

Original Investigation

Smoking and the Risk of Mortality and Vascular and Respiratory Events in Patients Undergoing Major Surgery

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IMPORTANCE The effects of smoking on postoperative outcomes in patients undergoing major surgery are not fully established. The association between smoking and adverse postoperative outcomes has been confirmed. Whether the associations are dose dependent or restricted to patients with smoking-related disease remains to be determined.

OBJECTIVE To evaluate the association between current and past smoking on the risk of postoperative mortality and vascular and respiratory events in patients undergoing major surgery.

DESIGN Cohort study using the American College of Surgeons National Surgical Quality Improvement Program database. We obtained data on smoking history, perioperative risk factors, and 30-day postoperative outcomes. We assessed the effects of current and past smoking (>1 year prior) on postoperative outcomes after adjustment for potential confounders and effect mediators (eg, cardiovascular disease, chronic obstructive pulmonary disease, and cancer). We also determined whether the effects are dose dependent through analysis of pack-year quintiles.


SETTING AND PARTICIPANTS A total of 607 558 adult patients undergoing major surgery in non-Veterans Affairs hospitals across the United States, Canada, Lebanon, and the United Arab Emirates during 2008 and 2009.

MAIN OUTCOMES AND MEASURES The primary outcome measure was 30-day postoperative mortality; secondary outcome measures included arterial events (myocardial infarction or cerebrovascular accident), venous events (deep vein thrombosis or pulmonary embolism), and respiratory events (pneumonia, unplanned intubation, or ventilator requirement >48 hours).

RESULTS The sample included 125 192 current (20.6%) and 78 763 past (13.0%) smokers. Increased odds of postoperative mortality were noted in current smokers only (odds ratio, 1.17 [95% CI, 1.10-1.24]). When we compared current and past smokers, the adjusted odds ratios were higher in the former for arterial events (1.65 [95% CI, 1.51-1.81] vs 1.20 [1.09-1.31], respectively) and respiratory events (1.45 [1.40-1.51] vs 1.13 [1.08-1.18], respectively). No effects on venous events were observed. The effects of smoking mediated through smoking-related disease were minimal. The increased adjusted odds of mortality in current smokers were evident from a smoking history of less than 10 pack-years, whereas the effects of smoking on arterial and respiratory events were incremental with increased pack-years.

CONCLUSIONS AND RELEVANCE Smoking cessation at least 1 year before major surgery abolishes the increased risk of postoperative mortality and decreases the risk of arterial and respiratory events evident in current smokers. These findings should be carried forward to evaluate the value and cost-effectiveness of intervention in this setting. Our study should increase awareness of the detrimental effects of smoking—and the benefits of its cessation—on morbidity and mortality in the surgical setting.

JAMA Surg. 2013;148(8):755-762. doi:10.1001/jamasurg.2013.2360
Published online June 19, 2013.

 Supplemental content at
jamasurgery.com

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Smoking remains a leading preventable cause of morbidity and mortality that is responsible for almost half a million deaths and about \$200 billion in added costs for health care and lost productivity each year in the United States alone.¹ The role of long-term tobacco dependence in increasing the risks of cancer and cardiovascular and pulmonary disease are well established. However, the effect of smoking on surgical outcomes has not been evaluated extensively. Until recently, most available clinical studies were small, reported data from a single surgical specialty, or evaluated only a few postoperative outcomes.²⁻¹² However, 2 recent large multicenter studies^{13,14} confirmed the association between smoking and adverse postoperative outcomes. Turan and colleagues¹³ showed higher adjusted odds of postoperative mortality and major morbidity in 82 304 current smokers compared with those who never smoked (approximately 30% higher odds) using data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). However, the authors did not evaluate the association between past smoking and the observed outcomes. Knowledge of whether smoking cessation modifies (reverses) the adverse effects of smoking remains crucial to promote smoking control measures. The effect of past smoking on postsurgical outcomes was evaluated recently through another large ($n = 393\,794$) multicenter study using the Veterans Affairs Surgical Quality Improvement Program¹⁴ that reported that past smokers also have increased odds of 30-day postoperative mortality and major morbidity (approximately 20% higher odds). However, the authors did not adjust for several potential confounders that could have affected outcome rates and the patient's decision to quit smoking and did not assess the effect of smoking that is not mediated by related disorders (eg, smoking leads to cardiac disease, which in turn leads to adverse postsurgical outcomes), and their study mainly involved men.¹⁴

