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Combined effects of occupational exposure to hazardous operations and lifestyle-related factors on cancer incidence

Kota Fukai[1] | Noriko Kojimahara[2] | Keika Hoshi[3,4] | Akihiro Toyota[5] | Masayuki Tatemichi[1]

[1]Department of Preventive Medicine, Tokai University School of Medicine, Isehara, Japan

[2]Research Support Center, Shizuoka General Hospital, Shizuoka, Japan

[3]Center for Public Health Informatics, National Institute of Public Health, Wako, Japan

[4]Department of Hygiene, School of Medicine, Kitasato University, Sagamihara, Japan

[5]Chugoku Rosai Hospital Research Center for the Promotion of Health and Employment Support, Japan Organization of Occupational Health and Safety, Hiroshima, Japan

Correspondence
Masayuki Tatemichi, Department of Preventive Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193 Japan.
Email: tatemichi@tokai-u.jp

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Abstract

We aimed to examine whether the number of types of hazardous operations at work experienced through a lifetime is associated with cancer incidence, and additionally examined the combined effects with lifestyle-related factors. Using a nationwide, multicenter, hospital inpatient dataset (2005-2015), we conducted a matched case-control study with 1 149 296 study subjects. We classified the participants into those with none, 1, or 2 or more types of hazardous operation experience, based on information of special medical examinations taken, mandatory in Japan for workers engaged in hazardous operations. Using those with no experience as the reference group, we estimated the odds ratios for cancer incidence (all sites, lung, stomach, colon and rectum, liver, pancreas, bile duct, and bladder) by conditional logistic regression with multiple imputations. We also examined the effects of the combination with hazardous operations and lifestyle-related factors. We observed increased risks for cancer of all sites, and lung, pancreas, and bladder cancer associated with the experience of hazardous operations. Multivariable-adjusted ORs (95% CIs) of cancer incidence of all sites were 1 (reference), 1.16 (1.12, 1.21), and 1.17 (1.08, 1.27) for none, 1, and 2 or more types of hazardous operation experience, respectively (*P* for trend <.001). Potential combined associations of hazardous operations with smoking were observed for lung, pancreas, and bladder cancer, and with diabetes for pancreas cancer. Engaging in hazardous operations at work and in combination with lifestyle-related factors may increase the risk of cancer. We highlight the potential for those engaged in hazardous work to avoid preventable cancers.

KEYWORDS

cancer incidence, case-control study, diabetes, occupational exposure, smoking

1 | INTRODUCTION

Risks associated with work that involves hazardous factors that are potentially carcinogenic are often complex and challenging to assess.[1,2] The International Agency for Research on Cancer (IARC) has continually updated its classification of some chemical, physical, and biological agents, and has contributed to the assessment of carcinogenicity of these individual agents through epidemiological and experimental studies.[3] The IARC Monograph Volume 125, published in 2019, lists 120 Group 1 (known human), 83 Group 2A (probable human), 314 Group 2B (possible human), and 500 Group 3 (unknown) agents as carcinogens.[4] In reality, however, hazardous operations at workplaces often involve a variety of combinations, and concerns about potential risks from exposure to various carcinogens in workplaces are increasing.[5,6] An individual can be engaged in multiple types of hazardous operations through their professional life.[7] Also, substantial numbers of chemical substances other than those listed above are used in workplaces, and some of them might be carcinogenic. It is estimated that roughly 100 000 chemicals exist as commodities worldwide, and the number of chemicals being invented on a commercial basis increases every year.[8] While allowing that these contribute to economic growth and technological improvement, concerns about the health effects of ubiquitous exposure to chemicals have been expressed.[9] Workers engaged in hazardous operations are naturally more likely to be exposed to unknown harmful factors. Accordingly, risk assessment based only on the measurement of exposure to known carcinogenic agents is largely limited to protecting workers health, and it is necessary to consider whether the risk of carcinogenesis varies according to the level of experience with hazardous operation work.

Lifestyle-related factors can also contribute to complex risk during occupational life.[6,10] Smoking and alcohol use plays an important role, and modifiable lifestyle-related factors are indeed the most influential cause of cancer worldwide.[2] Diabetes is increasing in prevalence in most countries and is associated with increased risk of several cancers.[11] Findings that the combination of asbestos and smoking further increases the risk of lung cancer led to an appreciation that understanding the relationship between the combination of occupational and lifestyle-related factors will aid in the prevention of cancer incidence.[6,12] Efforts to prevent cancer should accordingly include investigation of differences between subgroups with such lifestyle-related factors and their combined effects, in addition to hazardous work experience. The insights provided by these investigations will have a crucial impact on global occupational health, particularly in developing countries, where non-communicable diseases are on the rise.

Here, we assess the associations of hazardous operation work experience with cancer risk using data from a nationwide, multicenter, hospital survey of more than 1.1 million inpatients in Japan. Regarding hazardous operations, we focused on the number of types of hazardous work experienced before the incidence of cancer. Cancer outcomes were analyzed for all sites, and by each site for lung, stomach, colon, liver, pancreas, bile duct, and bladder. In addition, we assessed the combined association of hazardous work experience with smoking, alcohol use, and diabetes.

