

BMJ Open Effects of active smoking on postoperative outcomes in hospitalised patients undergoing elective surgery: a retrospective analysis of an administrative claims database in Japan

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ABSTRACT

Objectives The purpose of this study was to investigate the effects of smoking on prognosis after elective surgeries. Incidence of 30-day postoperative complications was compared between propensity score-matched ‘ever-smoker’ and ‘never-smoker’ cohorts. Thirty-day mortality and medical costs during the hospital stay were also compared.

Design and setting A large-scale retrospective study using deidentified administrative claims data obtained from 372 acute care hospitals across Japan using the Diagnosis Procedure Combination system (ie, a flat-fee payment system).

Participants Inpatients who were hospitalised to undergo elective surgery.

Primary and secondary outcome measures The primary endpoint of this study was incidence of 30-day postoperative complications. Secondary endpoints were 30-day mortality and total medical costs during hospitalisation. Comparison between ever-smokers and never-smokers was conducted using matched cohorts created by 1:1 propensity score matching.

Results Using 561 598 eligible patients, matched ever-smoker and never-smoker cohorts (n=1 55 593 each) were created. Ever-smokers were defined as patients with Brinkman Index ≥ 1 . The percentage of patients who were male was 76.7%, and mean ages for ever-smokers and never-smokers were 65.1 \pm 13.8 years old and 66.4 \pm 15.3 years old, respectively. The Brinkman Index of the ever-smoker cohort was 677.6 \pm 553.4. Smoking was significantly associated with higher risk of 30-day postoperative complications compared with not smoking (OR 1.15, 95% CI 1.13 to 1.17, p<0.001). Similarly, smoking was significantly associated with postoperative 30-day mortality, with OR of 1.22 (95% CI 1.08 to 1.39, p=0.002).

Conclusions Our results suggest that smoking could be associated with risk of poor postoperative outcomes. In particular, a history of smoking may increase the risk of 30-day postoperative complications as well as that of 30-day mortality. The results suggest that smoking might have a harmful effect on postoperative outcomes irrespective of types of surgery.

Strengths and limitations of this study

- This is the first large-scale retrospective study to investigate the impact of smoking on postoperative outcomes in Japan.
- The number of patients included and the number undergoing postoperative complications were large enough to conduct analysis with ample statistical power.
- As a limitation, smoking status was determined only using self-reported Brinkman Index, making it likely that some smokers who may not have reported their smoking status correctly were included in the never-smoker group; in addition, smoking status just before the surgery was unknown. Patients who had quit smoking before the surgery were included in the ever-smoker cohorts.
- Furthermore, this was an investigation of the relationship between smoking status and incidence of complications; severity of complication was not considered, although it could affect total medical cost during the hospital stay.

INTRODUCTION

The number of tobacco smokers has been decreasing over the last decade in most Western countries, while the percentage of smokers is still increasing in some developing countries.¹ Tobacco smoking is still one of the major causes of mortality and morbidity worldwide.^{2–3} In particular, it is well known that smoking is strongly associated with cardiovascular diseases, pulmonary diseases and cancer. In addition, it is also thought that smoking could increase the risk of poor postoperative outcomes, in ways including impaired wound healing,^{4–7} infections^{7–9} and cardiopulmonary complications.^{8–10} Randomised controlled trials have shown that preoperative cessation of tobacco smoking could result in decreased rates of postoperative complications.^{11 12} These results suggest

that smoking is associated not only with pathogenesis and worsening of various diseases but also with poor prognosis of patients after surgery. It should be noted that 30-day postoperative mortality after elective surgery has been reported to be around 2%.^{13 14} Thus, smoking is naturally not a factor in all these deaths, but could be a major cause.

In Japan, the population has been rapidly ageing and the number of elderly patients undergoing surgery is also increasing. Harmful effects of smoking have been suggested in studies that used cohorts including younger patients, but there are few data on older patients, who are at higher risk of postoperative complications and even death.

The current study was a large-scale retrospective analysis investigating the effects of smoking on prognosis after elective surgeries. Incidence of 30-day postoperative complications was compared between propensity score (PS)-matched ever-smoker and never-smoker cohorts. Thirty-day mortality and medical cost during the hospital stay were also compared.

MATERIALS AND METHODS

Study design and data source

This retrospective study investigated the effect of active smoking on postoperative outcomes in inpatients undergoing elective surgery. The study used deidentified data obtained from Medical Data Vision (MDV) (Tokyo, Japan), which consisted of administrative claims and insurance claims data obtained from 372 acute care hospitals across Japan using the Diagnosis Procedure Combination (DPC) system (a flat-fee payment system). This database comprised both inpatient and outpatient data (for a total of 25 million patients as of August 2018). It includes demographic characteristics of patients, including age and gender distributions, very similar to those of national statistics in Japan. The database is commercially available and based on a contract between Pfizer Japan and MDV; thus, we could access the data, which did not include any information that could be used for the identification of individuals. This study did not need institutional review board approval or informed consent from each individual whose data were considered, based on the Japanese 'Ethical Guidelines for Medical and Health Research Involving Human Subjects'. The protocol was internally approved by a scientific and ethical review board of Pfizer.

