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Length of employment in workplaces handling hazardous chemicals and risk of cancer among Japanese men

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ABSTRACT

Objectives In Japan, the risk of developing cancer among workers employed in workplaces where chemical substances are handled is unclear. This study aimed to assess the association between cancer risk and employment in workplaces handling hazardous chemicals.

Methods The Inpatient Clinico-Occupational Survey of the Rosai Hospital Group data of 120 278 male patients with incident cancer and 217 605 hospital controls matched for 5-year age group, hospital (34 hospitals) and year of admission (2005–2019) were analysed. Cancer risk in relation to lifetime employment in workplaces using regulated chemicals was assessed while controlling for age, region and year of diagnosis, smoking, alcohol consumption and occupation. Further analysis stratified by smoking history was performed to examine interaction effects.

Results In the longest group of employment in tertiles, ORs were increased for all cancers (OR=1.13; 95% CI: 1.07 to 1.19) and lung (OR=1.82; 95% CI: 1.56 to 2.13), oesophageal (OR=1.73; 95% CI: 1.18 to 2.55), pancreatic (OR=2.03; 95% CI: 1.40 to 2.94) and bladder (OR=1.40; 95% CI: 1.12 to 1.74) cancers. Employment of 1+ years was associated with risk for lung cancer; 11+ years for pancreatic and bladder cancers; and 21+ years for all cancers and oesophageal cancer. These positive relationships were particularly obvious among patients with a history of smoking; however, no significant interaction between smoking and length of employment was observed.

Conclusions There is a high risk of cancer among workers, especially smokers, employed in workplaces handling regulated chemicals in Japan. Thus, future measures for chemical management in workplaces are needed to prevent avoidable cancers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Occupational exposure to chemical carcinogens is an established risk factor for cancer development.
⇒ However, in Japan, the risk of cancer among workers in workplaces handling chemical substances is yet to be clarified.

WHAT THIS STUDY ADDS

⇒ This study found a high risk of cancer among workers in workplaces handling regulated chemicals in Japan, and the risk was even higher among smokers.
⇒ To our knowledge, this is the largest case–control study on cancer in Japan, with information on the lifetime handling of hazardous chemicals among workers, to date.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings provide baseline evidence for establishing measures for chemical management in these workplaces to prevent avoidable cancers.

INTRODUCTION

Occupational exposure to chemical, physical, biological and circumstantial carcinogens is a well-established risk factor for cancer development. According to estimates in several developed countries, between 2% and 5% of the overall cancer burden is attributed to occupational exposures, annually.[1–3] In Japan, 1 million newly diagnosed cancer cases are reported per year; hence, it is expected that approximately 20 000–50 000 of cases are attributable to occupational exposures annually. However, only around 1000 cancer cases reported each year are certified for workers' compensation for occupational diseases, including the majority of those caused by asbestos.[4] Such discrepancies have been observed worldwide, and this indicates that occupational cancers may be overlooked in cancer diagnosis as lifestyle-related behaviours are more frequently considered than occupational exposures, though both have a role to play.[5]

The large number of chemicals used in workplaces and the small proportion of known hazardous chemicals make it challenging to identify occupational cancers. Approximately 100 000 chemicals are estimated to be commodities throughout the world, and each year, more chemicals are being developed for commercial use.[6] The International Agency for Research on Cancer (IARC) Monographs lists 122 Group 1 (carcinogenic to humans), 93 Group 2A (probably carcinogenic to humans), 319 Group 2B (possibly carcinogenic to humans) and 501 Group 3 (not classifiable as to its carcinogenicity to humans) agents as carcinogens, to date.[7] Chemical risk assessment in the workplace should be implemented for all chemicals; however, it is

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practically difficult to assess every single exposure in the workplace in the context of cancer prevention. Naturally, workers who engage in workplace handling of known hazardous chemicals are more likely to be exposed to unknown components, some of which might be carcinogenic. Several occupational cancers that have occurred in Japan over the past decade were reportedly caused by chemicals that were not regulated at the time of the outbreak.[8 9]

We previously reported that the number of types of chemical hazards in lifetime occupation was associated with an increased risk of all cancers, including lung and pancreatic cancer, after adjusting for potential confounders.[10] The current study aimed to examine the association between cancer risk and length of employment in workplaces handling hazardous chemicals among Japanese adults. We hypothesised that workers who have been employed longer in workplaces that handle known hazardous chemicals also are more likely to have handled chemicals unknown to be carcinogenic and thus have a higher risk of cancer. If certain types of cancer are more common than in workers who do not handle hazardous chemicals, this would be the basis for reconsidering chemical health management in the workplace. Given that men are four to five times more likely to work in primary production jobs with higher occupational exposure than women,[11] we examined cancer risk in this study.