2 | MATERIALS AND METHODS

2.1 | Study setting

This study was a multicenter, hospital-based matched case-control study conducted using data obtained from 2005 to 2015 in the Inpatient Clinico-Occupational Survey of the Rosai Hospital Group, administered by the Japan Organization of Occupational Health and Safety. Details of this survey have been described elsewhere.[13-18] Briefly, the Inpatient Clinico-Occupational Survey has concurrently investigated both the clinical and occupational history of all inpatients admitted to facilities belonging to the nationwide Rosai Hospital Group (>13 000 beds in 34 hospitals as of 2015) since 1984. Previous studies using this database have shown relationships between overall and site-specific cancer incidence and longest-held occupational class among men[13] and women,[14] and lifetime alcohol consumption.[18] The clinical history survey utilizes the same specification as the hospitalization summary entered by the medical doctors. The hospitalization summary is generated for every inpatient at each admission and is composed of basic information (including sex, date of birth, admitted hospital, and date of admission) and medical information (including definitive diagnosis). The doctors register a maximum of 7 definitive diagnoses, including the primary diagnosis, which are eventually coded using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).[19] The registry rate for the clinical history survey was 99.5% during the study period.

The occupational history survey is conducted for all inpatients aged 15 y and older (even those with no occupational history), excluding those admitted overnight for a health checkup. For patients readmitted within 1 y of a previous survey, the survey at the time of readmission was omitted. The occupational history survey is conducted by a trained occupational history surveyor at each hospital, who interviews the participants or their families based on questionnaire at the time of hospitalization and collects information. The questionnaire includes the participants' current and 3 most recent job types and industries, including age at the start and end of each job, and the history of special medical examinations for hazardous operation work taken during the job, as well as smoking and alcohol use habits. Occupational information is coded in accordance with the Japan Standard Industrial Classification and the Japan Standard Occupational Classification, published by the Japanese Ministry of Internal Affairs and Communications.[20] Participation rate for the occupational history survey was 65.7% for the period 2005 to 2015. The present study included 1 149 296 participants aged 20 y or older whose occupational histories were available.

Written informed consent was obtained from each patient prior to completion of all the questionnaires. Access to the dataset was provided under a research agreement between the study authors and the Japan Organization of Occupational Health and Safety. This study was approved by the Research Ethics Committees of Tokai University School of Medicine, Kanagawa, Japan (Protocol Number 18R-309) and the Japan Organization of Occupational Health and Safety (Protocol Number R1-006).

2.2 | Cases and controls

The cases were defined as patients with a primary definitive diagnosis of cancer of all sites (ICD-10, C00-C97; n = 128 973). We also examined cancers by site for the following: lung (ICD-10, C34; n = 12 053), stomach (ICD-10, C16; n = 18 071), colon and rectum (ICD-10, C18-20; n = 19 829), liver (ICD-10, C22; n = 6672), pancreas (ICD-10, C25; n = 4006), bile duct (ICD-10, C22.1 and C24; n = 1885), and bladder (ICD-10, C67; n = 6213).

We randomly selected 5 control subjects for each cancer case from the eligible source with matching for sex (male or female), age (5-y strata), admission date (1-y strata), and admitting hospital (34 hospitals). Controls were those without cancer. The average number of controls for each case was 4.3 (range 1-5), and 60.7% of the cases matched 5 controls. The analytic sample included 684 227 participants (128 973 cancer cases and 555 254 controls). Mean age (mean [standard deviation]) of the eligible participants from the survey, cases, and controls of the present analytic sample were 62.4 (18.1) y, 68.2 (12.2) y, and 67.9 (12.7) y, respectively.

2.3 | Assessment of exposure to hazardous operations at work

The experience of hazardous operations at work was identified using the history of special medical examinations taken in accordance with the national government law. In Japan, workers engaged in specific hazardous operations must undergo special medical examinations mandated by the national government law, and the results of such examinations must be reported to the Labor Standards Inspection Office.[21] In this study, the participants were asked if they had undergone mandatory special medical examinations related to organic solvents, lead, tetra-alkyl lead, specified chemical substances, radiation, dust, or asbestos during the present or past work. If they had undertaken the same examination twice or more in different workplaces, it was counted as 1 hazardous operation experimented. The number of the types of health examination was considered as the exposure to hazardous operation work.

2.4 | Covariates

Sex, age, admission date, and admitting hospital were controlled by an exact matching procedure.[13-18] Smoking (never, former, current), alcohol consumption (never, former, and current), and a diagnosis of diabetes (ICD-10, E10-14; yes or no) were included in the regression models as cofounding variables.

2.5 | Statistical analysis

We conducted multiple imputations for missing data among the 684 227 study subjects, using the variables in the present study with the Multiple Imputation by Chained Equations method.[22] Five imputed data sets were generated. Overall, 28.2% (n = 193 083) of the respondents had missing data, broken down as 28.2% for smoking (n = 192 700) and 28.1% for alcohol consumption (n = 192 283). We performed multiple imputations for the missing data to account for background differences between participants with complete and incomplete data (Table S1). Odds ratio (OR) and 95% confidence interval (CI) of all cancer incidence were estimated by conditional logistic regression with multiple imputations. Similarly, ORs and 95% CIs for each cancer by site (lung, stomach, colon and rectum, liver, pancreas, bile duct, and bladder) were estimated separately. Participants with no experience of hazardous operation work served as the reference group for all analyses. Cases were matched to controls based on sex, age, admission date, and admitting hospital (Model 1). Smoking and alcohol consumption were additionally adjusted for in Model 2, and a diagnosis of diabetes was additionally adjusted for in Model 3. For subgroup analysis, the fully adjusted ORs were estimated by smoking, alcohol use, and diabetes.