Study population

Among patients registered in the database, adults (20 years of age or older) who were hospitalised to undergo elective surgery were eligible. Among them, patients meeting the following criteria were included: (1) patients who had a record of discharge from the indexed hospitalisation, irrespective of reason for discharge, such as recovery, transfer to another hospital or death, (2) patients whose duration of postoperative hospital stay was at least 3 days and (3) patients whose smoking status at

the time of admission was available. Patients with less than 3 days of postoperative hospital stay were not included, because in Japan, patients with minor surgery under local anaesthesia are generally discharged within 3 days. The following patients were excluded: (1) patients whose smoking status was unknown, (2) patients who underwent repeated surgeries on different dates during hospitalisation, (3) pregnant women, (4) patients undergoing haemodialysis, (5) patients whose surgery date was before 1 March 2011 and (6) patients whose data required for the analysis were missing. If patients had multiple records of hospitalisation for independent elective surgeries, only the earliest-appearing records were used for the analysis.

Smokers were defined using the Brinkman Index as of the day of admission. The Brinkman Index measures number of cigarettes smoked per day times smoking years (eg, 1 pack year, ie, 1 pack (20 cigarettes) per day \times 1 year smoking = Brinkman Index 20). If the Brinkman Index was greater than 0, the patient was considered as an ever-smoker irrespective of their current smoking status, and if 0, a never-smoker. Former smokers were included in the ever-smoker group if their Brinkman Index was greater than 0. Patients were excluded from the analysis if their Brinkman Index was unknown.

Statistical analysis

The date of the elective surgery was defined as the 'index date' for each patient, and the period of 120 days before the index date was defined as the baseline period. Demographic and clinical features of each patient during the baseline period or on the index date were collected to characterise the patients. Comorbid diseases were defined using ICD-10 (International Statistical Classification of Diseases and Related Health Problems) codes (see online supplementary table 1), and variables collected from the database are shown in online supplementary table 2.

Propensity score matching (PSM)

In this study, matched cohorts (ever-smokers vs never-smokers) were created from crude cohorts categorised by the Brinkman Index. PS (probability of being a smoker) was estimated for each subject by unconditional logistic regression analyses that incorporated potential factors associated with smoking as independent variables in the regression and smoking status as the outcome. The following covariates obtained during the 120-day baseline period or on the index date were included in the logistic regression: index date, age at admission date, gender, heart failure diagnosis, coronary heart disease diagnosis, renal dysfunction diagnosis, liver dysfunction diagnosis, hypertension diagnosis, diabetes mellitus diagnosis, cancer diagnosis and chronic obstructive pulmonary disease (COPD) diagnosis. To create matched pairs (ever-smokers with never-smokers as reference), a 1:1 PSM method without replacement was used. We applied the nearest neighbour method within calliper matching technique (width=0.01 times the SD of the logit of the PS). Standardised differences were calculated to assess