With these previous reports in mind, the purpose of our study was to determine the effects of current as well as past smoking on the incidence of postoperative mortality and arterial, venous, and respiratory events using a large data set from the ACS NSQIP. We also aimed to evaluate whether the observed associations are dose dependent and to establish whether they are restricted to patients who had already acquired smoking-related disease.

Methods

Study Design and Sample

This nested-cohort study used data from the ACS NSQIP database. Details of the ACS NSQIP (<http://acsnsqip.org>) have been recently described¹⁵ and are summarized in eTable 1 in Supplement. The database is a validated outcomes registry designed to provide feedback to participating hospitals on 30-day risk-adjusted surgical mortality and morbidity.^{16,17} The database includes de-identified data on demographics, perioperative variables, and 30-day postoperative outcomes for adult patients undergoing major surgery in participating non-Veterans Affairs hospitals.¹⁶ Trained surgical clinical review-

ers collect patient data on admission from the medical record, operative log, anesthesia record, interviews with the attending surgeon, and telephone interviews with the patient.¹⁶ Data quality is ensured through comprehensive training of the nurse reviewers, an interrater reliability audit of participating sites, regular conference calls, and an annual meeting.¹⁸

Included in this study were patients undergoing major surgery performed at participating ACS NSQIP medical centers during 2008 (271 368 patients from 211 sites) and 2009 (336 190 patients from 237 sites). In accordance with the American University of Beirut's guidelines (which follow the US Code of Federal Regulations for the Protection of Human Subjects), institutional review board approval was not needed or sought for our analysis because the data were collected as part of a quality assurance activity.

Smoking History

Data on smoking history are included in the ACS NSQIP as part of the preoperative risk assessment. Patients were categorized into 3 groups on the basis of their smoking status. If the patient has smoked cigarettes in the year before admission for surgery, the patient was considered a current smoker. This definition excluded patients who smoked cigars or pipes or used chewing tobacco. If the patient had ever been a smoker, smoking history measured in pack-years for this patient (the number of packs of cigarettes smoked per day \times the number of years the patient smoked) was also retrieved. In this study, patients with a record of pack-years who were not current smokers were categorized as past smokers. Patients who never smoked (ie, never smokers) were defined as patients who were classified as no for the current smoker variable and whose value for the pack-years variable was equal to 0 (325 434 patients [80.6% of never smokers]) or missing (78 169 [19.4% of never smokers]). We decided to classify those patients who had a *no* for current smoker and a *missing* for pack-years as never smokers because this approach was more conservative for the analysis of the relationship of smoking with surgical outcomes as determined by others.¹⁴ However, we also undertook 2 sensitivity analyses: one with such patients excluded and another with them considered past smokers.

Postoperative Outcomes

Evaluated outcomes included 30-day postoperative mortality, arterial events (myocardial infarction or cerebrovascular accident), venous events (deep vein thrombosis or pulmonary embolism), and respiratory events (pneumonia, unplanned intubation, or ventilator requirement >48 hours). The diagnoses were defined as described in eTable 2 in Supplement.