We further examined the combined effects of smoking, alcohol use, and diabetes in addition to hazardous operation work experience on cancer risks. Test for interaction between hazardous operation work and diabetes was conducted using the likelihood ratio test. An interaction term was generated by multiplying the variable of hazardous operation work experience (treated as a continuous variable) by diabetes (treated as a dichotomous variable) and added to Model 3. Alpha was set at .05, and all *P*-values were two-sided. All analyses were performed using the Statistical Analysis System (SAS) Software version 9.4 (SAS Institute).

3 | RESULTS

Background characteristics of the cases and controls are shown in Table 1. Distributions of most characteristics differed between them, including the number of types of hazardous operation work.

Compared with those with no experience of hazardous operation work, the incidence of cancer for all sites clearly increased as the number of types of hazardous operation work experience increased (Table 2). The ORs (95% CIs) of all site cancer incidence were 1 (reference), 1.16 (1.12, 1.21), and 1.17 (1.08, 1.27) for none, 1, and 2 or more types of hazardous operation work experience, respectively (*P* for trend <.001) after adjusting for potential confounders (Model 3). Similar trends were observed in cancers of the lung, bladder, and pancreas (Figure 1 and Tables 2, S2).

Table 3 shows the contribution of each type of hazardous operation work to all cancer incidence and by site. Organic solvent-, dust-, and asbestos-related work were associated with all site cancer. Furthermore, dust was associated with lung cancer, asbestos with colon and rectum cancer, organic solvents with pancreas cancer, and organic solvents and lead with bladder cancer.

As shown in Table 2 and Table S2, we then conducted analyses stratified by smoking, alcohol use, and diagnosis of diabetes by the number of types of hazardous operation work experience for all cancer incidence and by site. All cancer was related to the experience of hazardous operation work in all analyses. For lung cancer,

TABLE 1 Background characteristics of case and control subjects

	Controls	Cases	*P*-value[a]
Population, no.	555 254	128 973	
Male	312 429 (56.3%)	76 541 (59.3%)	<.001
Age, y	67.9 ± 12.7	68.2 ± 12.2	<.001
Admission date, y	2009 ± 3	2009 ± 3	.004
No. of types of hazardous operation work experience[b]			
None	541 142 (97.5%)	125 023 (96.9%)	<.001
One	11 392 (2.1%)	3171 (2.5%)	
Two or more	2720 (0.5%)	779 (0.6%)	
Smoking status[c]			
Never	184 991 (33.3%)	42 607 (33.0%)	<.001
Former	125 428 (22.6%)	37 094 (28.8%)	
Current	79 764 (14.4%)	21 643 (16.8%)	
Alcohol use[c]			
None	221 702 (39.9%)	53 174 (41.2%)	<.001
Former	40 645 (7.3%)	13 197 (10.2%)	
Current	128 204 (23.1%)	35 022 (27.2%)	
Diagnose of diabetes, yes	58 367 (10.5%)	8462 (6.6%)	<.001

[a]*P*-values for the *t* test and chi-squared test.
[b]Percentage may not total 100 because of rounding.
[c]Variables contained missing data.

no significant change was seen in the never-smoking group. Bladder cancer showed an increased risk for hazardous operation work, except for never smokers and never drinkers. Pancreas cancer showed a significant increasing trend among former smokers, current drinkers, and those without diabetes.

Regarding the combined effects of smoking, alcohol use, and diabetes with hazardous work experience, associations were observed for several combinations. Figure 2 shows the combined effects of hazardous operation work experience with lifestyle-related factors on lung, bladder, and pancreas cancer incidence. Having a former or current status of smoking clearly showed higher ORs on lung and bladder cancer than never smokers. Having diagnosis of diabetes showed higher ORs on the association between hazardous operation work experience with pancreas cancer, although the interaction by diabetes on the association between hazardous operation work did not reach a statistical significance level (*P* for interaction = .79).

4 | DISCUSSION

The analytic sample of incident cancer cases in 128 973 men and women revealed an association of the number of types of hazardous operation work experience with total, lung, pancreas, and bladder cancer, even after adjustment for or stratification by potential confounders. Furthermore, the combination of lifestyle-related factors with hazardous operations, former and current smokers showed higher odds with lung, and bladder cancer compared with never smokers, and patients with diabetes showed higher odds with pancreas cancer compared with those without diabetes. To the best of our knowledge, this is the largest epidemiologic study to investigate the association of engagement in hazardous operations with cancer risk and the combined association with lifestyle-related factors on the risk of cancer. This study highlights the potential for people engaged in hazardous work to avoid cancers.

Over the past few decades, estimates of the attribution of occupational activities to cancer deaths have ranged from 4% to 8% of all cancer deaths.[1,23,24] Compared with those with no experience of hazardous operation, those with 1 or more types of hazardous operation experience had a 16% or greater increased risk for total cancer (1 hazardous operation: multivariable-adjusted OR, 1.16; 95% CI, 1.12-1.21; 2 or more hazardous operation: multivariable-adjusted OR, 1.17; 95% CI, 1.08-1.27). Although simple comparison with population attributable risk is limited, unknown occupational carcinogens may be overlooked as contributors to the incidence of cancer.[1,2] One explanation for this is the complex of mixtures of chemical substances.[25,26] The United States, the European Union, and Japan strictly regulate chemicals used in the workplace and require systematic risk assessment.[27] These risk assessments are primarily based on information from the globally standardized Safety Data Sheet[9]; however, there are reports that fewer than one-fifth of these have exposure information, indicating that the main focus is on substances that have been previously identified as potentially harmful to human health.[8] A greater focus on the implementation of risk assessment for chemical hazards is warranted.