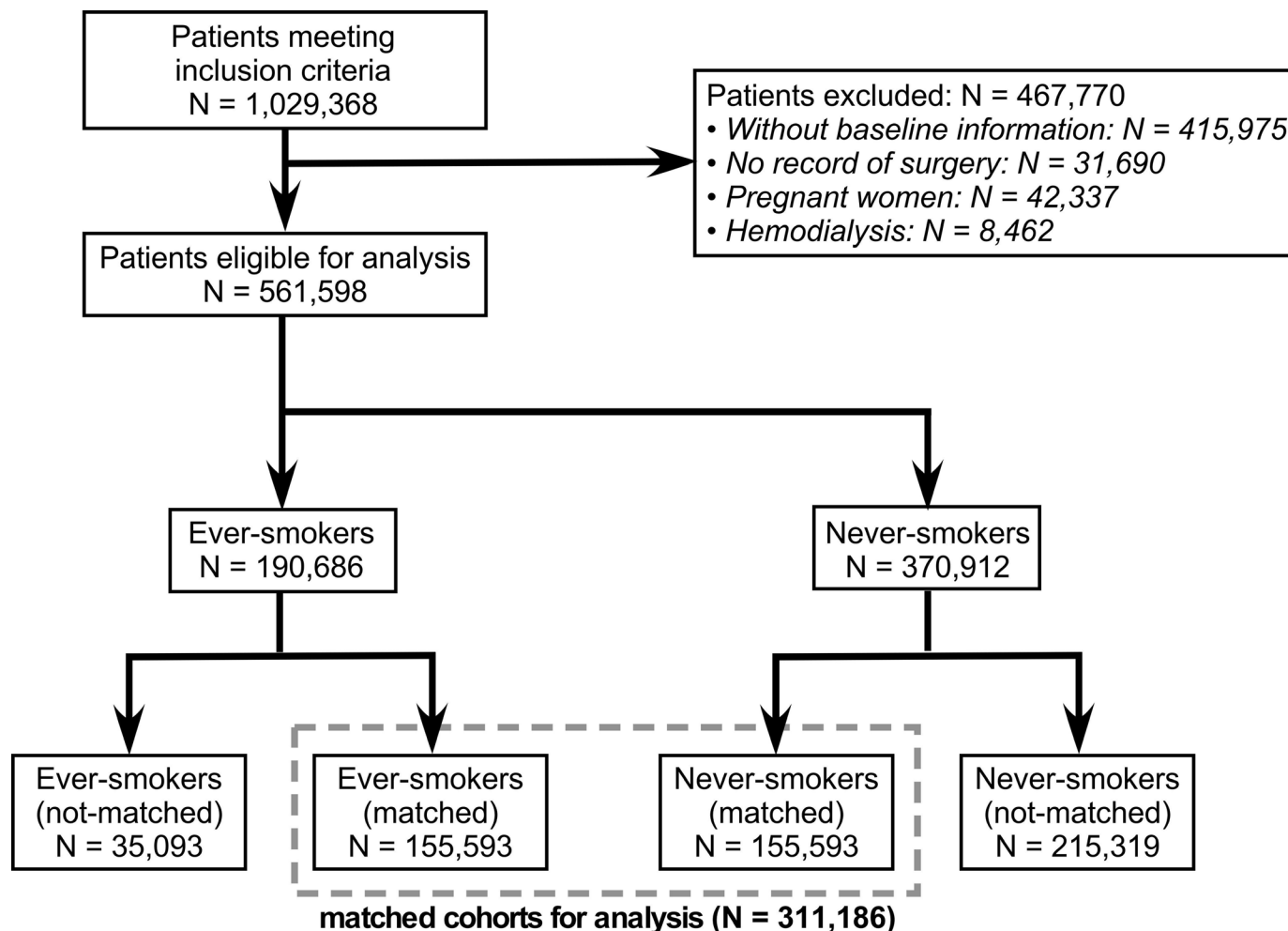


Figure 1 Patient selection flow from Medical Data Vision database.

the balance of covariates between ever-smoker and never-smoker groups. If the standardised difference was less than 10%, the covariates were considered balanced. All analyses were conducted using the matched cohorts. A logistic regression model was used to calculate the ORs with 95% CIs. Smoking status (ever-smoker or never-smoker) was included only as a covariate, and no other covariates were included in the logistic regression model because the two cohorts were well balanced after PSM.

Endpoints

The primary endpoint of this study was the incidence of 30-day postoperative complications. Postoperative complications were identified from the database (postoperative complication-specific ‘T codes’ or ICD-10 codes in combination with a flag for ‘postoperative complications’; see online supplementary table 3); if two or more complications were found within 30 days after the surgery, the earliest-observed complications were used for the analysis. Secondary endpoints were the following: (1) 30-day mortality and (2) total medical costs calculated from the insurance claims data. Thirty-day mortality was defined as all-cause death occurring before discharge from the hospital or within 30 days after the surgery (if hospitalisation was longer than 30 days). The total medical costs

were defined as all medical expenses charged for each patient from admission to death including hospitalisation costs, examination costs, medical procedure costs and medication costs. As a subgroup analysis, the incidence of 30-day postoperative complications per organ/tissue category was also investigated (see online supplementary table 4).

Statistics

All statistical analyses and the subsequent quality check of the results were conducted by an independent third party (EPS, Tokyo, Japan) using SAS software, version 9.4 (SAS Institute), according to the preapproved protocol and statistical analysis plan.

Patient or public involvement

No patients or members of the public were involved in the design or planning of this study.

RESULTS

Patient characteristics

A total of 1 029 368 patients, who had been hospitalised to have an elective surgery were identified from the MDV database (out of about 25 000 000 patients registered).

Table 1 Characteristics of ever-smokers and never-smokers before propensity score matching