Statistical Analysis

Descriptive data are given as mean (SD) or percentage. The primary study outcome was death within 30 days of the index surgery in the current and past smokers groups compared with the never smokers group. The secondary study outcome was the occurrence of arterial, venous, or respiratory events within 30 days of the index surgery in the current and past smokers groups compared with the never smokers group. We esti-

Table 1. Patient Demographics and Preoperative Medical Histories

Variable	Smoker Group ^a		
	Never (n = 403 603)	Past (n = 78 763)	Current (n = 125 192)
Age, mean (SD), y	55.5 (17.7)	63.6 (13.7)	51.1 (15.2)
Male sex	39.2	52.3	48.3
Race			
White	76.7	83.6	76.3
Black or African American	9.8	6.9	12.8
Other/unknown	13.5	9.5	10.9
ASA class ^b			
I or II	59.7	39.4	51.0
III	34.2	50.5	40.4
IV or V	6.1	10.1	8.6
Functional status			
Independent	93.5	92.8	93.0
Partially dependent	4.7	5.5	5.0
Totally dependent	1.9	1.7	1.9
Alcohol consumption ^c	1.4	3.6	6.3
Diabetic using oral agents or insulin	14.5	21.1	13.3
BMI ≥ 30	39.8	42.4	34.2
Hypertension requiring medication	44.8	61.3	42.0
Currently undergoing dialysis	1.9	2.3	1.8
History of chronic obstructive pulmonary disease	2.3	10.5	9.7
Dyspnea			
None	91.4	81.9	86.8
With moderate exertion	7.5	16.1	11.4
At rest	1.1	2.0	1.9
Congestive heart failure in 30 d prior	0.8	1.4	1.0
Angina in 30 d prior	0.8	1.4	1.2
Myocardial infarction in 6 mo prior	0.6	1.0	1.1
Previous percutaneous coronary intervention	4.4	10.2	6.2
Previous cardiac surgery	5.0	11.2	4.8
History of peripheral vascular disease ^d	2.4	6.9	7.2
Rest pain/gangrene	1.5	3.1	4.2
History of transient ischemic attack	2.5	4.9	3.2
History of cerebrovascular accident with neurologic deficit	2.0	3.3	2.8
History of cerebrovascular accident without neurologic deficit	1.8	3.0	2.3
Disseminated cancer	1.8	2.7	1.7
Tumor involving central nervous system	0.2	0.3	0.2
Pregnancy	0.3	0.1	0.3

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a Unless otherwise indicated, data are expressed as percentage of patients. Percentages have been rounded and might not total 100.

^b Class I indicates healthy; II, mild systemic disease but no functional limitations; III, severe systemic disease with definite functional limitations; IV, severe systemic disease that is a constant threat to life; and V, moribund and unlikely to survive 24 hours with or without operation.

^c Indicates more than 2 drinks/d in the 2 weeks prior.

^d Requiring revascularization, angioplasty, or amputation.

ated unadjusted odds ratios (OR) and 95% confidence intervals for outcomes in the current and past smokers groups. We then constructed 2 multivariate logistic regression models for each outcome to adjust the association between smoking (current and past) and outcomes for 2 types of a priori-defined variables. In model 1 (OR_{adj-1}), we adjusted for variables that are potential confounders but not mediators (ie, factors that could affect the decision of the patient to continue smoking, stop smoking, or never smoke but cannot be caused by smoking). In model 2 (OR_{adj-2}), we adjusted for the variables included in model 1 plus variables that are potential mediators (ie, diseases that may have been caused by smoking). In such analyses, OR_{adj-1} would represent the true overall effect of current

and past smoking on outcomes that is mediated and not mediated by smoking-related diseases; OR_{adj-2}, the true effect of current and past smoking on outcomes that is not mediated by smoking-related diseases. The difference between OR_{adj-2} and OR_{adj-1} would represent the true effect of current and past smoking that is mediated by smoking-related diseases. We also stratified data from model 2 per demographics and different surgical settings.

