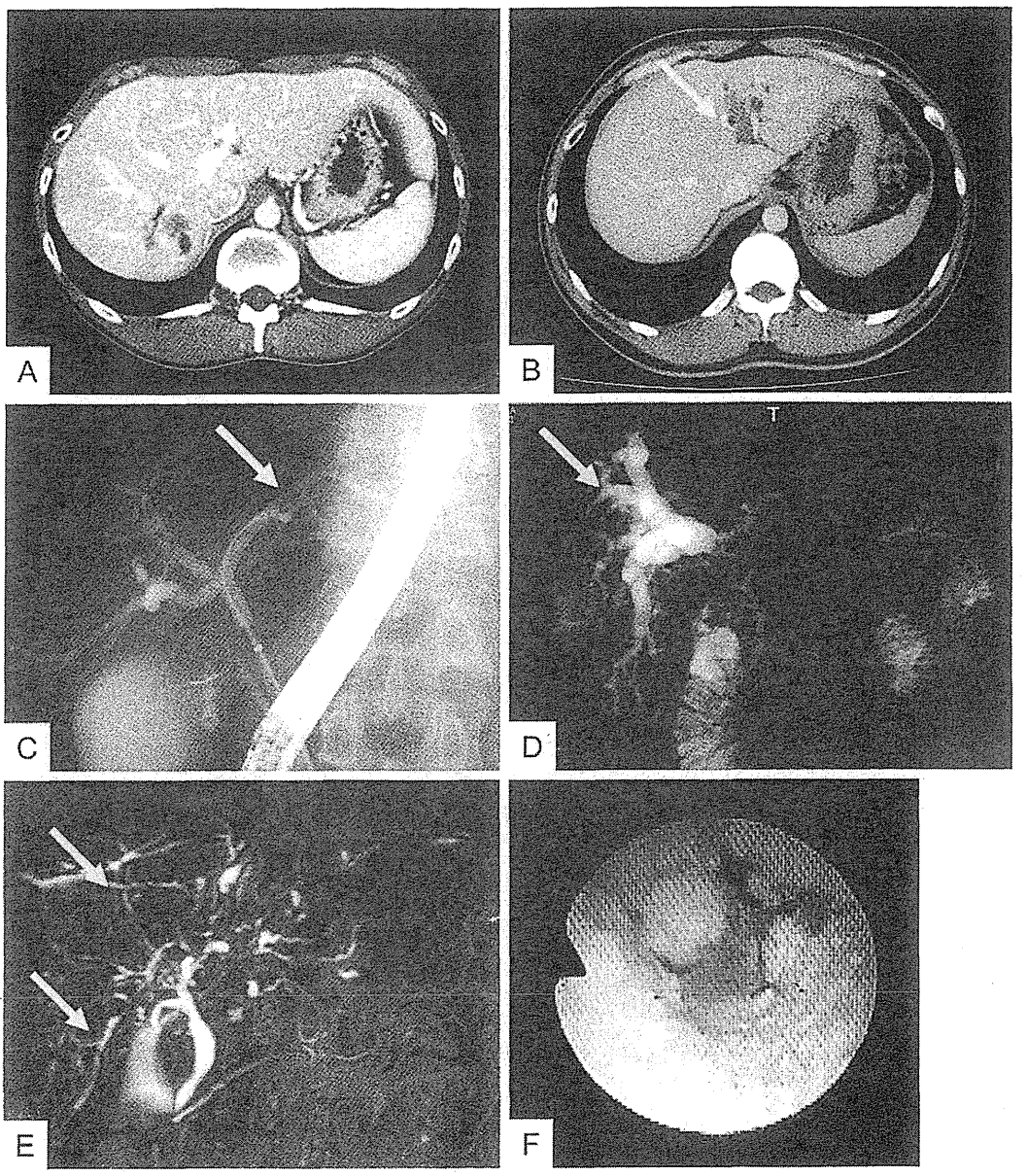

Figure 1. 胆管癌症例の画像診断（文献[3]より一部転載） **A**：肝内腫瘤像（矢印）．**B**：胆管内の腫瘍性病変（矢印）．**C**：胆管狭窄像（矢印）．**D**：腫瘍による末梢側胆管の拡張（矢印）．**E**：腫瘍と無関係な限局性の胆管拡張（矢印）．**F**：胆道内視鏡でみられた胆管内乳頭状病変．