MATERIALS AND METHODS

Study design and setting

This multicentre hospital-based matched case–control study was conducted using the Inpatient Clinico-Occupational Survey of the Rosai Hospital Group (ICOD-R) database. The ICOD-R has been conducted by the Japan Organization of Occupational Health and Safety (JOHAS) since 1984. It collects clinical, occupational and lifestyle information of inpatients from 34 regional core hospitals throughout Japan, with more than 3.6 million inpatients participating to date. Details of this survey have been described in previous studies, and these studies have shown relationships between occupational factors and cancer,[12–14] cardiovascular diseases,[15 16] diabetes,[17] and digestive[18] disorders.

Clinical data were based on a summary of inpatient treatment for each admission recorded by physicians. The physicians registered a maximum of seven definitive diagnoses, which were eventually coded using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Occupational and lifestyle information was based on interviews conducted by trained surveyors at each hospital. The participants' current and past three occupations, including age at the start and end of each employment, were coded using the Japan Standard Occupational Classification (JSOC) published by the Japanese Ministry of Internal Affairs and Communications.[19]

Participants were also interviewed about whether they had undergone special medical examinations, which are mandatory for those employed in workplaces that handle hazardous chemicals designated by the government's Industrial Safety and Health Law,[20] while they were engaged in their respective employment. Lifestyle habits, including smoking and alcohol consumption, were also recorded. Clinical and occupational history completion rates were 100% and 75%, respectively. Men with occupational histories were included in the current analysis. The inclusion criteria were age >20 years at the time of admission between 1 April 2005 (fiscal year (FY) 2005) and 31 March 2020 (FY 2019). Among the 120 278 male cases with all cancers analysed, 4499 (3.7%) were employed in workplaces handling hazardous chemicals, compared with 235 (0.3%) of the 79 628 female cases with all cancers. The study was limited to men because of the limited number of women in workplaces handling hazardous chemicals. Finally, 579 407 men were included in the analysis.

This study was according to the tenets of the Declaration of Helsinki. Access to the data set was provided via a research agreement between the study authors and JOHAS. Written informed consent was obtained from each patient prior to the completion of the questionnaires.

Cases and controls

The cases were defined as patients with a primary definitive diagnosis of all cancers (ICD-10, C00–C97; n=120 278). Cancers were also examined according to the site of the following organs: lung (ICD-10, C34; n=14 437), oesophagus (ICD-10, C15; n=3306), stomach (ICD-10, C16; n=19 462), colon and rectum (ICD-10, C18–C20; n=18 196), liver (ICD-10, C22; n=6958), biliary tract (ICD-10, C23–C24; n=2469), pancreas (ICD-10, C25; n=3566) and bladder (ICD-10, C67; n=7397). All cases were considered incident cancer because those with a history of cancer were excluded from the clinical information (ICD-10, Z85). If a participant had incident cancer in the course of multiple hospitalisations over the 15-year period, the patient was selected as a case and would be excluded from being an eligible control.

Controls were randomly matched among men admitted to the same hospital in the same year within the same 5-year age strata. Controls were those with no history of cancer or no cancer-related hospitalisation during the period (2005–2020) and who were hospitalised for diseases that were not considered to be related to occupational factors in previous studies.[10 12–14] Controls were those with no history of cancer or no cancer-related hospitalisation during the period (2005–2020) and who were hospitalised for a disease that was not considered to be related to occupational exposure to chemical substances. The common reasons for hospital admission for the controls were: infectious and parasitic diseases (ICD-10, A00–B99); diseases of eye and ear (ICD-10, H00–H95); diseases of circulatory system (ICD-10, I00–I99); diseases of digestive system (ICD-10, K00–K95); diseases of blood and immune mechanism (ICD-10, D50–D89); endocrine, nutritional and metabolic diseases (ICD-10, E00–E89); diseases of genitourinary system (ICD-10, N00–N99); diseases of musculoskeletal system (ICD-10, M00–M99); and factors influencing health status and contact with health services (ICD-10, Z00–Z99). Two controls were matched for each case; however, only 19% of the cases were matched to one control. None of the controls were selected more than once for the same participant. Overall, the analytical sample included 120 278 cases and 217 605 controls.

Exposure assessment

The length of employment in workplaces handling hazardous chemicals was determined based on occupational information. The number of years was calculated for the participants who had worked in occupations where they had received mandatory special medical examinations related to any chemical hazards (specified chemical substances, organic solvents or lead) or dust during their current or past work. The list of chemicals that are potentially subject to special medical examinations is shown in online supplemental table 1. Even if they had undertaken multiple special medical examinations in the same occupation, the years were not added multiple times. Work in workplaces handling hazardous chemicals for <1 year was defined as 'never' and >1 year was defined as 'ever'. Among participants who were

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ever employed, categorical variables for the length of employment in workplaces handling hazardous chemicals were created by tertiles (never, short (first tertile), moderate (second tertile) and long (third tertile)), and by years (never, 1–10, 11–20 and 20+years).