	Ever-smokers	Never-smokers	Standardised difference
N	190686	370912	
Index date (days from the origination date)	1685.0±631.8	1662.8±644.2	0.035
Male gender	154436 (81.0)	125704 (33.9)	1.083
Age	65.1±13.8	66.4±15.3	-0.086
Patients in hospitals with <500 beds	113571 (59.6)	234007 (63.1)	-
Brinkman Index	687.1±552.6	0	
Target organ of the elective surgery			
Skin or subcutaneous tissues	27030 (14.2)	51387 (13.9)	
Muscle, bone, limb or trunk	28735 (15.1)	77715 (21.0)	
Nervous system, head or CNS	3837 (2.0)	8630 (2.3)	
Eyes	5737 (3.0)	16015 (4.3)	
Ear, nose or throat	9136 (4.8)	12631 (3.4)	
Face, mouth or neck	4214 (2.2)	8558 (2.3)	
Chest	16803 (8.8)	32501 (8.8)	
Cardiovascular	29145 (15.3)	41977 (11.3)	
Abdomen	61430 (32.2)	99277 (26.8)	
Urological system or adrenal gland	15084 (7.9)	21407 (5.8)	
Genital	18383 (9.6)	53640 (14.5)	
Comorbidity			
Heart failure	26194 (13.7)	43000 (11.6)	-0.064
Coronary artery disease	33742 (17.7)	48221 (13.0)	-0.131
Peripheral artery disease	14275 (7.5)	19396 (5.2)	-
Myocardial infarction	5864 (3.1)	6620 (1.8)	-
Stroke/TIA/SE	15536 (8.1)	24967 (6.7)	-
Renal dysfunction	13197 (6.9)	20416 (5.5)	-0.059
Hepatic dysfunction	32266 (16.9)	51509 (13.9)	-
Hypertension	76458 (40.1)	134012 (36.1)	-0.082
Diabetes mellitus	60156 (31.5)	95561 (25.8)	-0.128
Cancer	105626 (55.4)	191698 (51.7)	-0.074
Infectious disease	29603 (15.5)	48032 (12.9)	-
COPD	16370 (8.6)	14580 (3.9)	-0.193

N (per cent) or mean±SD. Standardised difference was calculated only for variables used for the calculation of propensity score. CNS, central nervous system; COPD, chronic obstructive pulmonary disease; SE, systemic embolism; TIA, transient ischaemic attack.

Among them, 467770 patients were excluded from the analysis based on the exclusion criteria, leading to a final cohort consisting of 561598 eligible patients (190686 ever-smokers and 370912 never-smokers; Fig. 1). Demographic and clinical characteristics of ever-smokers and never-smokers are shown in Table 1. Compared with never-smokers, the percentage of males was much higher among ever-smokers, and ever-smokers had a greater number of comorbidities. In particular, coronary heart disease, hepatic dysfunction, hypertension, diabetes mellitus, cancer, infectious disease and COPD were significantly higher in ever-smokers. Mean age was similar between ever-smokers and never-smokers. The mean (±SD) Brinkman Index in the ever-smokers was

687.1±552.7. PSM at 1:1 ratio created matched ever-smoker and never-smoker cohorts (n=155593 each cohort). Table 2 shows the demographic and clinical characteristics of ever-smokers and never-smokers in the matched cohorts. Because the calculated standardised difference was less than 0.1 for all covariates considered for the estimation of the PSs, the ever-smokers and never-smokers in the matched cohorts were thought to be well balanced.

Postoperative complications in crude cohorts

Thirty-day postoperative complications in the crude ever-smoker and never-smoker cohorts are shown in Table 3. Complications were observed in 29.1% and 26.3% of

Table 2 Characteristics of ever-smokers and never-smokers after propensity score matching

	Ever-smokers	Never-smokers	Standardised difference
N	155 593	155 593	
Index date (days from the origination date)	1677.8±634.5	1675.4±640.6	0.004
Male gender	119 343 (76.7)	119 325 (76.7)	0.000
Age	65.8±13.9	65.5±15.2	0.021
Patients in hospitals with <500 beds	93 174 (59.9)	98 727 (63.5)	–
Brinkman Index	677.6±553.4	0	–
Target organ of the elective surgery			
Skin or subcutaneous tissues	21 982 (14.1)	20 855 (13.4)	–
Muscle, bone, limb or trunk	24 027 (15.4)	24 629 (15.8)	–
Nervous system, head or CNS	3217 (2.1)	3477 (2.2)	–
Eyes	4941 (3.2)	6444 (4.1)	–
Ear, nose or throat	7006 (4.5)	6576 (4.2)	–
Face, mouth or neck	3344 (2.1)	3097 (2.0)	–
Chest	13 549 (8.7)	9673 (6.2)	–
Cardiovascular	23 719 (15.2)	20 189 (13.0)	–
Abdomen	48 845 (31.4)	50 787 (32.6)	–
Urological system or adrenal gland	11 981 (7.7)	11 767 (7.6)	–
Genital	16 473 (10.6)	19 765 (12.7)	–
Comorbidity			
Heart failure	21 118 (13.6)	20 308 (13.1)	–0.016
Coronary artery disease	25 494 (16.4)	25 342 (16.3)	–0.003
Peripheral artery disease	11 723 (7.5)	9631 (6.2)	–
Myocardial infarction	4449 (2.9)	3808 (2.4)	–
Stroke/TIA/SE	12 867 (8.3)	12 303 (7.9)	–
Renal dysfunction	10 429 (6.7)	10 357 (6.7)	–0.002
Hepatic dysfunction	25 439 (16.3)	24 293 (15.6)	–
Hypertension	62 624 (40.2)	59 316 (38.1)	–0.044
Diabetes mellitus	49 380 (31.7)	46 383 (29.8)	–0.043
Cancer	83 974 (54.0)	84 357 (54.2)	0.005
Infectious disease	23 598 (15.2)	23 218 (14.9)	–
COPD	11 332 (7.3)	8630 (5.5)	–0.072

N (per cent) or mean±SD. Standardised difference was calculated only for variables used for the calculation of propensity score. CNS, central nervous system; COPD, chronic obstructive pulmonary disease; SE, systemic embolism; TIA, transient ischaemic attack.

patients in the ever-smoker and never-smoker cohorts, respectively. Gastrointestinal and cardiovascular complications were observed at higher rates compared with other complications. The incidence rates of complications were higher in the ever-smoker cohort than in the never-smoker cohort.

