INTRODUCTION

Risks associated with work that involves hazardous factors that are potentially carcinogenic are often complex and challenging to assess. 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. 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.\textsuperscript{6} 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.\textsuperscript{5,6} An individual can be engaged in multiple types of hazardous operations through their professional life.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6,10} Smoking and alcohol use plays an important role, and modifiable lifestyle-related factors are indeed the most influential cause of cancer worldwide.\textsuperscript{2} Diabetes is increasing in prevalence in most countries and is associated with increased risk of several cancers.\textsuperscript{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.\textsuperscript{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-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.\textsuperscript{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\textsuperscript{13} and women,\textsuperscript{15} and lifetime alcohol consumption.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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 | 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

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. 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. 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 confounding 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. 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,
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 operation 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).

### 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.\(^1,2,3,4\) 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 1 Background characteristics of case and control subjects

|                          | Controls  | Cases      | P-value* |
|--------------------------|-----------|------------|----------|
| Population, no.          | 555,254   | 128,973    | <.001    |
| Male                     | 312,429   | 76,541     | <.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   |

*P-values for the t test and chi-squared test.
\(^b\)Percentage may not total 100 because of rounding.
\(^c\)Variables contained missing data.
### 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)

| Smoking status | No. of controls (N=27 346) | No. of cases (%) | Smoking status | No. of controls (N=27 346) | No. of cases (%) |
|----------------|-----------------------------|------------------|----------------|-----------------------------|------------------|
| Never          | 17 021                      | 348              | Former         | 15 730                      | 72               |
|                | 2341 (12.1%)                | 38 (9.8%)        |                | 4159 (20.9%)                | 223 (23.5%)      |
|                | Model 4                      | 1 (Reference)    |                | 1 (Reference)               | 1.34 (1.15, 1.56) |
|                |                             | 0.77 (0.55, 1.09)|                |                             | 1.54 (1.16, 2.04) | <.001
| Former         | 17 021                      | 348              | Current        | 8604                        | 123              |
|                | 2341 (12.1%)                | 38 (9.8%)        |                | 2399 (21.8%)                | 141 (26.6%)      |
|                | Model 4                      | 1 (Reference)    |                |                             | 1.46 (1.20, 1.78) |
|                |                             | 1.32 (1.09, 1.58)|                |                             | 1.38 (0.97, 1.98) | <.001
| Current        | 21 411                      | 532              | Alcohol use    | 21 411                      | 532              |
|                | 4427 (17.1%)                | 146 (21.5%)      |                | 5257                        | 208              |
|                | Model 4                      | 1 (Reference)    |                |                             | 1.30 (0.98, 1.73) |
|                |                             | 1.32 (1.09, 1.58)|                |                             | 0.78 (0.38, 1.61) | .358
| Former         | 14 687                      | 724              | Diagnosis of diabetes | 14 687                      | 724              |
|                | 3123 (17.5%)                | 189 (20.7%)      |                |                             | 1.24 (1.05, 1.46) |
|                | Model 4                      | 1 (Reference)    |                |                             | 1.55 (1.18, 2.04) | <.001
| Yes            | 36 756                      | 1327             |                | 36 756                      | 1327             |
|                | 8270 (18.4%)                | 374 (22.0%)      |                |                             | 1.26 (1.12, 1.42) |
|                | Model 4                      | 1 (Reference)    |                |                             | 1.42 (1.14, 1.76) | <.001
| Yes            | 4599                        | 137              |                | 4599                        | 137              |
|                | 629 (12.0%)                 | 28 (17.0%)       |                |                             | 1.52 (1.00, 2.30) |
|                | Model 4                      | 1 (Reference)    |                |                             | 1.00 (0.43, 2.36) | .174
| Pancreas cancer |                              |                  |                | 13 565                      | 417              |
|                |                              |                  |                | 2775 (17.0%)                | 77 (15.6%)       |
|                |                              |                  |                | Model 4                      |                   |
|                |                              |                  |                |                             |                   |

(Continues)
| Smoking status          | Never | No. of controls | No. of cases (%) | P-value for trendf |
|-------------------------|-------|----------------|-----------------|-------------------|
| No. of controls         | 6788  | 143            | 1277 (15.8%)    | .023              |
| No. of cases (%)a       |       | 26 (15.4%)     | 6 (21.4%)       |                   |
| Model 4e                | 1 (Reference) | 1.00 (0.65, 1.52) | 1.44 (0.58, 3.58) | .632              |
| Former                  |       | 4231           | 865 (17.0%)     |                   |
| No. of cases (%)a       |       | 32 (16.8%)     | 17 (34.7%)      |                   |
| Model 4e                | 1 (Reference) | 1.06 (0.72, 1.57) | 2.70 (1.45, 5.04) | .013              |
| Current                 |       | 2546           | 633 (19.9%)     |                   |
| No. of cases (%)a       |       | 19 (14.2%)     | 13 (30.2%)      |                   |
| Model 4e                | 1 (Reference) | 0.76 (0.47, 1.21) | 1.95 (0.99, 3.84) | .463              |