Covariates

Age, year of admission and admitting hospital were controlled for using an exact matching procedure. Smoking (never, former and current), alcohol consumption (never, former and current) and longest-held occupation (12 major groups of JSOC) were included in the models as confounding variables. Given that occupations are associated with some cancer sites and may also affect the potential with unmeasured chemical exposures of unknown toxicity, we considered the longest held occupation as a potential confounding factor in our analysis. However, we acknowledge that this does not fully capture the variability in real-life exposures, including unknown carcinogenic components and differences in risk management practices, which is a limitation of our study.

Statistical analysis

Using conditional logistic regression models with multiple imputations, ORs and 95% CIs for all cancers and each site were estimated against variables related to the length of employment in workplaces handling hazardous chemicals. Given that our analytical sample had 2% of missing data on smoking or alcohol consumption, multiple imputations were conducted, and five imputed data sets were generated for the missing data using the Multiple Imputation by Chained Equations method.[21] First, the ORs for participants who were or ever employed in hazardous workplaces were examined. Model 1 was conditional logistic regression with multiple imputation, matched for age categories (5-year categories), hospital (34 hospitals) and year of admission (1-year); model 2 was additionally adjusted for smoking status and alcohol consumption status; and model 3 was additionally adjusted for the occupation of longest duration. The ORs in each tertile category were then examined in the fully adjusted model (model 3). The linear trend for the association of length of employment in workplaces handling hazardous chemicals was tested by treating the categorical variable as continuous.

The same analysis was conducted for the categorised years, as well as the 5-year increase in the length of employment in workplaces handling hazardous chemicals. In addition, the above analyses were conducted by limiting the age of participants to under 60 years and under 70 years. The association between year categories and cancer risk was also examined and cross-classified by smoking status (never/ever smoker), and participants who were never employed in workplaces handling hazardous chemicals and never smokers were set as references. Former smokers and former drinkers were defined as those who had quit for at least 1 year from the date of their admission. Interaction terms were added to the regression model to test the interactions between year categories and smoking status. Alpha was set at 0.05, and all p values were two-sided. All statistical analyses were performed using the Statistical Analysis System (SAS) software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

In the analysis, 337 883 men were included. The control group had a higher proportion of never smokers and a lower proportion of former alcohol consumers. There were no significant between-group differences with regard to matched factors. The background characteristics of patients and controls are shown in table 1. The proportion who were employed in workplaces handling hazardous chemicals, by JSOC classification of the longest occupation held were: 11.3% in manufacture, craft, repair and assemblers; 4.2% in construction and mining; 4.0% in professionals and technicians; 2.3% in carrying, cleaning and packing; 2.0% in managers; 1.5% in clerical support workers; 1.4% in police, fire-fighters and security workers; 1.1% in drivers, crews, transport and machine operators; 0.8% in sales workers; 0.5% in service workers; and 0.3% in agricultural, forestry and fishery workers. Table 2 shows the association between cancer incidence and employment for >1 year in workplaces that handle hazardous chemicals. High ORs for all cancers and lung, oesophagus, pancreas and bladder cancers were observed among patients with a history of employment in workplaces handling hazardous chemicals. These results were robust after adjusting for smoking and alcohol consumption status, and occupation with the longest duration.

Table 1 Characteristics of the study population by case–control status in a hospital-based case–control study, Japan, 2005–2019