Postoperative complications in matched cohorts

Risk of post-operative complications in ever-smokers was compared with that in never-smokers using the matched cohorts. Days of hospitalisation were not significantly different between the two cohorts (11.6±13.8 days for ever-smokers vs 11.4±13.7 days for never-smokers). Incidence rates of postoperative complications are shown

in [Table 3](#). Overall, 30-day postoperative complications were shown in 27.4% of patients. Among these complications, gastrointestinal tract-related and cardiovascular complications were most common (12.2% and 11.6%, respectively). Incidence rates were higher in ever-smokers compared with never-smokers irrespective of the type of complications, and as is shown in [Table 4](#) and [Fig 2](#), smoking was significantly associated with higher risk of 30-day postoperative complications when compared with never-smokers (OR 1.15, 95% CI 1.13 to 1.17, p<0.001). Among target organs/tissues, all but surgeries on eyes or ‘face, mouth or neck’ were at significantly higher risk of 30-day postoperative complications in ever-smokers, with

Table 3 Incidence of postoperative complications

	Before matching				After matching			
	Total	Ever-smokers	Never-smokers	Std. Diff.	Total	Ever-smokers	Never-smokers	Std. Diff.
N	561 598	190 686	370 912		311 186	155 593	155 593	
All complications	152 875 (27.2)	55 452 (29.1)	97 423 (26.3)	0.06260	85 224 (27.4)	44 782 (28.8)	40 442 (26.0)	0.06281
GI tract related	66 166 (11.8)	23 451 (12.3)	42 665 (11.5)	0.02471	36 921 (11.9)	18 909 (12.2)	18 012 (11.6)	0.01853
Wound related	32 458 (5.8)	12 263 (6.4)	20 195 (5.4)	0.04245	17 931 (5.8)	9895 (6.4)	8036 (5.2)	0.05136
Infectious	19 761 (3.5)	7808 (4.1)	11 953 (3.2)	0.04801	11 824 (3.8)	6296 (4.0)	5528 (3.6)	0.02092
Renal or endocrine	5951 (1.1)	2238 (1.2)	3713 (1.0)	0.01918	3530 (1.1)	1841 (1.2)	1689 (1.1)	0.00938
Cardiovascular	53 393 (9.5)	19 611 (10.3)	33 782 (9.1)	0.04055	29 677 (9.5)	15 777 (10.1)	13 900 (8.9)	0.04093
Pulmonary	10 015 (1.8)	4261 (2.2)	5754 (1.6)	0.04396	5931 (1.9)	3392 (2.2)	2539 (1.6)	0.04396
Neurological	3325 (0.6)	1342 (0.7)	1983 (0.5)	0.02590	2001 (0.6)	1112 (0.7)	889 (0.6)	0.01244

GI, gastrointestinal; Std. Diff, standardised difference.

chest surgeries and cardiovascular surgeries at particularly high risk (chest OR 1.34, 95% CI 1.27 to 1.42; cardiovascular OR 1.25, 95% CI 1.20 to 1.31 as shown in Table 4).

Thirty day-mortality showed a similar trend. Smoking was significantly associated with postoperative 30-day mortality, with an OR of 1.22 (95% CI 1.08 to 1.39, $p=0.002$). Only surgeries on 'nervous system, head or CNS' were at higher risk of 30-day mortality in ever-smokers compared with never-smokers; statistical significance was not obtained for other surgeries due to lower incidence rates of death within 30 days after the surgeries.

Medical cost during hospitalisation in matched cohorts

Total medical costs needed during the hospital stay were compared between matched ever-smoker and never-smoker cohorts. As is shown in table 5, smoking was significantly associated with higher medical costs.

Patients undergoing surgeries on most organs/tissues incurred higher medical costs if they were ever-smokers compared with never-smokers, although for 'urological system or adrenal gland' or genital tissue surgeries costs were higher in never-smoker cohorts.

DISCUSSION

In this study, we found that tobacco smoking was associated with poor postoperative outcomes in patients undergoing elective surgery. The investigation of the negative impact of active smoking on postoperative complications suggested that the risk of overall 30-day complications after surgery was increased by 15%. Smoking was also significantly associated with increased risk of 30-day mortality, by 22%.