The impact of occupational exposure to carcinogens on the risk of lung,[28] pancreas,[29] and bladder[30] cancer has been widely

TABLE 2 Odds ratios of hazardous operation work experience for cancer incidence

	No. of types of hazardous operation work experience			
	Never	One	Two or more	*P*-value for trend[f]
All sites				
Total population				
No. of controls	375 854	11 300	2717	
No. of cases (%)[a]	97 345 (20.6%)	3151 (21.8%)	777 (22.2%)	
Model 1[b]	1 (Reference)	1.20 (1.16, 1.25)	1.24 (1.14, 1.34)	<.001
Model 2[c]	1 (Reference)	1.17 (1.12, 1.22)	1.18 (1.09, 1.28)	<.001
Model 3[d]	1 (Reference)	1.16 (1.12, 1.21)	1.17 (1.08, 1.27)	<.001
Smoking status				
Never				
No. of controls	180 881	3406	560	
No. of cases (%)[a]	41 626 (18.7%)	833 (19.7%)	114 (16.9%)	
Model 4[e]	1 (Reference)	1.16 (1.07, 1.25)	0.98 (0.80, 1.20)	.004
Former				
No. of controls	119 255	4819	1266	
No. of cases (%)[a]	35 159 (22.8%)	1476 (23.5%)	436 (25.6%)	
Model 4[e]	1 (Reference)	1.18 (1.12, 1.26)	1.33 (1.19, 1.48)	<.001
Current				
No. of controls	75 718	3075	891	
No. of cases (%)[a]	20 560 (21.4%)	842 (21.5%)	227 (20.3%)	
Model 4[e]	1 (Reference)	1.12 (1.04, 1.21)	1.03 (0.89, 1.20)	.025
Alcohol use				
Never				
No. of controls	216 080	4678	889	
No. of cases (%)[a]	51 765 (19.3%)	1187 (20.2%)	211 (19.2%)	
Model 4[e]	1 (Reference)	1.15 (1.08, 1.23)	1.07 (0.92, 1.24)	<.001
Former				
No. of controls	39 187	1167	273	
No. of cases (%)[a]	12 672 (24.4%)	425 (26.7%)	98 (26.4%)	
Model 4[e]	1 (Reference)	1.29 (1.15, 1.44)	1.27 (1.00, 1.60)	<.001
Current				
No. of controls	120 587	5455	1555	
No. of cases (%)[a]	32 908 (21.4%)	1539 (22.0%)	468 (23.1%)	
Model 4[e]	1 (Reference)	1.13 (1.07, 1.20)	1.20 (1.08, 1.33)	<.001
Diagnosis of diabetes				
No				
No. of controls	335 852	10 199	2480	
No. of cases (%)[a]	90 958 (21.3%)	2938 (22.4%)	730 (22.7%)	
Model 4[e]	1 (Reference)	1.16 (1.11, 1.20)	1.16 (1.07, 1.26)	<.001
Yes				
No. of controls	40 002	1101	237	
No. of cases (%)[a]	6387 (13.8%)	213 (16.2%)	47 (16.6%)	
Model 4[e]	1 (Reference)	1.29 (1.11, 1.49)	1.30 (0.95, 1.79)	<.001
Lung cancer				
Total population				

(Continues)

TABLE 2 (Continued)

	No. of types of hazardous operation work experience			
	Never	One	Two or more	*P*-value for trend[f]
No. of controls	41 355	1464	384	
No. of cases (%)[a]	8899 (17.7%)	402 (21.5%)	114 (22.9%)	
Model 1[b]	1 (Reference)	1.38 (1.24, 1.55)	1.51 (1.22, 1.86)	<.001
Model 2[c]	1 (Reference)	1.29 (1.15, 1.44)	1.39 (1.13, 1.71)	<.001
Model 3[d]	1 (Reference)	1.28 (1.14, 1.43)	1.39 (1.12, 1.71)	<.001
Smoking status				
Never				
No. of controls	17 021	348	72	
No. of cases (%)[a]	2341 (12.1%)	38 (9.8%)	8 (10.0%)	
Model 4[e]	1 (Reference)	0.77 (0.55, 1.09)	0.84 (0.40, 1.76)	.172
Former				
No. of controls	15 730	727	189	
No. of cases (%)[a]	4159 (20.9%)	223 (23.5%)	65 (25.6%)	
Model 4[e]	1 (Reference)	1.34 (1.15, 1.56)	1.54 (1.16, 2.04)	<.001
Current				
No. of controls	8604	389	123	
No. of cases (%)[a]	2399 (21.8%)	141 (26.6%)	41 (25.0%)	
Model 4[e]	1 (Reference)	1.46 (1.20, 1.78)	1.38 (0.97, 1.98)	<.001
Alcohol use				
Never				
No. of controls	21 411	532	122	
No. of cases (%)[a]	4427 (17.1%)	146 (21.5%)	36 (22.8%)	
Model 4[e]	1 (Reference)	1.32 (1.09, 1.58)	1.36 (0.94, 1.97)	.001
Former				
No. of controls	5257	208	49	
No. of cases (%)[a]	1349 (20.4%)	67 (24.4%)	9 (15.5%)	
Model 4[e]	1 (Reference)	1.30 (0.98, 1.73)	0.78 (0.38, 1.61)	.358
Current				
No. of controls	14 687	724	213	
No. of cases (%)[a]	3123 (17.5%)	189 (20.7%)	69 (24.5%)	
Model 4[e]	1 (Reference)	1.24 (1.05, 1.46)	1.55 (1.18, 2.04)	<.001
Diagnosis of diabetes				
No				
No. of controls	36 756	1327	341	
No. of cases (%)[a]	8270 (18.4%)	374 (22.0%)	108 (24.1%)	
Model 4[e]	1 (Reference)	1.26 (1.12, 1.42)	1.42 (1.14, 1.76)	<.001
Yes				
No. of controls	4599	137	43	
No. of cases (%)[a]	629 (12.0%)	28 (17.0%)	6 (12.2%)	
Model 4[e]	1 (Reference)	1.52 (1.00, 2.30)	1.00 (0.43, 2.36)	.174
Pancreas cancer				
Total population				
No. of controls	13 565	417	84	
No. of cases (%)[a]	2775 (17.0%)	77 (15.6%)	36 (30.0%)	