	Cases	Controls
	N (%)	N (%)
Total population (men)	120 278 (100)	217 605 (100)
Age categories, years		
<40	1291 (1.1)	2580 (1.2)
40–49	3284 (2.7)	6566 (3.0)
50–59	12 783 (10.6)	25 543 (11.7)
60–69	35 527 (29.5)	66 874 (30.7)
70–79	45 584 (37.9)	77 780 (35.7)
80+	21 809 (18.1)	38 262 (17.6)
Admission year		
2005–2009	42 473 (35.3)	78 279 (36.0)
2010–2014	35 221 (29.3)	62 942 (28.9)
2015–2019	42 584 (35.4)	76 384 (35.1)
Smoking status		
Never	24 927 (20.7)	57 855 (26.6)
Former	63 195 (52.5)	101 666 (46.7)
Current	31 352 (26.1)	55 083 (25.3)
Missing	804 (0.7)	3001 (1.4)
Alcohol consumption status		
Never	26 331 (21.9)	52 407 (24.1)
Former	21 458 (17.8)	28 705 (13.2)
Current	71 410 (59.4)	133 459 (61.3)
Missing	1079 (0.9)	3034 (1.4)
Longest occupation held (major groups of JSOC)		
Managers	7948 (6.6)	14 565 (6.7)
Professionals and technicians	13 025 (10.8)	23 825 (10.9)
Clerical support workers	14 385 (12.0)	25 764 (11.8)
Sales workers	12 227 (10.2)	21 520 (9.9)
Service workers	3883 (3.2)	6995 (3.2)
Police, firefighters and security workers	2336 (1.9)	4509 (2.1)
Agricultural, forestry and fishery workers	5889 (4.9)	11 286 (5.2)
Manufacture, craft, repair and assemblers	23 247 (19.3)	39 782 (18.3)
Drivers, crews, transport and machine operators	8658 (7.2)	14 768 (6.8)
Construction and mining	11 089 (9.2)	19 394 (8.9)
Carrying, cleaning and packing	3452 (2.9)	5971 (2.7)
Housewives, unemployed or unclassifiable	14 139 (11.8)	29 226 (13.4)

JSOC, Japan Standard Occupational Classification.

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Table 2 Association between cancer incidence and employment in workplaces handling hazardous chemicals more than 1 year in a hospital-based case–control study, Japan, 2005–2019

				Model 1*		Model 2†		Model 3‡	
Cancer site	ICD-10 code	Cases	Controls	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
All cancers	C00–C99	120 278	217 605	1.09	(1.05 to 1.13)	1.08	(1.04 to 1.12)	1.05	(1.01 to 1.10)
Lung	C34	14 437	28 858	2.08	(1.86 to 2.33)	1.99	(1.78 to 2.24)	1.87	(1.66 to 2.11)
Oesophagus	C15	3306	6612	1.78	(1.34 to 2.37)	1.66	(1.23 to 2.22)	1.63	(1.21 to 2.21)
Stomach	C16	19 462	38 920	1.09	(0.99 to 1.21)	1.08	(0.98 to 1.19)	1.05	(0.95 to 1.16)
Colorectal	C18–C20	18 196	36 381	1.01	(0.91 to 1.12)	1.00	(0.90 to 1.11)	0.99	(0.89 to 1.10)
Liver	C22	6958	13 911	0.95	(0.80 to 1.13)	0.92	(0.77 to 1.11)	0.92	(0.77 to 1.10)
Biliary tract	C23–C24	2469	4933	1.06	(0.75 to 1.50)	1.04	(0.74 to 1.47)	0.99	(0.70 to 1.41)
Pancreas	C25	3566	7130	1.71	(1.28 to 2.26)	1.84	(1.38 to 2.46)	1.80	(1.35 to 2.41)
Bladder	C67	7397	14 786	1.41	(1.19 to 1.67)	1.41	(1.18 to 1.67)	1.38	(1.16 to 1.65)

*Model 1 (M1) was conditional logistic regression with multiple imputation, matched for age categories (5-year categories), hospital (34 hospitals) and admitted year (1-year).
†Model 2 (M2) was adjusted for M1 plus smoking and alcohol consumption status.
‡Model 3 (M3) was adjusted for M2 plus the longest occupation held.
ICD-10, International Classification of Diseases 10th Revision.

Table 3 Length of employment (in tertiles) in workplaces handling hazardous chemicals and risk of cancer among men in a hospital-based case–control study, Japan, 2005–2019

Cancer site	Length (in tertiles)*	N of exposed cases	OR†	(95% CI)	P for trend‡
All cancers	Short	685	0.94	(0.86 to 1.03)	<0.01
	Moderate	1333	0.99	(0.92 to 1.06)	
	Long	2481	1.13	(1.07 to 1.19)	
Lung	Short	104	1.59	(1.20 to 2.11)	<0.01
	Moderate	235	2.12	(1.74 to 2.59)	
	Long	385	1.82	(1.56 to 2.13)	
Oesophagus	Short	16	1.19	(0.62 to 2.27)	<0.01
	Moderate	38	1.77	(1.09 to 2.87)	
	Long	63	1.73	(1.18 to 2.55)	
Stomach	Short	98	0.91	(0.71 to 1.16)	0.11
	Moderate	215	0.95	(0.80 to 1.13)	
	Long	405	1.15	(1.01 to 1.32)	
Colorectal	Short	121	1.16	(0.92 to 1.46)	0.60
	Moderate	192	0.94	(0.79 to 1.13)	
	Long	319	0.96	(0.84 to 1.11)	
Liver	Short	32	0.84	(0.54 to 1.30)	0.33
	Moderate	84	1.05	(0.78 to 1.41)	
	Long	124	0.87	(0.68 to 1.10)	
Biliary tract	Short	9	0.78	(0.35 to 1.73)	0.64
	Moderate	13	0.65	(0.34 to 1.26)	
	Long	46	1.25	(0.81 to 1.91)	
Pancreas	Short	16	1.61	(0.82 to 3.17)	<0.01
	Moderate	34	1.53	(0.95 to 2.46)	
	Long	65	2.03	(1.40 to 2.94)	
Bladder	Short	40	1.23	(0.82 to 1.85)	<0.01
	Moderate	82	1.44	(1.06 to 1.94)	
	Long	155	1.40	(1.12 to 1.74)	