To determine whether the observed effects of current and past smoking in model 2 are dose dependent, we also constructed multivariate logistic regression models with the current and past smokers groups divided into 5 equal quintiles according to pack-years of smoking. Data on pack-years were

Table 2. Association Between Smoking and 30-Day Postoperative Outcomes

Outcome ^a	Smoker Group, OR (95% CI)		
	Never (n = 403 603)	Past (n = 78 763)	Current (n = 125 192)
Mortality, No. (%)	6194 (1.5)	1636 (2.1)	2200 (1.8)
Unadjusted	1 [Reference]	1.36 (1.29-1.44)	1.15 (1.09-1.21)
Adjusted model 1	1 [Reference]	1.00 (0.94-1.06)	1.21 (1.14-1.28)
Adjusted model 2	1 [Reference]	0.91 (0.85-0.97)	1.17 (1.10-1.24)
Arterial events, No. (%)	1915 (0.5)	701 (0.9)	898 (0.7)
Unadjusted	1 [Reference]	1.88 (1.73-2.06)	1.52 (1.40-1.64)
Adjusted model 1	1 [Reference]	1.28 (1.17-1.40)	1.78 (1.63-1.93)
Adjusted model 2	1 [Reference]	1.20 (1.09-1.31)	1.65 (1.51-1.81)
Myocardial infarction, No. (%)	1039 (0.3)	425 (0.5)	503 (0.4)
Unadjusted	1 [Reference]	2.10 (1.88-2.35)	1.56 (1.41-1.74)
Adjusted model 1	1 [Reference]	1.40 (1.24-1.57)	1.92 (1.72-2.16)
Adjusted model 2	1 [Reference]	1.28 (1.14-1.44)	1.77 (1.57-1.99)
Cerebrovascular accident, No. (%)	907 (0.2)	289 (0.4)	416 (0.3)
Unadjusted	1 [Reference]	1.64 (1.43-1.87)	1.48 (1.32-1.66)
Adjusted model 1	1 [Reference]	1.14 (1.00-1.31)	1.63 (1.44-1.84)
Adjusted model 2	1 [Reference]	1.10 (0.96-1.26)	1.55 (1.36-1.76)
Venous events, No. (%)	3643 (0.9)	966 (1.2)	1086 (0.9)
Unadjusted	1 [Reference]	1.36 (1.27-1.46)	0.96 (0.90-1.03)
Adjusted model 1	1 [Reference]	1.05 (0.98-1.13)	0.94 (0.87-1.00)
Adjusted model 2	1 [Reference]	1.05 (0.98-1.13)	0.94 (0.87-1.01)
Deep vein thrombosis, No. (%)	2661 (0.7)	708 (0.9)	802 (0.6)
Unadjusted	1 [Reference]	1.37 (1.26-1.49)	0.97 (0.90-1.05)
Adjusted model 1	1 [Reference]	1.05 (0.96-1.14)	0.91 (0.84-0.99)
Adjusted model 2	1 [Reference]	1.05 (0.96-1.14)	0.92 (0.85-1.00)
Pulmonary embolism, No. (%)	1274 (0.3)	352 (0.4)	343 (0.3)
Unadjusted	1 [Reference]	1.42 (1.26-1.60)	0.87 (0.77-0.98)
Adjusted model 1	1 [Reference]	1.12 (0.99-1.26)	0.91 (0.81-1.03)
Adjusted model 2	1 [Reference]	1.10 (0.98-1.25)	0.91 (0.80-1.03)
Respiratory events, No. (%)	11 422 (2.8)	3571 (4.5)	5691 (4.5)
Unadjusted	1 [Reference]	1.63 (1.57-1.69)	1.64 (1.58-1.69)
Adjusted model 1	1 [Reference]	1.21 (1.17-1.27)	1.53 (1.47-1.58)
Adjusted model 2	1 [Reference]	1.13 (1.08-1.18)	1.45 (1.40-1.51)
Pneumonia, No. (%)	4826 (1.2)	1605 (2.0)	2572 (2.1)
Unadjusted	1 [Reference]	1.72 (1.62-1.82)	1.73 (1.65-1.82)
Adjusted model 1	1 [Reference]	1.25 (1.18-1.33)	1.63 (1.55-1.72)
Adjusted model 2	1 [Reference]	1.16 (1.09-1.23)	1.50 (1.43-1.59)
Unplanned intubation, No. (%)	4247 (1.1)	1551 (2.0)	2179 (1.7)
Unadjusted	1 [Reference]	1.90 (1.78-2.00)	1.67 (1.58-1.76)
Adjusted model 1	1 [Reference]	1.35 (1.27-1.43)	1.63 (1.54-1.72)
Adjusted model 2	1 [Reference]	1.25 (1.17-1.32)	1.51 (1.43-1.60)
Ventilator requirement for >48 h, No. (%)	7249 (1.8)	2185 (2.8)	3663 (2.9)
Unadjusted	1 [Reference]	1.56 (1.49-1.64)	1.65 (1.58-1.72)
Adjusted model 1	1 [Reference]	1.19 (1.13-1.25)	1.44 (1.38-1.51)
Adjusted model 2	1 [Reference]	1.14 (1.08-1.20)	1.43 (1.36-1.50)