Table 4 ORs and 95% CIs of postoperative complications and 30-day mortality

Target organs/tissues of surgery	Postoperative complications		30-day mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Whole	1.15 (1.13 to 1.17)	<0.001	1.22 (1.08 to 1.39)	0.002
Skin or subcutaneous tissues	1.18 (1.14 to 1.23)	<0.001	1.15 (0.85 to 1.56)	0.370
Muscle, bone, limb or trunk	1.12 (1.07 to 1.17)	<0.001	1.39 (0.74 to 2.60)	0.306
Nervous system, head or CNS	1.21 (1.08 to 1.34)	<0.001	2.99 (1.33 to 6.72)	0.008
Eyes	1.01 (0.89 to 1.13)	0.932	<0.01 (<0.01→999.9)	0.947
Ear, nose or throat	1.19 (1.09 to 1.29)	<0.001	1.46 (0.81 to 2.64)	0.209
Face, mouth or neck	1.06 (0.95 to 1.18)	0.332	0.93 (0.06 to 14.81)	0.956
Chest	1.34 (1.27 to 1.42)	<0.001	0.95 (0.63 to 1.43)	0.790
Cardiovascular	1.25 (1.20 to 1.31)	<0.001	1.22 (0.96 to 1.55)	0.111
Abdomen	1.08 (1.05 to 1.11)	<0.001	1.17 (0.98 to 1.40)	0.088
Urological system or adrenal gland	1.10 (1.03 to 1.17)	0.002	0.90 (0.51 to 1.59)	0.725
Genital	1.09 (1.04 to 1.15)	<0.001	0.80 (0.13 to 4.79)	0.806

ORs were calculated by using a logistic regression model to obtain the relative risk of ever-smokers compared with that of never-smokers (reference).

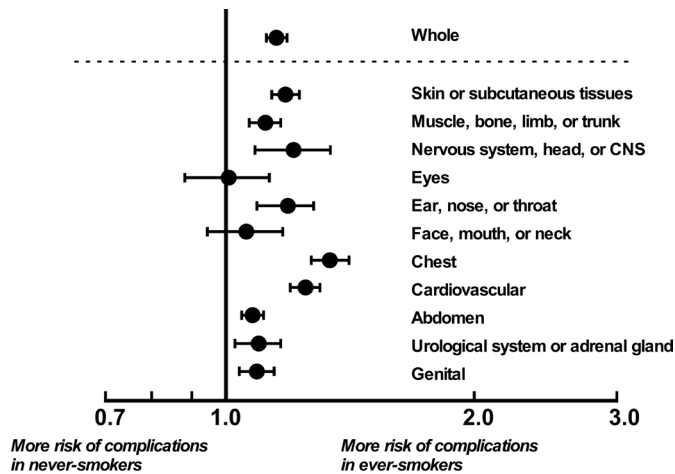


Figure 2 Forest plot showing results of logistic regression analysis using matched cohorts to evaluate the impact of smoking on postoperative complications. ORs with 95% CIs. CNS, central nervous system.

The relationship between elective surgery and its postoperative complications has been investigated in previous studies, most of which have shown an association of active smoking with poor postoperative outcomes, as was also shown here. In the present study, we investigated the impact of smoking on postoperative outcomes in patients undergoing any elective surgery, not only specific surgeries, unlike previous studies; we found that irrespective of target organs or types of surgery, smoking was associated with poor outcomes, almost without exception. One characteristic of our study was that the mean age of the patients used for the analysis, 65.1±13.8 years old for ever-smokers and 66.4±15.3 years old for never-smokers, was higher than those in the previous studies (40s–50s in most previous studies). This may be a result of the fact that Japan is a rapidly ageing society and the mean age of

smokers is thus higher than that in other countries. The higher rate of postoperative complications (about 27% for all complications) could also be attributable to the higher mean age of the sample. In previous studies, the relationship between smoking and short-term postoperative complications was controversial; many studies failed to demonstrate association between smoking and poor cardiovascular outcomes,^{5 15–17} whereas in the present study the risk of cardiovascular complications was significantly associated with smoking (OR 1.25, 95% CI 1.20 to 1.31). This difference could also be attributed to the higher age of the population at a higher risk of cardiovascular complications, whose incidence rate was about 10% (n=29 677 out of n=311 186). Regarding CNS, there are also conflicting results regarding the effects of smoking on postoperative outcomes. The present study shows the harmful effects of smoking, while in some other previous studies, an association between smoking and postoperative outcomes was not demonstrated.^{18 19} Reasons for such a discrepancy are not clear; however, it might come from the difference in definitions of smokers. Former smokers were included in the smoker group in the present study, while previous studies separated former and current smokers. In addition, differences in the target populations might underlie the differences in the results.