*The median (range) length of employment was 10 (1–17), 28 (18–34) and 41 (32–58) years for short, moderate and long, respectively.
†ORs and 95% CIs were calculated using conditional logistic regression with multiple imputation, matched for age categories (5-year categories), hospital (34 hospitals) and admitted year (1-year) with additional adjustment for smoking status, alcohol consumption status and longest occupation held (the reference categories were never exposed).
‡Trend test was performed for the associations between exposed length as a continuous variable and cancer incidence.

Table 3 shows the association between the length of employment in tertiles in workplaces that handle hazardous chemicals and the risk of cancer. The median (range) length of employment was 10 (1–17), 28 (18–34) and 41 (32–58) years for short, moderate and long lengths of employment, respectively. Increased ORs were observed in the long group for all cancers: in all groups for lung cancer, moderate and long groups for oesophageal cancer, long group for stomach cancer, long group for pancreatic cancer and moderate and long groups for bladder cancer. Trend tests indicated a trend toward an increased risk of all cancers, lung cancer, oesophageal cancer, pancreatic cancer and bladder cancer as the length of employment in workplaces handling hazardous chemicals increased.

Table 4 shows the association between the length of employment in categorical and continuous years in workplaces that handle hazardous chemicals and the risk of cancer. The ORs for all cancers were increased in 21+ years; lung cancer, 1+ years of employment; oesophageal cancer, 21+ years of employment; pancreatic cancer, 11+ years; and bladder cancer, 11+ years. Trend tests indicated a trend toward an increased risk of all cancers, lung cancer, oesophageal cancer, pancreatic cancer and bladder cancer with the length of employment in workplaces handling hazardous chemicals. In the continuous model of a 5-year increase in employment, significant increases in ORs were observed for all cancers, lung cancer, oesophageal cancer, stomach cancer, pancreatic cancer and bladder cancer.

Similar results were obtained when the analyses were limited to younger participants, with increased risk for all cancers, lung, pancreatic and bladder cancers among those aged under 70 years and an increased risk for lung and oesophageal cancers among those aged under 60 years (online supplemental tables 2 and 3). The results of the analysis of the association between cancer risk and length of employment in workplaces handling dust, organic solvents, specified chemical substances and lead are shown in online supplemental tables 4–7.

Figure 1 shows the combined effects of smoking and employment at workplaces that handle hazardous chemicals. The risk of cancer was higher among participants who had ever smoked and in those with longer employment duration. Among participants who never smoked, there was no significantly increased risk of cancer according to the length of employment, except for lung cancer. For lung cancer, although no significant interaction between smoking and length of employment (in years) in workplaces handling hazardous chemicals was observed (p=0.07),

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Table 4 Length of employment (in years) in workplaces handling hazardous chemicals and risk of cancer among men* in a hospital-based case–control study, Japan, 2005–2019

			Categorical cumulative exposure		Continuous cumulative exposure (5-year increase)	
Cancer site	Length (years)	N of exposed cases	OR	(95% CI)	OR	(95% CI)
All cancers	1–10	363	0.86	(0.75 to 0.97)	1.01	(1.01 to 1.02)
	11–20	505	1.00	(0.89 to 1.12)		
	21+	3 631	1.09	(1.04 to 1.13)		
Lung	1–10	57	1.75	(1.19 to 2.56)	1.08	(1.07 to 1.10)
	11–20	80	1.71	(1.23 to 2.36)		
	21+	587	1.91	(1.68 to 2.17)		
Oesophagus	1–10	8	1.12	(0.45 to 2.83)	1.08	(1.03 to 1.12)
	11–20	14	1.55	(0.76 to 3.16)		
	21+	95	1.72	(1.24 to 2.39)		
Stomach	1–10	51	0.81	(0.58 to 1.13)	1.01	(1.00 to 1.03)
	11–20	71	0.95	(0.71 to 1.27)		
	21+	596	1.09	(0.98 to 1.22)		
Colorectal	1–10	62	0.95	(0.70 to 1.30)	1.00	(0.98 to 1.01)
	11–20	85	1.26	(0.95 to 1.67)		
	21+	485	0.96	(0.85 to 1.08)		
Liver	1–10	17	0.82	(0.45 to 1.47)	0.99	(0.96 to 1.01)
	11–20	26	0.87	(0.52 to 1.45)		
	21+	197	0.93	(0.77 to 1.14)		
Biliary tract	1–10	2	0.52	(0.11 to 2.47)	1.01	(0.97 to 1.07)
	11–20	10	1.03	(0.47 to 2.23)		
	21+	56	1.02	(0.70 to 1.50)		
Pancreas	1–10	9	1.60	(0.66 to 3.87)	1.09	(1.05 to 1.14)
	11–20	15	2.46	(1.17 to 5.19)		
	21+	91	1.74	(1.26 to 2.39)		
Bladder	1–10	23	1.03	(0.61 to 1.74)	1.04	(1.02 to 1.07)
	11–20	30	1.64	(1.00 to 2.69)		
	21+	224	1.39	(1.15 to 1.69)		