| Alcohol use            | Never | No. of controls | No. of cases (%)a | P-value for trendf |
|------------------------|-------|----------------|------------------|-------------------|
| No. of controls        | 7971  | 191            | 1602 (16.7%)     |                   |
| No. of cases (%)a      |       | 24 (11.2%)     | 10 (27.0%)       |                   |
| Model 4e               | 1 (Reference) | 0.65 (0.43, 1.00) | 1.85 (0.90, 3.82) | .685              |
| Former                 |       | 1454           | 447 (23.5%)      |                   |
| No. of cases (%)a      |       | 19 (27.5%)     | 2 (10.0%)        |                   |
| Model 4e               | 1 (Reference) | 1.39 (0.81, 2.37) | 0.41 (0.09, 1.79) | .915              |
| Current                |       | 4140           | 726 (14.9%)      |                   |
| No. of cases (%)a      |       | 34 (16.2%)     | 24 (38.1%)       |                   |
| Model 4e               | 1 (Reference) | 1.13 (0.77, 1.66) | 3.33 (1.96, 5.65) | <.001             |

| Diagnosis of diabetes  | No    | No. of controls | No. of cases (%)a | P-value for trendf |
|------------------------|-------|----------------|------------------|-------------------|
| No. of controls        | 12 069| 389            | 2226 (15.6%)     | .028              |
| No. of cases (%)a      |       | 67 (14.7%)     | 30 (29.1%)       |                   |
| Model 4e               | 1 (Reference) | 0.95 (0.73, 1.23) | 2.23 (1.44, 3.44) |                   |
| Yes                    |       | 1496           | 549 (26.9%)      |                   |
| No. of cases (%)a      |       | 10 (26.3%)     | 6 (35.3%)        |                   |
| Model 4e               | 1 (Reference) | 0.98 (0.48, 2.01) | 1.50 (0.53, 4.23) | .547              |

| Bladder cancer         | Total population | No. of controls | No. of cases (%)a | P-value for trendf |
|------------------------|------------------|----------------|------------------|-------------------|
| No. of controls        | 20 593           | 643            | 4850 (19.1%)     | <.001             |
| No. of cases (%)a      |       | 184 (22.3%)    | 50 (23.0%)       |                   |
| Model 1b               | 1 (Reference)    | 1.44 (1.22, 1.70) | 1.51 (1.10, 2.08) | <.001             |
| Model 2c               | 1 (Reference)    | 1.36 (1.15, 1.61) | 1.42 (1.03, 1.95) | <.001             |

(Continues)
TABLE 2 (Continued)

| Smoking status | No. of types of hazardous operation work experience |  |  |  |
|----------------|-----------------------------------------------|---|---|---|
|                | Never                                        | One (Reference) | Two or more (Reference) | P-value for trend<sup>f</sup> |
| Smoking status |                                              | 1.37 (1.16, 1.62) | 1.39 (1.00, 1.91) | <.001 |
| Model 3<sup>d</sup> |                                              |  |  |  |
| Smoking status | Never                                        | 1 (Reference) | 1.26 (0.84, 1.88) | 0.84 (0.29, 2.44) | .540 |
| Model 4<sup>e</sup> |                                              |  |  |  |
| Smoking status | Former                                       | 1.41 (1.10, 1.81) | 1.57 (1.01, 2.43) | .001 |
| Model 4<sup>e</sup> |                                              |  |  |  |
| Smoking status | Current                                      | 1.37 (1.03, 1.82) | 1.35 (0.78, 2.31) | .023 |
| Model 4<sup>e</sup> |                                              |  |  |  |
| Alcohol use    |                                              |  |  |  |
|                | Never                                        | 1 (Reference) | 1.34 (0.99, 1.81) | 1.09 (0.58, 2.04) | .130 |
| Model 4<sup>e</sup> |                                              |  |  |  |
|                | Former                                       | 1.88 (1.19, 2.98) | 0.99 (0.32, 3.00) | .053 |
| Model 4<sup>e</sup> |                                              |  |  |  |
|                | Current                                      | 1.29 (1.03, 1.62) | 1.62 (1.08, 2.42) | .002 |
| Model 4<sup>e</sup> |                                              |  |  |  |
| Diagnosis of diabetes | No                                            | 1 (Reference) | 1.27 (1.06, 1.51) | 1.26 (0.90, 1.76) | .005 |
| Model 4<sup>e</sup> |                                              |  |  |  |
|                | Yes                                           | 1 (Reference) | 3.24 (1.93, 5.43) | 5.29 (1.83, 15.29) | <.001 |
| Model 4<sup>e</sup> |                                              |  |  |  |

<sup>a</sup>Percentage = cases/(cases + controls).