が130～360ppm，DCPが60～210ppmであり，これは米国産業衛生専門家会議（ACGIH）[23]の8時間平均許容濃度（DCM 50ppm，DCP 10ppm）のそれぞれ2.6～7.2倍，6～21倍程度の曝露であったと報告されている．なお，大阪の事業場（本工場，第2工場）においては，TCEは1992年12月まで，DCMは1996年3月まで，DCPは2006年10月まで使用されていた．現在，当時使用されていた同じ溶剤の入手は不可能となっている．

本件事業場における胆管癌症例

前述のように本件事業場の元あるいは現従業員にみられた胆管癌症例は17例で，診断時年齢は25歳から45歳（中央値36歳）であった[3]．業務内容が各従業員によって異なることや，1991年に現在の大阪本工場に移転したこと，大阪の事業場（本工場，第2工場）や東京支社などがあったことから，それぞれの患者での曝露状況の評価は困難

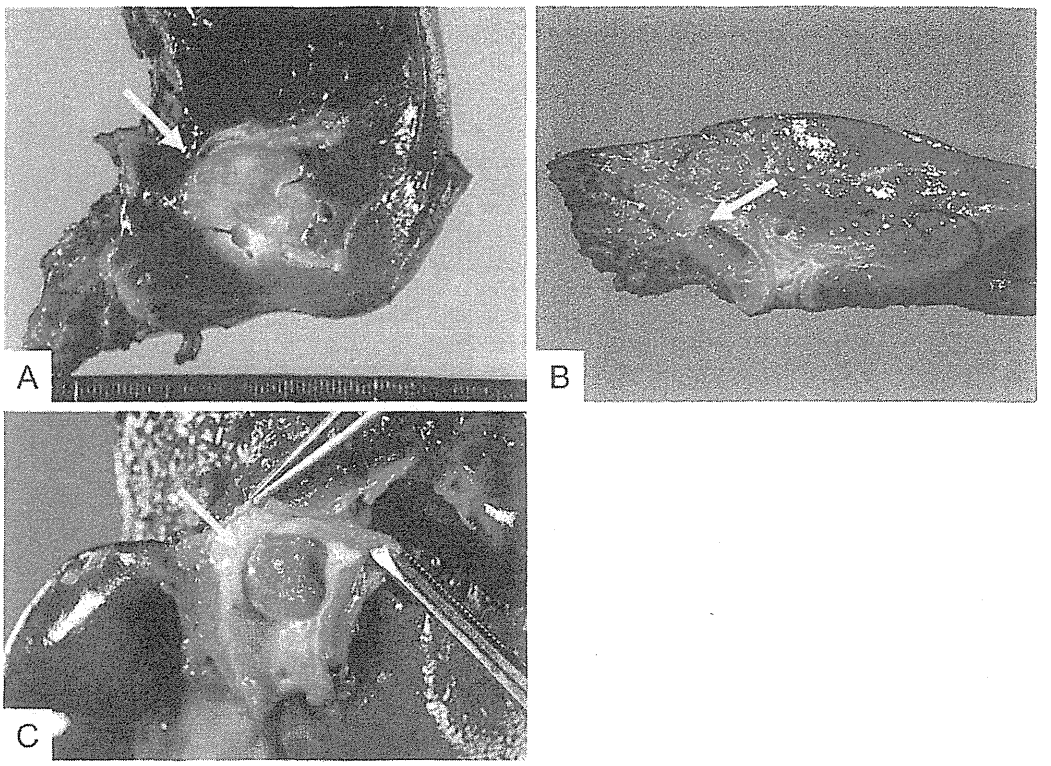

Figure 2. 胆管癌症例の切除標本（文献[3]より一部転載） A：腫瘤形成型胆管癌（矢印），B：胆管内発育型胆管癌（矢印），C：乳頭型肝外胆管癌（矢印）．

な点が少なくないものの，塩素系有機溶剤（大阪の事業場）使用中（2006年10月まで）での勤務期間（曝露期間と推定される）は，6年1カ月から16年1カ月（中央値9年7カ月）であった．また，退職9年7カ月後に胆管癌と診断された症例があり，曝露終了後も長期間を経過してから胆管癌と診断される症例がみられた．胆管癌症例の就業中における急性症状には，嘔気，眩暈，頭痛などの全身症状や皮膚が荒れるなどの皮膚症状がみられた．