*ORs and 95% CIs were calculated by conditional logistic regression with multiple imputation, matched for age categories (5-year categories), hospital (34 hospitals) and year of admission (1-year) with additional adjustment for smoking status, alcohol consumption status and longest occupation held (the reference for categorical cumulative exposure was never exposed).

positive relationships were particularly obvious among participants with a history of smoking. In all analyses, the same results were obtained when the variable settings for smoking and alcohol consumption were implemented with continuous variables treated as amounts (data not shown).

DISCUSSION

There is a paucity of information on the latency of cancers due to occupational carcinogens.[1] This study of 120 278 incident cancer cases showed that the length of employment in workplaces handling hazardous chemicals was associated with the risk of all cancers and lung, oesophagus, pancreas and bladder cancers among Japanese male adults. The exposure assessment was based on the number of years spent in workplaces where hazardous substances regulated by law were handled. In the relationship between longer occupation exposure to hazardous chemicals and a high risk of cancer, the risk was considered to be increased by both legally controlled hazardous chemicals and unregulated hazardous chemicals.

Our current findings indicate a greater risk of all cancer, and lung, oesophagus, pancreas and bladder cancers among male employees who have worked in hazardous workplaces for a long time. This is consistent with previous reports from European countries that have analysed population-attributable factors and concluded that these cancers were attributable to occupation.[1–3 22] In addition, the finding that the risk of cancer increases with the length of employment in hazardous workplaces is relevant with those of several previous epidemiological studies. Some occupations are assessed by IARC as carcinogenic by the occupation itself. The IARC categorised firefighting and painting as Group 1 carcinogens in 2010.[7] In a Canadian cohort study, firefighters were found to have a high risk of mesothelioma and bladder cancer.[23] Swanson *et al*[24] found that long-term black male painters had a greater lung cancer risk. In Japan, socioeconomic factors have been studied in which the risk of lung cancer was increased among workers in the lowest occupational class.[14] Assessing the risk of cancer risk among specific occupations may provide leads to identifying the carcinogenic chemicals to which the occupations are exposed. Long-term occupational exposure and carcinogenesis are currently being re-evaluated, and chronic inflammation is considered to play a crucial role.[25] The results are consistent with an increased risk of carcinogenesis with long-term observation, even with low-dose exposures, as linear no-threshold relationships have been reported for carcinogenesis.[26]

Among the several cancer sites that were examined in the current study, the risk of cancer in the lung, oesophagus, stomach, pancreas and bladder, but not in the colon and rectum, liver and biliary tract, was associated with the length of employment in workplaces that handle hazardous chemicals. Smoking,