(Continues)

TABLE 2 (Continued)

	No. of types of hazardous operation work experience			
	Never	One	Two or more	*P*-value for trend[f]
Model 1[b]	1 (Reference)	0.93 (0.73, 1.19)	2.15 (1.45, 3.18)	.023
Model 2[c]	1 (Reference)	0.92 (0.72, 1.17)	2.10 (1.40, 3.13)	.037
Model 3[d]	1 (Reference)	0.95 (0.74, 1.21)	2.09 (1.40, 3.14)	.024
Smoking status				
Never				
No. of controls	6788	143	22	
No. of cases (%)[a]	1277 (15.8%)	26 (15.4%)	6 (21.4%)	
Model 4[e]	1 (Reference)	1.00 (0.65, 1.52)	1.44 (0.58, 3.58)	.632
Former				
No. of controls	4231	159	32	
No. of cases (%)[a]	865 (17.0%)	32 (16.8%)	17 (34.7%)	
Model 4[e]	1 (Reference)	1.06 (0.72, 1.57)	2.70 (1.45, 5.04)	.013
Current				
No. of controls	2546	115	30	
No. of cases (%)[a]	633 (19.9%)	19 (14.2%)	13 (30.2%)	
Model 4[e]	1 (Reference)	0.76 (0.47, 1.21)	1.95 (0.99, 3.84)	.463
Alcohol use				
Never				
No. of controls	7971	191	27	
No. of cases (%)[a]	1602 (16.7%)	24 (11.2%)	10 (27.0%)	
Model 4[e]	1 (Reference)	0.65 (0.43, 1.00)	1.85 (0.90, 3.82)	.685
Former				
No. of controls	1454	50	18	
No. of cases (%)[a]	447 (23.5%)	19 (27.5%)	2 (10.0%)	
Model 4[e]	1 (Reference)	1.39 (0.81, 2.37)	0.41 (0.09, 1.79)	.915
Current				
No. of controls	4140	176	39	
No. of cases (%)[a]	726 (14.9%)	34 (16.2%)	24 (38.1%)	
Model 4[e]	1 (Reference)	1.13 (0.77, 1.66)	3.33 (1.96, 5.65)	<.001
Diagnosis of diabetes				
No				
No. of controls	12 069	389	73	
No. of cases (%)[a]	2226 (15.6%)	67 (14.7%)	30 (29.1%)	
Model 4[e]	1 (Reference)	0.95 (0.73, 1.23)	2.23 (1.44, 3.44)	.028
Yes				
No. of controls	1496	28	11	
No. of cases (%)[a]	549 (26.9%)	10 (26.3%)	6 (35.3%)	
Model 4[e]	1 (Reference)	0.98 (0.48, 2.01)	1.50 (0.53, 4.23)	.547
Bladder cancer				
Total population				
No. of controls	20 593	643	167	
No. of cases (%)[a]	4850 (19.1%)	184 (22.3%)	50 (23.0%)	
Model 1[b]	1 (Reference)	1.44 (1.22, 1.70)	1.51 (1.10, 2.08)	<.001
Model 2[c]	1 (Reference)	1.36 (1.15, 1.61)	1.42 (1.03, 1.95)	<.001

(Continues)

TABLE 2 (Continued)

	No. of types of hazardous operation work experience			
	Never	One	Two or more	*P*-value for trend[f]
Model 3[d]	1 (Reference)	1.37 (1.16, 1.62)	1.39 (1.00, 1.91)	<.001
Smoking status				
Never				
No. of controls	7516	143	30	
No. of cases (%)[a]	1343 (15.2%)	29 (16.9%)	4 (11.8%)	
Model 4[e]	1 (Reference)	1.26 (0.84, 1.88)	0.84 (0.29, 2.44)	.540
Former				
No. of controls	8504	307	86	
No. of cases (%)[a]	2009 (19.1%)	84 (21.5%)	27 (23.9%)	
Model 4[e]	1 (Reference)	1.41 (1.10, 1.81)	1.57 (1.01, 2.43)	.001
Current				
No. of controls	4573	193	51	
No. of cases (%)[a]	1498 (24.7%)	71 (26.9%)	19 (27.1%)	
Model 4[e]	1 (Reference)	1.37 (1.03, 1.82)	1.35 (0.78, 2.31)	.023
Alcohol use				
Never				
No. of controls	9935	214	54	
No. of cases (%)[a]	2167 (17.9%)	55 (20.5%)	12 (18.2%)	
Model 4[e]	1 (Reference)	1.34 (0.99, 1.81)	1.09 (0.58, 2.04)	.130
Former				
No. of controls	2719	73	20	
No. of cases (%)[a]	678 (20.0%)	27 (27.0%)	4 (16.7%)	
Model 4[e]	1 (Reference)	1.88 (1.19, 2.98)	0.99 (0.32, 3.00)	.053
Current				
No. of controls	7939	356	93	
No. of cases (%)[a]	2005 (20.2%)	102 (22.3%)	34 (26.8%)	
Model 4[e]	1 (Reference)	1.29 (1.03, 1.62)	1.62 (1.08, 2.42)	.002
Diagnosis of diabetes				
No				
No. of controls	18 157	572	156	
No. of cases (%)[a]	4621 (20.3%)	164 (22.3%)	45 (22.4%)	
Model 4[e]	1 (Reference)	1.27 (1.06, 1.51)	1.26 (0.90, 1.76)	.005
Yes				
No. of controls	2436	71	11	
No. of cases (%)[a]	229 (8.6%)	20 (22.0%)	5 (31.3%)	
Model 4[e]	1 (Reference)	3.24 (1.93, 5.43)	5.29 (1.83, 15.29)	<.001

