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Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane

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Abstract: Risk of bile duct cancer among printing workers exposed to 1,2-dichloropropane and/or dichloromethane: Tomotaka Sobue, *et al*. Department of Environmental Medicine and Population Sciences, Graduate School of Medicine, Osaka University— Objectives: We conducted a retrospective cohort study to examine the risk of bile duct cancer among current and former workers in the offset color proof printing department at a printing company in Osaka, Japan. **Methods:** Standardized incidence ratios (SIRs) between January 1, 1985, and December 31, 2012, were estimated for the cumulative years of exposure to two chemicals, dichloromethane (DCM) and 1,2-dichloropropane (1,2-DCP), using the national incidence level as a reference. In addition, we examined risk patterns by the calendar year in which observation started. **Results:** Among 106 workers with a total of 1,452.4 person-years of exposure, 17 bile duct cancer cases were observed, resulting in an estimated overall SIR of 1,132.5 (95% confidence interval (CI): 659.7−1,813.2). The SIR was 1,319.9 (95% CI: 658.9−2,361.7) for those who were exposed to both DCM and 1,2-DCP, and it was 1,002.8 (95% CI: 368.0−2,182.8) for those exposed to 1,2-DCP only. SIRs tended to increase according to years of exposure to 1,2-DCP but not DCM when a 5-year lag time was assumed. The SIRs were higher for the cohorts in which observation started in 1993−2000, particularly in cohorts in which it started in 1996−1999, compared with those in which it started before or after 1993−2000. **Conclusions:** We observed an extraordinarily high risk of bile duct cancer among the offset color proof printing workers. Elevated risk may be related to cumulative exposure to 1,2-DCP, but there remains some possibility that a portion of the risk is due to other unidentified substances.
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Key words: Bile duct cancer, Occupational cohort, Printing workers

In 2013, Kumagai *et al*. reported an unusual cluster occurrence of cholangiocarcinoma of the bile duct among current and former workers in the offset color proof printing department at a printing company in Osaka, Japan[1)]. Kubo *et al*. further reported in 2014 detailed clinical findings of 17 men with cholangiocarcinoma of the bile duct who worked at the same company and were diagnosed between 1996 and 2012[2)]. Here, we report the risk of bile duct cancer among the same workers according to the cumulative years of exposure to two chemicals, dichloromethane (DCM) and 1,2-dichloropropane (1,2-DCP), using the standardized incidence rate (SIR) with reference to the nationwide incidence. Our goal was to evaluate separately the effect of DCM and 1,2-DCP on the risk of bile duct cancer and further evaluate these dose-response relationships. In addition, we examined retrospectively patterns of the risk of bile duct cancer according to the calendar year in which observation started.

Subjects and Methods

Study population

We identified this study population based on employee lists including one for vital status confirmation and information for current and former workers at a printing company in Osaka, Japan, which we obtained from the Ministry of Health, Labour and Welfare, Japan, and the printing company. The

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Osaka Labour Bureau, Ministry of Health, Labour and Welfare, Osaka, Japan, had started a detailed survey about bile duct cancer at this printing company in April 2012 and had made a list based on this survey. We used the list made as of February 2013. The printing company provided a list of current and past employees for as far back as the inauguration of the company in 1969. After combining these two lists, we confirmed 116 workers (94 men and 22 women) who had worked in the offset color proof printing section at the printing company in Osaka between 1985 and 2012. We excluded 8 workers with missing information for date of birth, date of employment, or date of retirement and 2 workers with unknown vital statuses. The final number of workers included in the analyses was 106 (86 men and 20 women).

Methods of identifying the incident cases of bile duct cancer

The incident cases of bile duct cancer were based on claims of Industrial Accident Compensation Insurance submitted to the Labour Standards Inspection Office, Japan[2]. We confirmed all diagnoses of bile duct cancer by examining copies of medical records, such as imaging findings and/or pathological findings, which the Ministry of Health, Labour and Welfare, Japan, provided to us. These processes were based on the Japanese "Act on the Protection of Personal Information Held by Administrative Organs". The Ministry of Health, Labour and Welfare, Japan, also obtained written informed consent from the workers themselves or the surviving families.