Abbreviation: OR, odds ratio.

^a Adjustment in model 1 was undertaken for the following potential confounders: age, sex, race (white, black or African American, or other), American Society of Anesthesiologists class (described in footnote b of Table 1), functional status (totally dependent, partially dependent, or independent), alcohol consumption (>2 drinks/d in 2 weeks prior), diabetes mellitus (receiving oral agents or insulin), obesity (body mass index [calculated as weight in kilograms divided by height in meters squared] ≥30), and pregnancy. Adjustment in model 2 was undertaken for the variables listed for model 1 plus the following potential mediators: hypertension (requiring medication), renal failure (currently undergoing dialysis), chronic obstructive pulmonary disease, dyspnea (at rest, on moderate exertion, or none), congestive heart failure (in 30 days prior), angina (in 30 days prior), myocardial infarction (in 6 months prior), previous percutaneous coronary intervention, previous cardiac surgery, peripheral vascular disease (requiring revascularization, angioplasty, or amputation), rest pain, transient ischemic attack, cerebrovascular accident without or with neurologic deficit, disseminated cancer, and tumor involving the central nervous system.

available for all past smokers (part of the definition) and for 84 338 current smokers (67.4%).

Data were nearly complete, with missing values only for body mass index (16 343 patients [2.7%]), which were imputed by the respective means of similar sex and age groups. All analyses were performed using commercially available software (SAS, version 9.2; SAS Institute, Inc).

Results

We included data for 607 558 patients. Their mean age was 55.7 (SD, 17.1; range, 16-90) years, and 42.7% were men. A total of 125 192 patients (20.6%) were current smokers; 78 763 (13.0%), past smokers; and 403 603 (66.4%), never smokers. **Table 1**

compares demographics and preoperative medical histories among the 3 groups. Past smokers were oldest and most likely to be male or white. They were most likely to have an unfavorable American Society of Anesthesiologists class and had the highest prevalence of diabetes mellitus, obesity, hypertension, renal failure, chronic obstructive pulmonary disease, cardiovascular disease, and cancer (Table 1).