また，「以前に比較して，就業してから飲酒により酔いやすくなった」や「飲酒すると発疹が出現するようになった」との情報もあった．なお，17例中1例は就業開始1カ月後に急性肝炎のため入院加療を受けていたが，当時の診療録は残されていないため詳細は不明であった．喫煙歴は13例に，アルコール多飲歴は3例にみられた．

17例中5例では腹痛や黄疸などの症状が，11例では検診時の臨床検査値異常や肝腫瘤像の指摘が，1例では副鼻腔炎治療時の肝機能異常が，胆管癌診断のきっかけとなった．胆管癌診断時の臨床検査値をみると，総ビリルビン高値は8例に，ASTやALT高値はそれぞれ13例と14例に，γ-GTP高値は全例にみられた．CEAは11例で，CA19-9は13例で高値であった．HBs抗原およびHCV抗体は全例で陰性で，HBc抗体あるいはHBs抗体は測定された11例中1例のみで陽性であった．腹部超音波検査，CTやMRIにおいて，腫瘤像（Figure 1A），胆管内の乳頭状病変や隆起性病変（Figure 1B）がみられた．Magnetic resonance cholangiopancreatography（MRCP）や直接胆道造影（endoscopic retrograde cholangiopancreatography（ERCP）あるいはpercutaneous transhepatic biliary drainage（PTBD））においては，胆管の狭窄像や閉塞像（Figure 1C）は5例にみられた．主腫瘍による末梢側胆管の拡張像（Figure 1D）は11例にみられた．一方，今回の事例における特徴の1つである主腫瘍と無関係な限局性胆管拡張像（Figure 1E）は5例にみられた．これら胆管の狭