As the incident cases of bile duct cancer were based on claims for Industrial Accident Compensation Insurance, it was possible that there were incident cases other than those individuals who made claims for Industrial Accident Compensation Insurance. Beginning in July 2013, we performed health check-ups for current and former workers in the offset color proof printing department at this company, excluding 17 individuals with bile duct cancer, and we mailed a questionnaire in October 2013 to those who did receive this health check-up. Excluding the 17 individuals with bile duct cancer, we obtained vital status and health information for 76 of 89 workers in the study population based on these health check-ups and questionnaire, and we could not detect any cases of bile duct cancer. Thirteen workers (89 minus 76) who did not received a health examination or provide any answers, we were treated as non-incident cases of bile duct cancer.

Data collection

In this study, we obtained data including existing materials and information, from the Ministry of Health, Labour and Welfare, Japan, and the printing company. After combining these data, we confirmed the data based on our health check-up examination or questionnaire. We checked these data again with the assistance of the company. The information about use of the chemicals at this company was obtained from the Ministry of Health, Labour and Welfare, Japan.

Person-time and cumulative exposure duration

For each worker, person-times were accumulated for the period in which the worker was at risk of development of bile duct cancer, with the period starting either from January 1, 1985, or from the date of employment after 1985 and ending on the date of diagnosis of bile duct cancer, or December 31, 2012, whichever came first.

DCM and 1,2-DCP were used to remove ink from the ink rollers. Both chemicals were used between April 1991 and February 1996, and subsequently only 1,2-DCP was used until October 2006 (Fig. 1). Cumulative exposure years were calculated for each chemical on an individual basis from the date of beginning employment at the company or the date of initial use of the chemical, whichever occurred latest, until the date of retirement or the date of bile duct cancer diagnosis, whichever occurred first. Person-years were accumulated throughout the entire cohort according to years of exposure.

To allow for a possible latent period between exposure and its consequences, cumulative exposure durations were calculated using a range of different lag times (0, 3, and 5 years). Duration of lag time was included in the calculation of cumulative exposure duration at time t , altering the calculation to reflect the possibility of having been exposed at or before time year t minus 0, 3, or 5 years.

We conducted another sub-cohort analysis restricted to workers who were employed in a given calendar year and with observation starting from that point onwards. The years of employment were from 1985 to 2012, and SIRs were calculated for each sub-cohort.

Statistical analysis

To examine the difference between the incidence rates of bile duct cancer in the workers and in the general population of Japan, the SIR, which is the ratio of the observed to the expected incidences, was calculated for bile duct cancer (codes 155.1 and 156.1 in the International Classification of Diseases ninth revision and codes C22.1 and C24.0 in tenth revision). The expected incidence was calculated using age- and sex-specific incidence rates of bile duct cancer in the general population of Japan between 1985 and 2007 for the following 2- or 3-year periods: 1985–

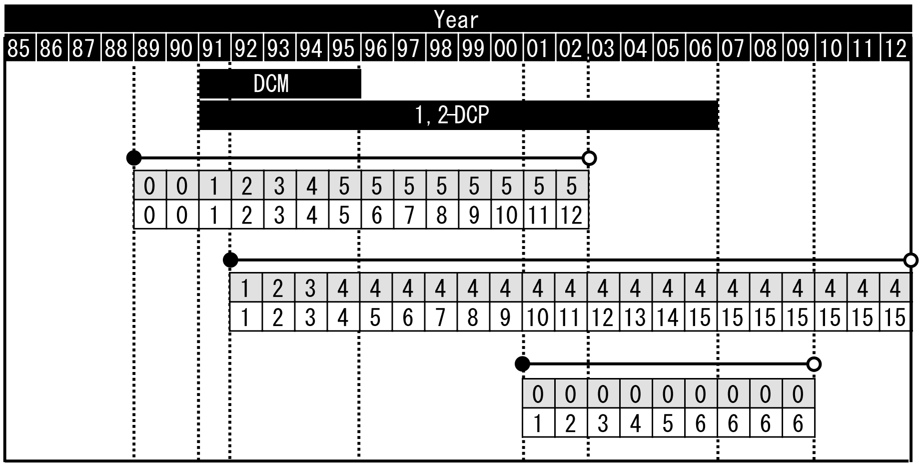

Fig. 1. Three examples of calculation of cumulative years of exposure to DCM and 1,2-DCP Start of observation, black circles; end of observation, white circles; employment durations, black lines; cumulative exposure years to DCM, values in gray squares; cumulative exposure years to 1,2-DCP, values in white squares; DCM and 1,2-DCP denote dichloromethane and 1,2-dichloropropane, respectively.