[a]Percentage = cases/(cases + controls).

[b]Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.

[c]Additional adjustment for smoking and alcohol consumption from Model 1.

[d]Additional adjustment for diagnosis of diabetes from Model 2.

[e]Full adjustment for factors in Model 3, except the stratified factors.

[f]Trend test was calculated for the associations between no. of types of hazardous operation work experience as a continuous variable (0, 1, 2) and cancer incidence.

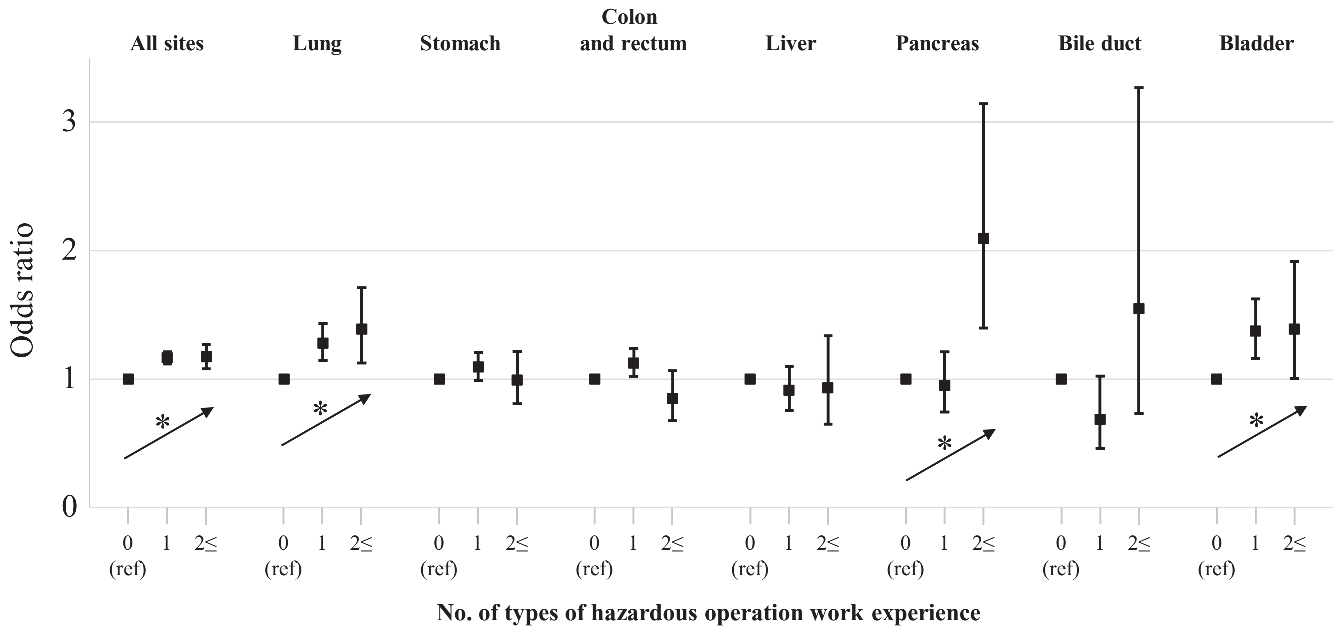

FIGURE 1 Risk for cancer incidence associated with the number of types of hazardous operation work experience. The odds ratio (OR) (dot) and 95% confidence interval (CI) (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, sex, admission date, and admitting hospital, and additionally adjusted for smoking, alcohol use, and diagnosis of diabetes. The trend test was calculated for the associations between the number of types of hazardous operation work as a continuous variable (0, 1, 2) and cancer incidence. (*) means the *P*-value was <.05 for the trend test

investigated. We observed an increased risk of colon cancer solely from engagement in asbestos-related work, as previously reported.[31] However, despite efforts to identify agents that cause cancer, cases of unknown occupational cause have been reported. In 2013, Kumagai et al[32] reported an outbreak of cancer incidence in the bile duct among printing workers in Japan, estimating the relative risk for this rare and generally fatal cancer was extraordinarily high. Further epidemiological investigation by the national government found that affected workers were employed in the offset color proof-printing section and were exposed to 1,2-dichloropropane, classified by the IARC at that time as Group 3 (unknown).[33] Thus, new occupational cancers may be discovered in workers who are originally engaged in hazardous work and are thus more likely to be exposed to unknown harmful factors. Furthermore, given that economic activity continues to increase in both developing and developed countries, avoidance of cancer will require a broad and comprehensive reduction in hazardous occupational exposures. Our results also suggested a combined effect of exposure with factors such as smoking and diabetes on cancer incidence, which therefore indicates the need for a more inclusive consideration of occupational and individual factors.