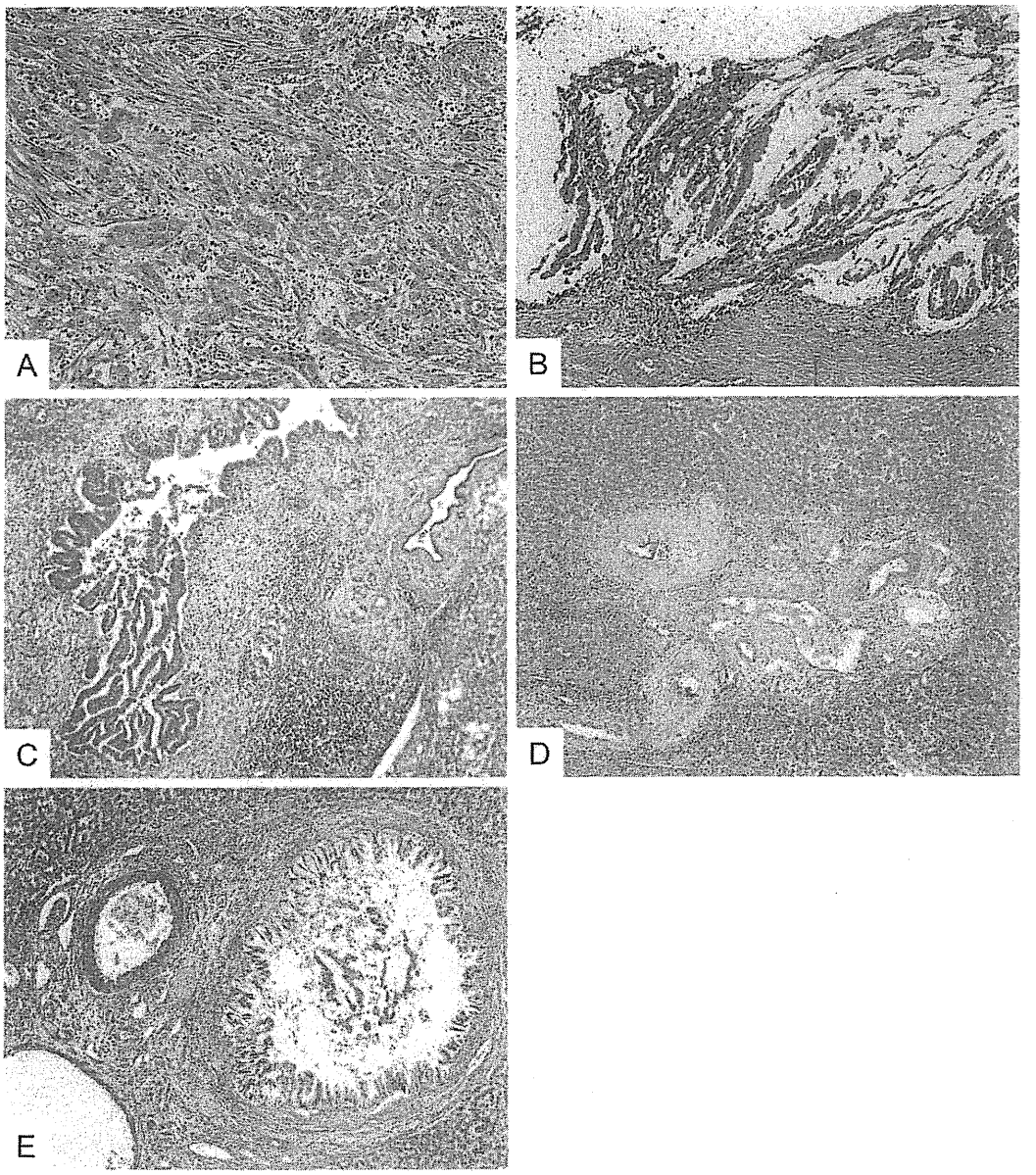

Figure 3. 胆管癌症例の病理組織学的所見　**A**：腫瘤形成型胆管癌．**B**：浸潤型胆管内乳頭状腫瘍（invasive intraductal papillary neoplasm of the bile duct）．**C**：biliary intraepithelial neoplasia．**D**：胆管の硬化像と上皮傷害．**E**：胆管上皮の腫瘍性増殖．

窄像や限局性胆管拡張像はPSCの画像所見と類似しており，実際，当初PSCと診断され経過観察されていた症例がみられた．術中，胆道内視鏡が3例に行われたが，胆管内の不整像や胆管内乳頭状腫瘍（intraductal papillary neoplasm of the bile duct；IPNB）を示唆する乳頭状病変が観察された（Figure 1F）．

17例中10例は肝内胆管癌，5例は肝外胆管癌（肝門部胆管癌を含む），2例が肝内および肝外胆管癌と臨床的に診断されたが，広範囲進展例や後述する前癌病変や早期癌病変が広範囲にみられた症例が多く，分類が困難な症例が少なくなかった．肝内胆管癌12例中8例に腫瘤形成型胆管癌（Figure 2A）が，4例に胆管内発育型胆管癌（Figure 2B）がみられた．肝外胆管癌7例のうち乳頭型（Figure 2C）が5例に，結節型が2例にみられた．2例では診断時にすでに進行癌であったため，原発部位の同定は困難であったが，他の15例の主