1986, 1987–1989, 1990–1992, 1993–1995, 1996–1998, 1999–2001, 2002–2004, and 2005–2007[3]. The incidence rates between 2008 and 2011 were assumed to be the same as the latest documented incidence rates in 2005–2007. The 95% confidence intervals (CIs) of the SIRs were calculated using Fisher's exact test, which is accurate when the expected numbers are small[4,5]. To investigate the effect of exposure duration, SIRs were also calculated according to duration of exposure to DCM or 1,2-DCP.

This study was approved by the ethics committee of Osaka City University.

Results

Among 106 workers with a total of 1,452.4 person-years of exposure, 17 bile duct cancer cases (17 males and no females) were observed (Table 1). Age at diagnosis was between 20–29 years for 2 cases, 30–39 years for 11 cases and 40–49 years for 4 cases. When no lag time was assumed, the SIRs were estimated to be 1,132.5 (95% CI: 659.7–1,813.2) for both sexes and 1,163.2 (95% CI: 677.6–1,862.4) for males only. As longer lag times (3 and 5 years) were assumed, the estimated SIR increased slightly. When the cohort was divided according to exposure to DCM and 1,2-DCP (11 cases were exposed to both DCM and 1,2-DCP, 6 cases were exposure to 1,2-DCP only, and no cases were exposed to neither), the estimated SIRs were as follows: 1,319.9 (95% CI: 658.9–2,361.7) for those who were exposed to both DCM and 1,2-DCP and 1,002.8 (95% CI: 368.0–2,182.8) for those exposed to 1,2-DCP only. These SIRs increased slightly as longer lag times were assumed.

Table 2 shows the SIRs according to exposure to DCM and 1,2-DCP when more detailed categories for years of exposure were used. Because of the sparse distribution of bile duct cancer cases, which resulted in many categories with zero cases, the estimated SIRs were higher for the categories with few numbers of positive cases. Although no clear dose-response relationship appeared when assuming a 0- or 3-year lag time, the SIRs tended to increase with years of exposure to 1,2-DCP but not DCM when a 5-year lag time was assumed.

Table 3 shows the SIRs for bile duct cancer for the cohort employed in a specific calendar year, using that year as the time in which observation started. The SIRs were higher for the cohorts employed in 1993–2000, particularly for those employed in 1996–1999, than in those employed before or after 1993–2000.

Discussion

Extraordinarily high SIRs (>1,000) for bile duct cancer were observed in workers exposed to both DCM and 1,2-DCP and to 1,2-DCP only, and these magnitudes were consistent with those reported in a previous study[1]. It was shown that there is no clear difference between the two groups.

In this study, we further tried to evaluate a dose-response relationship according to the years of exposure to DCM and 1,2-DCP. Although no clear finding was observed when we assumed a 0- or 3-year lag time, there was evidence of a dose-response relationship for exposure to 1,2-DCP when a 5-year lag time was assumed. This implies that 1,2-DCP played