A full understanding of the development of cancer by hazardous occupational activity requires a mechanistic explanation. Vigorous investigation of the specific mechanisms of carcinogenic agents to date has identified mutagenicity,[34] inflammation-inducing and oxidative stress,[35] hormone secretion mutations,[36] signal transduction and epigenetic abnormalities,[37] and autophagy abnormalities,[38] among others. It appears easy to assume that they will be synergistic when mixed. The main pathways include mutagenicity and oxidative stress for lung cancer; accumulation of mutagens for bladder cancer; and mutagenicity, inflammation, and signaling abnormalities for pancreatic cancer.[35,39] Although the mechanism of carcinogenesis of pancreatic cancer remains unclear, occupational linkages have been reported. Because of the abnormally high frequency of *KRAS* mutations in pancreatic cancer, the mechanism of chemical carcinogenesis in this regard may lead to better understanding of pancreatic carcinogenesis.[39]

4.1 | Strengths and limitations

Strengths of this study included its more than 120 000 cases of cancer and availability of rich data for selection of controls. This enabled us to comprehensively investigate the potential role of hazardous operation work experience and combined factors in the development of cancer, with consideration to a range of potential confounders. Detailed data on individual occupational history together with accurate medical diagnoses allowed us to undertake a highly in-depth analysis of the association of hazardous operation work with cancer.

Nevertheless, we acknowledge several limitations. First, the study may have been subject to selection bias regarding the controls (eg Berkson's bias).[40] Considering the hospital-based setting, we selected controls from among inpatients admitted without cancer. Hospital admission probability is defined as the probability that the members of a community group will be admitted to a hospital in that community.[40] We therefore selected controls by matching cases with patients admitted to the same hospital in the same period. The Rosai Hospital Group used as the data resource for this study includes core hospitals in regions throughout Japan; we

TABLE 3 Odds ratios and number of cases on each cancer site by hazardous operation work types

OR (95% CI) No. of cases	All sites	Lung	Stomach	Colon and rectum	Liver	Pancreas	Bile duct	Bladder
Organic solvents	1.13 (1.05, 1.21)	1.09 (0.89, 1.33)	1.10 (0.93, 1.30)	1.00 (0.84, 1.19)	1.32 (0.99, 1.75)	1.48 (1.01, 2.17)	0.72 (0.36, 1.44)	1.35 (1.02, 1.78)
	1349	162	211	186	73	45	11	90
Lead	1.05 (0.90, 1.23)	1.20 (0.75, 1.91)	1.31 (0.90, 1.91)	0.83 (0.53, 1.29)	0.81 (0.38, 1.71)	0.49 (0.17, 1.43)	–	1.94 (1.10, 3.40)
	212	26	36	24	8	4	No cases	21
Tetra-alkyl lead	1.02 (0.65, 1.59)	0.51 (0.10, 2.63)	1.48 (0.54, 4.05)	1.04 (0.30, 3.63)	0.98 (0.11, 8.35)	2.57 (0.14, 48.02)	–	0.79 (0.06, 10.87)
	27	2	5	3	1	1	No cases	1
Specified chemical substances	1.09 (0.99, 1.19)	1.27 (0.99, 1.63)	0.93 (0.73, 1.17)	1.02 (0.80, 1.29)	0.77 (0.49, 1.21)	1.03 (0.59, 1.81)	1.69 (0.75, 3.77)	1.20 (0.84, 1.73)
	683	106	104	97	26	21	9	50
Radiation	1.10 (0.97, 1.25)	0.88 (0.62, 1.26)	1.03 (0.76, 1.38)	0.93 (0.67, 1.29)	0.50 (0.25, 1.02)	1.56 (0.79, 3.07)	1.58 (0.52, 4.77)	0.91 (0.49, 1.72)
	312	39	55	44	9	12	4	12
Dust	1.08 (1.01, 1.14)	1.34 (1.15, 1.56)	1.02 (0.88, 1.18)	0.95 (0.81, 1.12)	0.96 (0.74, 1.25)	1.15 (0.82, 1.62)	0.94 (0.54, 1.63)	0.99 (0.77, 1.27)
	1428	248	240	186	70	47	15	87
Asbestos	1.17 (1.09, 1.26)	1.11 (0.87, 1.42)	0.97 (0.79, 1.20)	1.28 (1.08, 1.51)	0.71 (0.46, 1.10)	0.97 (0.65, 1.44)	0.84 (0.44, 1.57)	1.62 (1.11, 2.37)
	937	79	106	168	24	29	11	37

Note: The ORs and 95% CIs (shown in upper row) were estimated by conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital, and additionally adjusted for smoking, alcohol consumption, diagnosis of diabetes, and all other types of hazardous operation work experience (yes or no). Reference was no experience of any type of hazardous operation work. The number of cases on each cancer site by types of hazardous operation work is shown in lower row.