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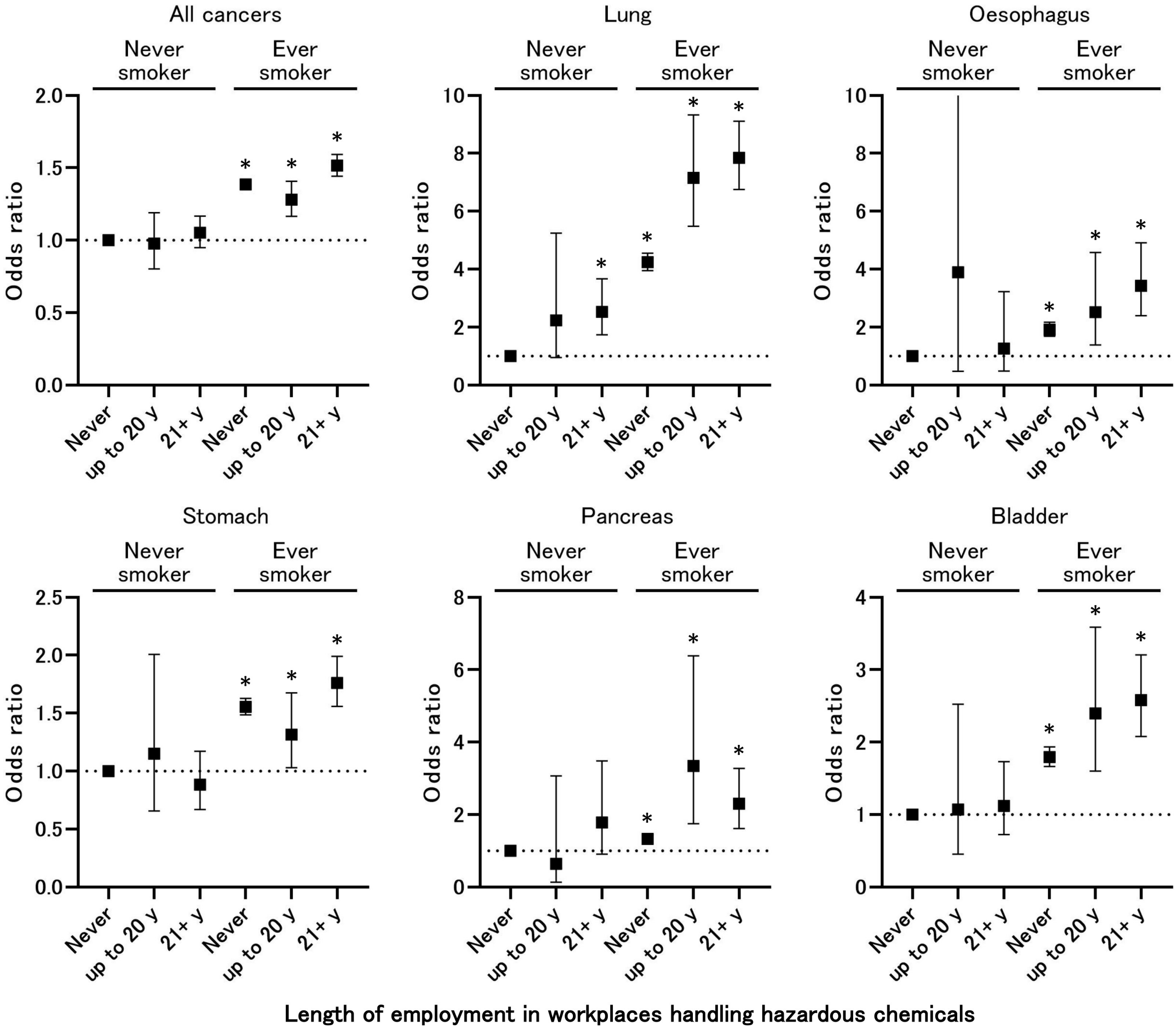

Figure 1 Association between cancer and length of employment in workplaces handling hazardous chemicals combined with the history of smoking among men in a hospital-based case–control study, Japan, 2005–2019. The ORs (squares) and 95% CIs (bars) were calculated by conditional logistic regression with multiple imputation, matched for age categories (5-year categories), hospital (34 hospitals) and admitted year (1-year) with additional adjustment for alcohol consumption status, and longest occupation held. Reference was the group with never employment in workplaces handling hazardous chemicals and never smokers. Asterisks (*) represent categories with increased ORs statistically significant. y, years.

as a major risk factor for cancer, is positively associated with the length of work involving hazardous chemicals.[27] Interaction effects between smoking and occupational factors have been reported to increase the risk for some cancers, such as asbestos and lung cancer[28] or paint components and bladder cancer.[29] In the present study, although no interaction was observed between exposure and smoking, higher ORs were found among participants with a history of smoking. In the analyses stratified by smoking history, there was a significant association between duration of employment and all cancers and lung, oesophageal, stomach, pancreatic and bladder cancers only among smokers.

However, it should be noted that although we statistically adjusted for smoking in the analytical model, the possibility of a selection bias that may not have been adjusted for, cannot be ruled out. Alternatively, tobacco exerts its carcinogenicity through more than 60 carcinogenetic chemicals that bind and mutate DNA.[30 31] For cancers for which cigarette smoking is a risk factor, it may also be inferred that there is a high sensitivity to chemicals, which may contribute toward the results with respect to target organs. Genetic signatures in organs with genomic instability in response to smoking may also be present during occupational exposure to exogenous mutagens.[32] Therefore, the concordance between the distribution of DNA mutations in tobacco carcinogenesis and chemical carcinogenesis requires further investigation.