Table 1. SIR of bile duct cancer according to the exposure from DCM and 1,2-DCP

Cumulative exposure (years)		Both sexes (n=106)						Men (n=86)						Women (n=20)			
						95%CI						95%CI					
DCM	1,2-DCP	Person-years	Observed	Expected	SIR	Lower	Upper	Person-years	Observed	Expected	SIR	Lower	Upper	Person-years	Observed	Expected	SIR
Lag time=0 year																	
0	0	170.4	0	0.000693	0.0	—	—	149.0	0	0.000692	0.0	—	—	21.4	0	0.000001	0
0	1–16	721.7	6	0.005983	1,002.8	368.0	2,182.8	518.1	6	0.005656	1,060.8	389.3	2,309.0	203.6	0	0.000327	0
1–5	1–16	560.3	11	0.008334	1,319.9	658.9	2,361.7	538.6	11	0.008267	1,330.6	664.2	2,380.8	21.8	0	0.000068	0
Total		1,452.4	17	0.015011	1,132.5	659.7	1,813.2	1,205.7	17	0.014615	1,163.2	677.6	1,862.4	246.7	0	0.000396	0
Lag time=3 year																	
0	0	445.0	0	0.001780	0.0	—	—	372.9	0	0.001768	0.0	—	—	72.1	0	0.000013	0
0	1–16	540.0	6	0.005215	1,150.5	422.2	2,504.2	384.1	6	0.004896	1,225.5	449.7	2,667.4	155.9	0	0.000319	0
1–5	1–16	467.4	11	0.008015	1,372.4	685.1	2,455.7	448.7	11	0.007951	1,383.5	690.6	2,475.4	18.8	0	0.000064	0
Total		1,452.4	17	0.015011	1,132.5	659.7	1,813.2	1,205.7	17	0.014615	1,163.2	677.6	1,862.4	246.7	0	0.000396	0
Lag time=5 year																	
0	0	629.0	0	0.002734	0.0	—	—	522.9	0	0.002701	0.0	—	—	106.1	0	0.000033	0
0	1–16	418.0	6	0.004546	1,319.8	484.4	2,872.7	294.1	6	0.004245	1,413.4	518.7	3,076.4	123.9	0	0.000301	0
1–5	1–16	405.4	11	0.007731	1,422.9	710.3	2,545.9	388.7	11	0.007669	1,434.3	716.0	2,566.4	16.8	0	0.000062	0
Total		1,452.4	17	0.015011	1,132.5	659.7	1,813.2	1,205.7	17	0.014615	1,163.2	677.6	1,862.4	246.7	0	0.000396	0

SIR denotes standardized incidence ratio. DCM and 1,2-DCP denotes dichloromethane and 1,2-dichloropropane, respectively.

an important role in the carcinogenesis of bile duct cancer in this cohort.

Cohort analysis using the calendar year in which observation started revealed an elevated risk in the period of 1993–2000. Although this elevated risk can be explained by exposure to DCM or 1,2-DCP, there is the possibility of risk due to other unidentified chemicals used in this period.

Recent analyses of cancer statistics in Japan have shown that bile duct cancer has not increased in younger age groups in Japan at the national[3] and local levels[6]. Additionally, there is no clear local clustering when analyzing the geographical distribution of bile duct cancer, especially in younger age groups. When focusing on occupational groups, such as printing workers, there is again no evidence of elevated risk of bile duct cancer at the national level according to data from health insurance claims[7]. These findings indicate that the elevated risk observed among the proof printing workers may not apply to all workers in the printing industry. On the other hand, a recent report from Nordic countries observed modestly elevated risk of intrahepatic cholangiocarcinoma among printers and lithographers, which suggests that elevated risk can be observed beyond this specific factory[8].

Although exposure to DCM and 1,2-DCP was associated with an increased risk of bile duct cancer in this cohort, it may be possible that some other substances could play a role. Actually, it was observed that those who had worked during the period of 1996–1999 had higher risks, which implies that some substances or conditions present in this period have some role in increasing the risk of bile duct cancer.

There is a limitation in this study. It is possible that we did not get accurate information because of the historical nature of our data. We believe that we were able to get as accurate information as possible by using employee lists provided by both the Ministry of Health, Labour and Welfare, Japan, and the printing company, performing health check-ups and mailing questionnaire to participants who did not receive a check-up.

In conclusion, we observed an extraordinarily high risk of bile duct cancer among current and former workers in the offset color proof printing department of a printing company in Osaka, Japan. Elevated risk may be related to cumulative exposure to 1,2-DCP, but there remains some possibility of its being also due to other unidentified substances.