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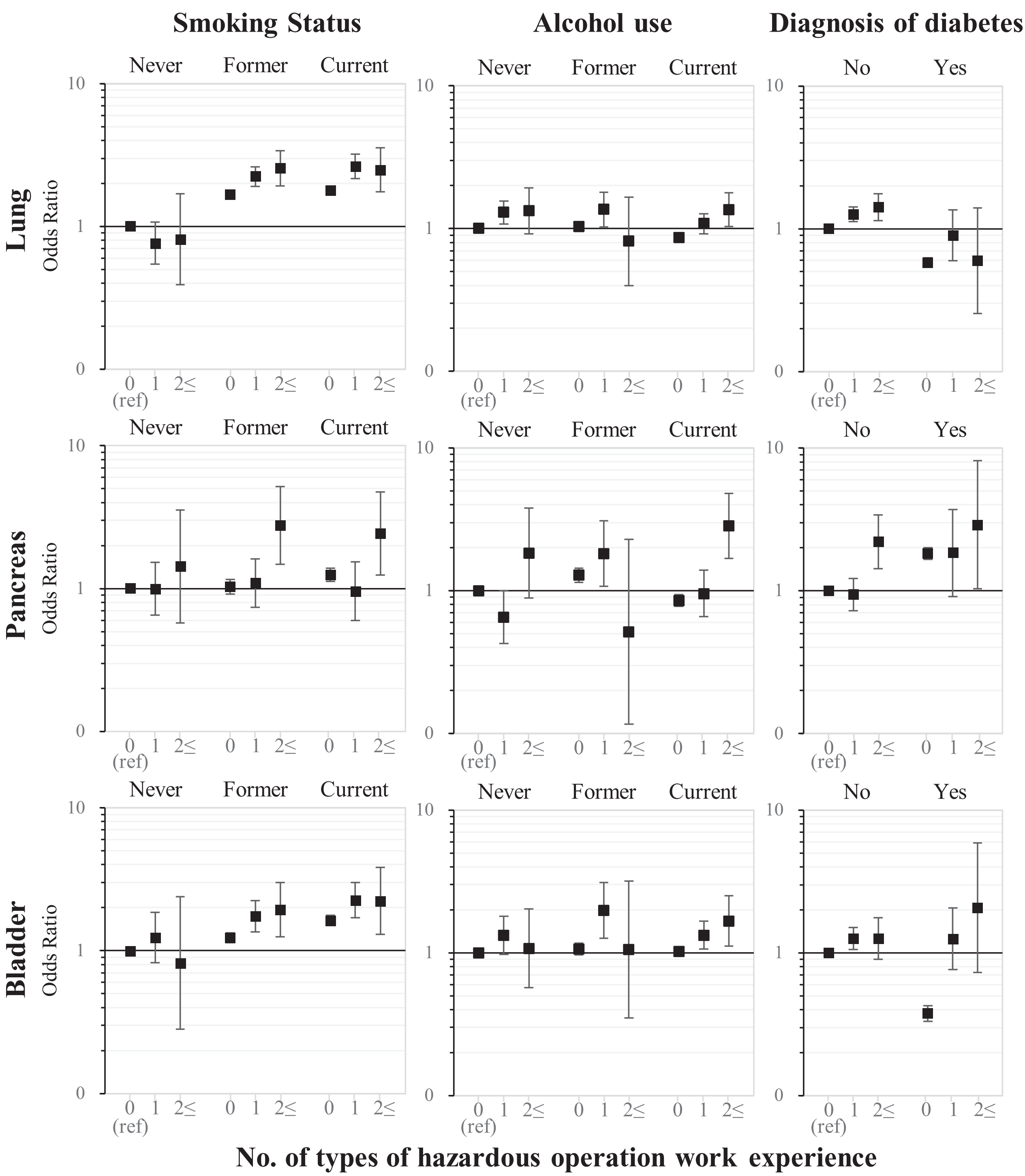

FIGURE 2 Combined effects of hazardous operation work experience with lifestyle-related factors on cancer incidence. The odds ratio (OR) (dot) and 95% confidence interval (CI) (bar) were estimated by conditional logistic regression with multiple imputation, matched for age, sex, admission date, and admitting hospital, and additionally adjusted for smoking, alcohol use, and/or diagnosis of diabetes, except the combined factors. Reference was the combination group with no experience of hazardous operation work and never smoker, never alcohol user, or no diagnosis of diabetes

therefore considered that the cases and controls were drawn from the same large community population. Second, data regarding other clinical risk factors for cancer, such as for overweight, physical inactivity, diet, or second-hand smoke, were unavailable. Third, we did not consider the amount and duration of exposure, or the interval between exposure and cancer incidence. Instead, this study focused on the types of hazardous operations engaged in, assuming that the number of hazardous operations may have been a proxy for exposure to unknown hazardous factors. Fourth, the occupational environment was not assessed due to the lack of data. Risk assessment, proper use of protective equipment, and adjustment of working hours may all reduce the risk of carcinogenesis, and future studies should consider the effects of occupational hygiene management on the incidence of cancer. Finally, the underlying mechanisms remain unexplainable. In particular, the number of chemical combinations and mixtures is enormous. Further studies are needed if we are to clarify the carcinogenicity identified in the present study.

In this large case-control study, after adjusting for a possible range of known cancer risk factors, we found that experience of hazardous occupational operations was associated with an increased risk of several cancers. Combinations with lifestyle-related factors on hazardous operation work may have potential additional risks to further increase the risk of cancer. While our findings should be internally validated in cohort studies and externally validated in other counties and regions, there is a need to establish a comprehensive system in each country that verifies whether hazardous occupational work activities are associated with increased risk of cancer.

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DISCLOSURE

The authors have no conflict of interest to declare.

ORCID

Kota Fukai https://orcid.org/0000-0002-8319-8467
Noriko Kojimahara https://orcid.org/0000-0003-4099-6167
Keika Hoshi https://orcid.org/0000-0003-1912-0718
Akihiro Toyota https://orcid.org/0000-0002-4101-1131
Masayuki Tatemichi https://orcid.org/0000-0002-5051-8591

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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