The history of chemical management in Japan is reflected by chemical pollution incidents and occupational diseases that occurred during the period of rapid economic growth that started in the 1950s.[33] Since then, workplace chemical management in Japan has been based on the compliance approach. Employers must follow these laws and regulations to prevent illnesses caused by chemical substances, but these regulatory

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obligations apply to a limited number of listed chemicals.[34] Thus, there are few legal obligations for many chemicals that are not listed as hazardous, and there are not enough measures in place to protect the health of workers in chemical-hazardous workplaces. Within this context, there have been outbreaks of bile duct cancer among workers in printing plants[9] and of bladder cancer among workers in chemical plants[8] in the past decade, and the chemicals that were later identified as causes were not on the list of regulated chemicals.

Since the Robens Report[35] European countries and the USA have stressed the significance of systems that provide hazard information to workers regarding chemicals and conduct risk assessments based on that information from an occupational health and safety perspective. Currently, Japan is making a policy shift in its approach based on autonomous chemical management[33] following the principles in Europe and the USA. Although it is difficult to simply compare across countries because of several variables such as characteristics of the individual workers, workplace environment and economic situation, the results of this study provide evidence that, at least, the current compliance approach alone is not sufficient to prevent cancer in workers. We emphasise the importance of risk assessment in chemical management in workplaces handling chemical substances as well as measures against smoking in the workplace.

Strengths and limitations

The major strength of this study is the large number of more than 120 000 cases of cancer and the availability of rich data for the selection of controls. In addition, detailed data on individual occupational history as well as accurate medical diagnoses allowed us to conduct an in-depth analysis of the relationships of length of employment in workplaces handling hazardous chemicals with cancer, with consideration of several potential confounders. Although smoking is a strong risk factor for some cancers, an assessment focused on the occupational history of participants in a clinical population is also important from the viewpoint of occupational medicine. In the current study, the length of employment in workplaces handling hazardous chemicals remained to be associated with cancer even after adjusting for other factors, suggesting the involvement of unknown chemical carcinogens.

This study has some limitations. First, the study may have been affected by a bias in the control group selection (Berkson's bias). The hospital admission probability is defined as the likelihood that members of a community group will be admitted to a hospital. The controls were selected from patients admitted to the same hospitals, and the distribution of occupational categories in the controls was nationally representative.[10 13] Given the substantial size of our hospitalisation database, we analysed various combinations of diseases leading to hospitalisation within the control group. Our analysis confirmed that these variations did not influence the outcome of this study. However, bias toward or away from the null association may occur in the selection of hospital controls, which may be more prejudiced than the general population toward risk factors for hospitalisation for any condition. Second, data regarding other clinical risk factors for cancer, such as overweight, physical activity, diet or secondhand smoke, were unavailable. Third, the occupational environment was not assessed because of lack of data. Risk assessment, proper use of personal protective equipment and adjustment of working hours may reduce the risk of carcinogenesis. Future studies should consider the effects of occupational hygiene management on the incidence of cancer. Fourth, bias regarding occupational information is undeniable. Participants may have failed to receive special medical examinations even if required for some reason. Or, they may not have handled hazardous chemicals during all of their employment as reported. If, however, the participant worked for the same company but changed roles (eg, from line work to management), the exposure was assessed as a different occupation. Furthermore, while we consider the current and past three occupations to be a reasonable reflection of a Japanese lifetime occupational history, given that the number of job changes among Japanese workers is low on average,[36] we acknowledge that this might not fully apply to workers handling hazardous chemicals, who could potentially have a higher job turnover rate. This constitutes a limitation of our study and is a point that warrants further investigation in future research. Also, we consider the current and past three occupations to be a reasonable reflection of a Japanese lifetime occupational history, given that the number of job changes among Japanese workers is low on average. Fifth, in addition to chemical carcinogens, there are other types of carcinogens, such as physical or biological agents, which may also contribute to cancer risk among workers. Future research should investigate the impact of these additional occupational exposures on cancer risk among workers handling hazardous chemicals. Finally, this case–control study exclusively included male workers because of the limited number of female workers in workplaces handling hazardous chemicals. Thus, the findings cannot be applied to women, and future research should focus on women.

CONCLUSIONS

This large case–control study, after adjusting for a possible range of known cancer risk factors, found that a long length of employment in workplaces handling hazardous chemicals was associated with a high risk of several cancers. Particularly, the combination of smoking history and employment involving hazardous chemicals may further increase the risk of cancer. Although our findings should be internally validated in cohort studies and externally validated in other counties and regions, they highlight the need for the development of a comprehensive system to verify whether the approaches used to manage chemicals in the workplace are adequate for lowering the risk of cancer.

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Data availability statement Data are available upon reasonable request. The data sets are not publicly available due to restrictions used under the license for the current study. They are available on reasonable request from the corresponding author.

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