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Table 2. SIR of bile duct cancer according to the years of cumulative exposure to DCM and 1,2-DCP

Cumulative exposure (years)		Both sexes (n=106)					
		Person-years	Observed	Expected	SIR	95% CI	
DCM	1,2-DCP					Lower	Upper
Lag time=0 years							
0	0	170.4	0	0.000693	0.0	—	—
0	1–2	409.9	0	0.003015	0.0	—	—
0	3–4	138.7	0	0.000501	0.0	—	—
0	5–6	112.2	1	0.002402	416.4	10.5	2,319.6
0	7–8	47.2	5	0.000042	119,617.2	38,654.4	277,817.4
0	9–10	13.7	0	0.000023	0.0	—	—
0	11–12	0.0	0	—	—	—	—
0	13–14	0.0	0	—	—	—	—
0	15–16	0.0	0	—	—	—	—
1–3	0	0.0	0	—	—	—	—
1–3	1–2	175.9	0	0.005973	0.0	—	—
1–3	3–4	130.9	0	0.000386	0.0	—	—
1–3	5–6	22.8	0	0.000022	0.0	—	—
1–3	7–8	17.8	0	0.000041	0.0	—	—
1–3	9–10	10.5	1	0.000028	35,587.2	904.2	198,987.3
1–3	11–12	4.6	1	0.000015	65,789.5	1,687.9	371,442.9
1–3	13–14	6.9	1	0.000013	76,923.1	1,947.5	428,588.0
1–3	15–16	0.0	0	—	—	—	—
4–5	0	0.0	0	—	—	—	—
4–5	1–2	0.0	0	—	—	—	—
4–5	3–4	31.8	0	0.000100	0.0	—	—
4–5	5–6	27.6	2	0.000074	26,917.9	3,273.1	97,630.9
4–5	7–8	27.5	2	0.000184	10,857.8	1,316.4	39,264.6
4–5	9–10	55.1	3	0.000397	7,566.2	1,558.4	22,083.8
4–5	11–12	18.8	0	0.000192	0.0	—	—
4–5	13–14	15.0	1	0.000232	4,306.6	109.1	24,015.7
4–5	15–16	15.2	0	0.000677	0.0	—	—
Lag time=3 years							
0	0	445.0	0	0.001780	0.0	—	—
0	1–2	321.3	0	0.002817	0.0	—	—
0	3–4	108.7	0	0.000616	0.0	—	—
0	5–6	73.2	1	0.001729	578.3	14.6	3,222.5
0	7–8	29.2	5	0.000033	150,602.4	49,196.6	353,585.8
0	9–10	7.7	0	0.000020	0.0	—	—
0	11–12	0.0	0	—	—	—	—
0	13–14	0.0	0	—	—	—	—
0	15–16	0.0	0	—	—	—	—
1–3	0	0.0	0	—	—	—	—
1–3	1–2	158.0	0	0.005756	0.0	—	—
1–3	3–4	112.6	1	0.000396	2,527.8	63.9	14,069.8
1–3	5–6	19.8	0	0.000017	0.0	—	—
1–3	7–8	14.8	0	0.000043	0.0	—	—
1–3	9–10	7.1	2	0.000028	72,727.3	8,650.3	258,024.6

Table 2. SIR of bile duct cancer according to the years of cumulative exposure to DCM and 1,2-DCP (continued)