<sup>b</sup>Conditional logistic regression with multiple imputation, matched for sex, age, admission date, and admitting hospital.

<sup>c</sup>Additional adjustment for smoking and alcohol consumption from Model 1.

<sup>d</sup>Additional adjustment for diagnosis of diabetes from Model 2.

<sup>e</sup>Full adjustment for factors in Model 3, except the stratified factors.

<sup>f</sup>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.
investigated. We observed an increased risk of colon cancer solely from engagement in asbestos-related work, as previously reported.\textsuperscript{31} However, despite efforts to identify agents that cause cancer, cases of unknown occupational cause have been reported. In 2013, Kumagai et al.\textsuperscript{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).\textsuperscript{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,\textsuperscript{34} inflammation-inducing and oxidative stress,\textsuperscript{35} hormone secretion mutations,\textsuperscript{36} signal transduction and epigenetic abnormalities,\textsuperscript{37} and autophagy abnormalities,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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
| 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) | 1349 | 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) |
| Lead | 1.05 (0.90, 1.23) | 212 | 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) |
| Tetra-alkyl lead | 1.02 (0.65, 1.59) | 27 | 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) |
| Specified chemical substances | 1.09 (0.99, 1.19) | 683 | 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) |
| Radiation | 1.10 (0.97, 1.25) | 312 | 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) |
| Dust | 1.08 (1.01, 1.14) | 1428 | 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) |
| Asbestos | 1.17 (1.09, 1.26) | 937 | 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) |

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.
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.

ACKNOWLEDGMENTS

We would like to acknowledge all the participants and their families for participation in the study. We would also like to thank all the study staff at the Rosai Hospital Group for their commitment to data collection. This work was supported by Industrial Disease Clinical Research Grants from the Ministry of Health, Labor, and Welfare (No. 170201-01).

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

REFERENCES

1. Labrèche F, Kim J, Song C, et al. The current burden of cancer attributable to occupational exposures in Canada. Prev Med. 2019;122:128-139.

2. Gakidou E, Afshin A, Abajobir AA, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1345-1422.

3. Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: an update from the IARC monographs. Occup Environ Med. 2018;75:593-603.

4. International Agency for Research on Cancer, World Health Organization. Agents classified by the IARC monographs, volumes 1–125. IARC Monographs on the identification of carcinogenic hazards to humans. https://monographs.iarc.fr/agents-classified-by-the-iarc/. Accessed June 1, 2020

5. Shirai T, Ogawa K, Takahashi S. Carcinogenic effects of mixtures of chemicals. J Toxicol Pathol. 2006;19:1-13.

6. Silins I, Högborg J. Combined toxic exposures and human health: Biomarkers of exposure and effect. Int J Environ Res Public Health. 2011;8:629-647.

7. Peters S, Vermeulen R, Cassidy A, et al. Comparison of exposure assessment methods for occupational carcinogens in a multi-centre lung cancer case-control study. Occup Environ Med. 2011;68:148-153.

8. Egeghy PP, Judson R, Gangwal S, et al. The exposure data landscape for manufactured chemicals. Sci Total Environ. 2012;414:159-166.

9. Wilson MP, Schwarzenberg MR. Toward a new U.S. chemicals policy; rebuilding the foundation to advance new science, green chemistry, and environmental health. Environ Health Perspect. 2009;117:1202-1209.

10. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. JAMA Oncol. 2016;2:1154-1161.

11. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci. 2013;104:9-14.

12. Olsson AC, Vermeulen R, Schüz J, et al. Exposure-response analyses of asbestos and lung cancer subtypes in a pooled analysis of case-control studies. Epidemiology. 2017;28:288-299.

13. Zaitsu M, Kaneko R, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I. Occupational class and male cancer incidence: nationwide, multicenter, hospital-based case-control study in Japan. Cancer Med. 2019;8:795-813.

14. Zaitsu M, Kaneko R, Takeuchi T, Sato Y, Kobayashi Y, Kawachi I. Occupational inequalities in female cancer incidence in Japan: hospital-based matched case-control study with occupational class. SSM Popul Health. 2018;5:129-137.

15. Zaitsu M, Cuevas AG, Trudel-Fitzgerald C, Takeuchi T, Kobayashi Y, Kawachi I. Occupational class and risk of renal cell cancer. Health Sci Rep. 2018;1:e49.

16. Zaitsu M, Kato S, Kim Y, et al. Occupational class and risk of cardiovascular disease incidence in Japan: nationwide, multicenter, hospital-based case-control study. J Am Heart Assoc. 2019;8:e011350.