The mechanism underlying smoking-associated poor postoperative outcomes is not clear, although several possible mechanisms have been proposed. It has been suggested that smoking could affect mucus transport and/or production in the pulmonary tract,^{20 21} promote pulmonary inflammation²² and ameliorate the pulmonary immune system,²³ resulting in pulmonary complications including respiratory dysfunction and pneumonia. It is also suggested that smoking-delivered substances including nicotine and carbon monoxide could have

Table 5 Total medical costs during hospitalisation in ever-smokers and never-smokers

Target organs/tissues of surgery	Ever-smokers	Never-smokers	P value
Whole	1 183 853±1 074 679	1 104 623±997 021	<0.001
Skin or subcutaneous tissues	1 678 630±1 460 673	1 514 621±1 398 867	<0.001
Muscle, bone, limb or trunk	1 410 137±1 049 762	1 377 554±1 029 976	<0.001
Nervous system, head or CNS	2 045 967±1 804 032	1 975 733±1 651 279	0.011
Eyes	692 155±399 067	688 019±336 221	0.140
Ear, nose or throat	980 397±1 558 145	893 854±1 421 525	0.304
Face, mouth or neck	743 574±571 278	709 701±479 285	0.068
Chest	1 435 903±1 003 955	1 205 665±932 353	<0.001
Cardiovascular	1 952 217±1 717 837	1 830 087±1 650 512	<0.001
Abdomen	1 053 418±959 008	1 011 904±923 050	<0.001
Urological system or adrenal gland	724 049±631 612	728 223±660 790	0.006
Genital	833 273±414 224	851 435±411 710	<0.001

Total medical costs during hospitalisation were compared between matched ever-smokers and matched never-smokers by Mann-Whitney U test. CNS, central nervous system.



effects on the cardiovascular system, including on vascular tone and/or platelet activities,^{24 25} which might in turn be related to cardiovascular complications or impaired wound healing. In this way, smoking-derived substances/molecules and smoking-induced ischaemia might act together to cause postoperative complications.

In the present study, comparisons were made between ever-smokers and never-smokers. The ever-smoker cohort contained former smokers who had quit smoking at the timing of surgery due to the limited availability of data regarding their current smoking status. Therefore, unfortunately, it is unclear in this study whether smoking cessation before the surgery could reduce the risk of poor postoperative outcomes. It is likely that the timing of smoking cessation might be critical. It has been suggested that smoking cessation at least 4 weeks before surgery could decrease the risk of postoperative complications.^{11 12} In Japan, the Japanese Society of Anesthesiologists has issued 'Guideline for Perioperative Smoking Cessation', where smoking cessation at least 4 weeks before elective surgery is recommended to reduce the risk of postoperative complications.²⁶ However, the days until elective surgery are less than 4 weeks for many patients in general practice. Therefore, an important question is 'how long is long enough' for smoking cessation to significantly reduce the risk of postoperative complications, which could differ depending on the duration of past smoking. Further study is necessary to elucidate the minimum duration of preoperative abstinence to obtain significant or maximal effects of smoking cessation.

Regardless, a systematic programme to educate patients undergoing elective surgery about the harmful effects of smoking should be established.

In conclusion, our results suggest that smoking, current or past, could be associated with a higher risk for poor postoperative outcomes. In particular, smoking may increase the risk of 30-day postoperative complications as well as that of 30-day mortality. The results suggest that smoking might have a harmful effect on postoperative outcomes, irrespective of the type of surgery.

LIMITATIONS

Retrospective analyses using claims data from the DPC hospitals have several intrinsic limitations, and certain biases are to be expected. First, smoking status was determined only by using self-reported Brinkman Index. This likely led some smokers to be included in the never-smoker group because they did not correctly report their smoking status, which could lead to an underestimation about the effects of smoking. In addition, we could not distinguish current smokers from former smokers, and both were included in the ever-smoker cohort, which might have a significant impact on the results, and the effects of smoking cessation before surgery was not investigated in the present study. Second, this analysis investigated the relationship between smoking status and incidence of complications; severity of complication was

not considered. Although the total medical cost during the hospital stay could be affected by severity of complications, we did not carry out any further analysis. Third, covariates used for calculation of PS were selected based on previous studies. However, patient background might not be balanced in variables that were not considered for PS. Fourth, the present study only elucidated the association between smoking status and postoperative outcomes but could not determine a causal relationship. It should be noted that the effects of smoking cessation before elective surgery were not examined in the present study. Finally, our findings may not be widely generalised to other countries because healthcare systems differ from country to country.

Contributors RY designed the study, managed the data analysis and critically reviewed the manuscript. JK prepared the protocol and its statistical analysis plan and drafted the manuscript.

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Competing interests RY and JK are employees of Pfizer Japan.

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Ethics approval Approval by IRB/IEC was not required according to Japanese guidelines. The protocol and statistical analysis plan were internally approved by non-commercial medical peers before data acquisition from the database.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All major results generated in this study and codes used for this study are shown in the published article or its online supplemental content. Raw data obtained from MVD Inc. are undisclosed due to contract between MDV Inc. and Pfizer Inc.