Cumulative exposure (years)		Both sexes (n=106)					
		Person-years	Observed	Expected	SIR	95% CI	
DCM	1,2-DCP					Lower	Upper
1–3	11–12	2.0	0	—	—	—	—
1–3	13–14	3.9	1	0.000013	76,923.1	1,947.5	428,588.0
1–3	15–16	0.0	0	—	—	—	—
4–5	0	0.0	0	—	—	—	—
4–5	1–2	0.0	0	—	—	—	—
4–5	3–4	27.0	1	0.000141	7,092.2	179.6	39,515.2
4–5	5–6	20.9	1	0.000123	8,136.7	205.8	45,297.9
4–5	7–8	24.3	1	0.000158	6,329.1	160.2	35,263.6
4–5	9–10	43.1	3	0.000386	7,772.0	1,602.8	22,713.1
4–5	11–12	14.1	1	0.000212	4,710.3	119.4	26,281.3
4–5	13–14	10.8	0	0.000238	0.0	—	—
4–5	15–16	9.2	0	0.000505	0.0	—	—
Lag time=5 years							
0	0	629.0	0	0.002734	0.0	—	—
0	1–2	261.3	0	0.002682	0.0	—	—
0	3–4	87.1	1	0.000870	1,148.9	29.1	6,404.2
0	5–6	48.8	0	0.000961	0.0	—	—
0	7–8	17.2	5	0.000018	271,739.1	90,193.7	648,240.6
0	9–10	3.7	0	0.000014	0.0	—	—
0	11–12	0.0	0	—	—	—	—
0	13–14	0.0	0	—	—	—	—
0	15–16	0.0	0	—	—	—	—
1–3	0	0.0	0	—	—	—	—
1–3	1–2	143.9	2	0.005620	355.9	43.1	1,285.5
1–3	3–4	98.8	1	0.000389	2,572.0	65.1	14,323.0
1–3	5–6	17.8	0	0.000023	0.0	—	—
1–3	7–8	12.4	1	0.000050	19,960.1	506.4	111,432.9
1–3	9–10	3.5	1	0.000007	137,741.0	3,616.8	795,949.1
1–3	11–12	2.0	0	0.000004	0.0	—	—
1–3	13–14	1.9	1	0.000009	110,987.8	2,813.1	619,071.5
1–3	15–16	0.0	0	—	—	—	—
4–5	0	0.0	0	—	—	—	—
4–5	1–2	0.0	0	—	—	—	—
4–5	3–4	23.8	0	0.000130	0.0	—	—
4–5	5–6	20.0	0	0.000117	0.0	—	—
4–5	7–8	22.3	1	0.000170	5,889.3	148.9	32,774.4
4–5	9–10	33.3	4	0.000387	10,341.3	2,816.2	26,464.1
4–5	11–12	11.8	0	0.000237	0.0	—	—
4–5	13–14	8.8	0	0.000258	0.0	—	—
4–5	15–16	5.2	0	0.000332	0.0	—	—

SIR denotes standardized incidence ratio. DCM and 1,2-DCP denotes dichloromethane and 1,2-dichloropropane, respectively.

Table 3. SIR of bile duct cancer for the cohort by the calendar year in which observation started

Year	Both sexes						
	n	Person-years	Observed	Expected	SIR	95% CI	
						Lower	Upper
1985	6	135.4	2	0.001400	1,429.0	173.0	5,160.5
1986	9	210.1	2	0.007419	269.6	32.6	973.8
1987	11	253.1	2	0.007738	258.5	31.3	933.7
1988	13	281.3	4	0.007790	513.5	139.9	1,314.7
1989	16	322.7	6	0.007870	762.4	279.8	1,659.4
1990	18	344.6	7	0.007895	886.7	356.5	1,826.8
1991	18	326.5	7	0.007652	914.8	367.8	1,884.8
1992	20	349.7	8	0.007681	1,041.5	449.7	2,052.2
1993	20	329.3	9	0.002193	4,104.5	1,876.6	7,790.6
1994	25	392.3	11	0.002398	4,588.1	2,289.9	8,207.7
1995	23	335.2	11	0.002168	5,073.8	2,532.8	9,078.4
1996	25	334.4	12	0.002045	5,867.4	3,032.1	10,250.2
1997	31	432.3	12	0.002188	5,484.5	2,833.9	9,580.2
1998	37	508.3	11	0.002253	4,882.8	2,437.3	8,735.9
1999	31	392.3	12	0.001919	6,253.6	3,231.1	10,923.2
2000	28	326.6	12	0.002772	4,329.0	2,236.9	7,561.9
2001	31	335.5	11	0.003915	2,809.9	1,402.6	5,027.3
2002	35	357.4	9	0.005560	1,618.6	740.2	3,072.8
2003	35	324.7	9	0.004217	2,134.4	975.9	4,051.4
2004	32	265.9	7	0.003787	1,848.2	743.2	3,808.5
2005	30	230.4	5	0.003426	1,459.4	473.9	3,405.8
2006	32	214.2	5	0.003191	1,567.2	508.8	3,656.6
2007	36	205.8	4	0.002956	1,353.4	368.7	3,464.7
2008	35	170.8	3	0.002611	1,148.9	236.9	3,357.8
2009	36	139.8	3	0.002244	1,336.8	275.7	3,907.0
2010	33	95.6	3	0.001759	1,705.3	351.7	4,984.2
2011	28	55.3	2	0.001249	1,601.5	193.9	5,784.4
2012	26	25.3	2	0.000560	3,570.2	432.5	12,901.2

SIR denotes standardized incidence ratio.

Printing Company” (PI: Ginji Endo).

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