17. Kaneko R, Zaitsu M, Sato Y, Kobayashi Y. Risk of cancer and longest-held occupations in Japanese workers: a multicenter hospital-based case-control study. Cancer Med. 2019;8:6139-6150.

18. Zaitsu M, Takeuchi T, Kobayashi Y, Kawachi I. Light to moderate amount of lifetime alcohol consumption and risk of cancer in Japan. Cancer. 2020;126:1031-1040.

19. World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision (2nd ed.). Geneva: World Health Organization; 2004.

20.Japanese Ministry of Internal Affairs and Communications. Japan standard occupational classification. http://www.soumu.go.jp/enGLISH/ggpp_sseido/shokyou/index-co.htm. Accessed June 1, 2020.

21. Japan International Center for Occupational Safety and Health. Outline of Japan’s Industrial Safety and Health Law 9. Regulations for maintaining and promoting health. https://www.jniosh.johas.go.jp/ icpro/jicosh-old/english/osh/index-c.html. Accessed June 1, 2020.

22. Royston P, White IR. Multiple imputation by chained equations (MICE): implementation in Stata. J Stat Softw. 2011;45:1-20.

23. Nurminen M, Karjalainen A. Epidemiologic estimate of the proportion of fatalities related to occupational factors in Finland. Scand J Work Environ Health. 2001;27:161-213.

24. Rush ton L, Hutchings SJ, Fortunato L, et al. Occupational cancer burden in Great Britain. Br J Cancer. 2012;107:3-7.

25. Jarvis IWH, Dreij K, Mattsson Å, Jernström B, Stenius U. Building the foundation to advance new science, green chemistry, and environmental health. Environ Health Perspect. 2009;117:1202-1209.

26. Boobis A, Budinsky R, Collie S, et al. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment. Crit Rev Toxicol. 2011;41:369-383.

27. Kavlock RJ, Bahadori T, Barton-Maclaren TS, Gwinn MR, Rasenberg M, Thomas RS. Accelerating the pace of chemical risk assessment. Chem Res Toxicol. 2018;31:287-290.
28. Matteis SD, Consonni D, Bertazzi PA. Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction. *Acta Biomed*. 2008;79(Suppl 1):34-42.

29. Ojajärvi A, Partanen TJ, Ahlbom A, et al. Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med*. 2000;57:316-324.

30. Cumberbatch MGK, Cox A, Teare D, Catto JWF. Contemporary occupational carcinogen exposure and bladder cancer. *JAMA Oncol*. 2015;1:1282-1290.

31. Paris C, Thaon I, Hérin F, et al. Occupational asbestos exposure and incidence of colon and rectal cancers in French men: The Asbestos-Related Diseases Cohort (ARDCo-Nut). *Environ Health Perspect*. 2017;125:409-415.

32. Kumagai S, Kurumatani N, Arimoto A, Ichihara G. Cholangiocarcinoma among offset colour proof-printing workers exposed to 1,2-dichloropropane and/or dichloromethane. *Occup Environ Med*. 2013;70:508-510.

33. Kubo S, Nakanuma Y, Takemura S, et al. Case series of 17 patients with cholangiocarcinoma among young adult workers of a printing company in Japan. *J Hepatobiliary Pancreat Sci*. 2014;21:479-488.

34. Luch A. Nature and nurture – lessons from chemical carcinogenesis. *Nat Rev Cancer*. 2005;5:113-125.

35. Kawanishi S, Ohnishi S, Ma N, Hiraku Y, Murata M. Crosstalk between DNA damage and inflammation in the multiple steps of carcinogenesis. *Int J Mol Sci*. 2017;18:1808.

36. Shafei A, Ramzy MM, Hegazy AI, et al. The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer. *Gene*. 2018;647:235-243.

37. Chen QY, Murphy A, Sun H, Costa M. Molecular and epigenetic mechanisms of Cr(VI)-induced carcinogenesis. *Toxicol Appl Pharmacol*. 2019;377:114636.

38. Guo JY, White E. Autophagy, metabolism, and cancer. *Cold Spring Harb Symp Quant Biol*. 2016;81:73-78.

39. Storz P, Crawford HC. Carcinogenesis of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2020;158:2072-2081.

40. Berkson J. Limitations of the application of fourfold table analysis to hospital data. *Int J Epidemiol*. 2014;43:511-515.

**SUPPORTING INFORMATION**

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

How to cite this article: Fukai K, Kojimahara N, Hoshi K, Toyota A, Tatemichi M. Combined effects of occupational exposure to hazardous operations and lifestyle-related factors on cancer incidence. *Cancer Sci* 2020;111:4581–4593. [https://doi.org/10.1111/cas.14663](https://doi.org/10.1111/cas.14663)