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REFERENCES

- 1 WHO. *Global report on trends in prevalence of tobacco smoking 2000–2025, second edition*. Geneva: World Health Organization, 2018.
- 2 Akter S, Nakagawa T, Honda T, *et al*. Smoking, Smoking Cessation, and Risk of Mortality in a Japanese Working Population- Japan Epidemiology Collaboration on Occupational Health Study. *Circ J* 2018;82:3005–12.
- 3 Samet JM. Tobacco smoking: the leading cause of preventable disease worldwide. *Thorac Surg Clin* 2013;23:103–12.
- 4 Kean J. The effects of smoking on the wound healing process. *J Wound Care* 2010;19:5–8.
- 5 Sharif-Kashani B, Shahabi P, Mandegar M-H, *et al*. Smoking and wound complications after coronary artery bypass grafting. *J Surg Res* 2016;200:743–8.
- 6 Sørensen LT, Hørbj J, Friis E, *et al*. Smoking as a risk factor for wound healing and infection in breast cancer surgery. *Eur J Surg Oncol* 2002;28:815–20.
- 7 Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. *Arch Surg* 2012;147:373–83.
- 8 Grønkvær M, Eliassen M, Skov-Ettrup LS, *et al*. Preoperative smoking status and postoperative complications: a systematic review and meta-analysis. *Ann Surg* 2014;259:52–71.
- 9 Gajdos C, Hawn MT, Campagna EJ, *et al*. Adverse effects of smoking on postoperative outcomes in cancer patients. *Ann Surg Oncol* 2012;19:1430–8.
- 10 Singh JA, Hawn M, Campagna EJ, *et al*. Mediation of smoking-associated postoperative mortality by perioperative complications in veterans undergoing elective surgery: data from Veterans Affairs

- Surgical Quality Improvement Program (VASQIP)--a cohort study. *BMJ Open* 2013;3:e002157.
- 11 Lindström D, Azodi OS, Wladis A, *et al*. Effects of a perioperative smoking cessation intervention on postoperative complications. *Ann Surg* 2008;248:739–45.
 - 12 Møller AM, Villebro N, Pedersen T, *et al*. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *The Lancet* 2002;359:114–7.
 - 13 Eslami MH, Rybin DV, Doros G, *et al*. Description of a risk predictive model of 30-day postoperative mortality after elective abdominal aortic aneurysm repair. *J Vasc Surg* 2017;65:65–74.
 - 14 Cavaliere F, Conti G, Costa R, *et al*. Intensive care after elective surgery: a survey on 30-day postoperative mortality and morbidity. *Minerva Anestesiol* 2008;74:459–68.
 - 15 Al-Sarraf N, Thalib L, Hughes A, *et al*. Lack of correlation between smoking status and early postoperative outcome following valve surgery. *Thorac Cardiovasc Surg* 2008;56:449–55.
 - 16 Utley JR, Leyland SA, Fogarty CM, *et al*. Smoking is not a predictor of mortality and morbidity following coronary artery bypass grafting. *J Card Surg* 1996;11:377–84.
 - 17 Hollenberg M, Mangano DT, Browner WS, *et al*. Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. the study of perioperative ischemia Research Group. *JAMA* 1992;268:205–9.
 - 18 Alan N, Seicean A, Seicean S, *et al*. Smoking and postoperative outcomes in elective cranial surgery. *J Neurosurg* 2014;120:811–9.
 - 19 Seicean A, Seicean S, Alan N, *et al*. Effect of smoking on the perioperative outcomes of patients who undergo elective spine surgery. *Spine* 2013;38:1294–302.
 - 20 Saetta M, Turato G, Baraldo S, *et al*. Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. *Am J Respir Crit Care Med* 2000;161:1016–21.
 - 21 Di YP, Zhao J, Harper R. Cigarette smoke induces MUC5AC protein expression through the activation of Sp1. *J Biol Chem* 2012;287:27948–58.
 - 22 Koczulla A-R, Noeske S, Herr C, *et al*. Acute and chronic effects of smoking on inflammation markers in exhaled breath condensate in current smokers. *Respiration* 2010;79:61–7.
 - 23 Eapen MS, Sharma P, Moodley YP, *et al*. Dysfunctional immunity and microbial adhesion molecules in smoking-induced pneumonia. *Am J Respir Crit Care Med* 2019;199:250–1.
 - 24 Benowitz NL. The role of nicotine in smoking-related cardiovascular disease. *Prev Med* 1997;26:412–7.
 - 25 Zevin S, Saunders S, Gourlay SG, *et al*. Cardiovascular effects of carbon monoxide and cigarette smoking. *J Am Coll Cardiol* 2001;38:1633–8.
 - 26 Japanese Society of Anesthesiologists. A guideline for perioperative smoking cessation (in Japanese), 2015. Available: <http://www.anesth.or.jp/guide/pdf/20150409-1guidelin.pdf> [Accessed 22 January 2019].