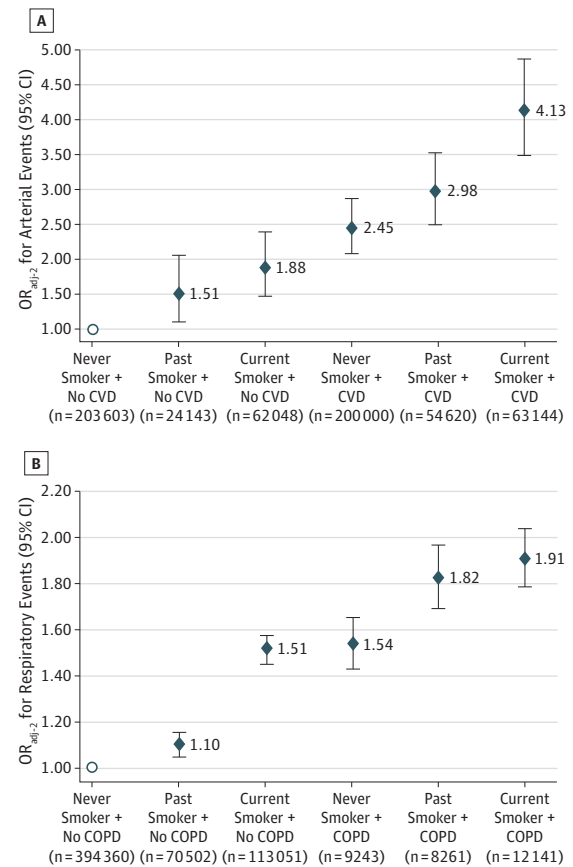
The crude rates (cumulative incidence) of postoperative outcomes plus the potential confounders and mediators for which we adjusted the models are summarized in Table 2. Current and past smokers had increased unadjusted odds of 30-day postoperative mortality and arterial and respiratory events compared with never smokers. However, on adjustment for potential confounders, only current smokers had increased odds of mortality after surgery (OR_{adj-1} , 1.21 [95% CI, 1.14-1.28]). On further adjustment for potential mediators, the odds of mortality associated with current smoking dropped by only 4% (smoking-related disease effect), and patients maintained an increased odds of death (OR_{adj-2} , 1.17 [95% CI, 1.10-1.24]). Moreover, on adjustment for potential confounders, the effect estimates of 30-day postoperative arterial and respiratory events were higher in current smokers (OR_{adj-1} , 1.78 [95% CI, 1.63-1.93] and 1.53 [1.47-1.58], respectively) than in past smokers (1.28 [1.17-1.40] and 1.21 [1.17-1.27], respectively) when compared with never smokers. On further adjustment for potential mediators, a similar minimal effect of smoking-related disease on arterial and respiratory events was noted for current smokers (OR_{adj-2} , 1.65 [95% CI, 1.51-1.81] and 1.45 [1.40-1.51], respectively) and past smokers (1.20 [1.09-1.31] and 1.13 [1.08-1.18], respectively). Current and past smokers did not have increased adjusted odds of 30-day venous events compared with never smokers (Table 2).

In the sensitivity analyses of patients who were not current smokers but had missing past pack-years data, results did not differ for the primary and secondary study outcomes whether they were considered past smokers rather than never smokers (eTable 3 in Supplement) or were excluded (eTable 4 in Supplement).

The increased adjusted odds of mortality and arterial and respiratory events in current smokers were generally noted across all age groups (mostly in those >40 years), in both sexes, in inpatients and outpatients, in those who underwent surgery with general or other types of anesthesia, in elective and emergency cases, and in various surgical subspecialties (eTable 5 in Supplement). We also stratified the analyses for postoperative arterial and respiratory events according to the presence of preoperative cardiovascular or chronic obstructive pulmonary disease, respectively (Figure 1).

When we considered history of cigarette smoking in pack-year data (dose-dependent effect), the increased adjusted odds of mortality in current smokers were evident in light (<10 pack-years) and heavy (≥ 50 pack-years) smokers. Past smokers did not have increased odds of mortality even with a cigarette smoking history of at least 50 pack-years (Figure 2A). The increased adjusted odds for arterial and respiratory events were incremental with increased pack-years, with current smokers generally having higher effect estimates across the whole range of pack-years of smoking. In fact, increased odds of ar-

Figure 1. Odds Ratios Adjusted for Potential Confounders and Mediators Described in Table 2 (OR_{adj-2}) for 30-Day Postoperative Arterial and Respiratory Events for the 3 Smoker Groups (Past, Current, and Never)



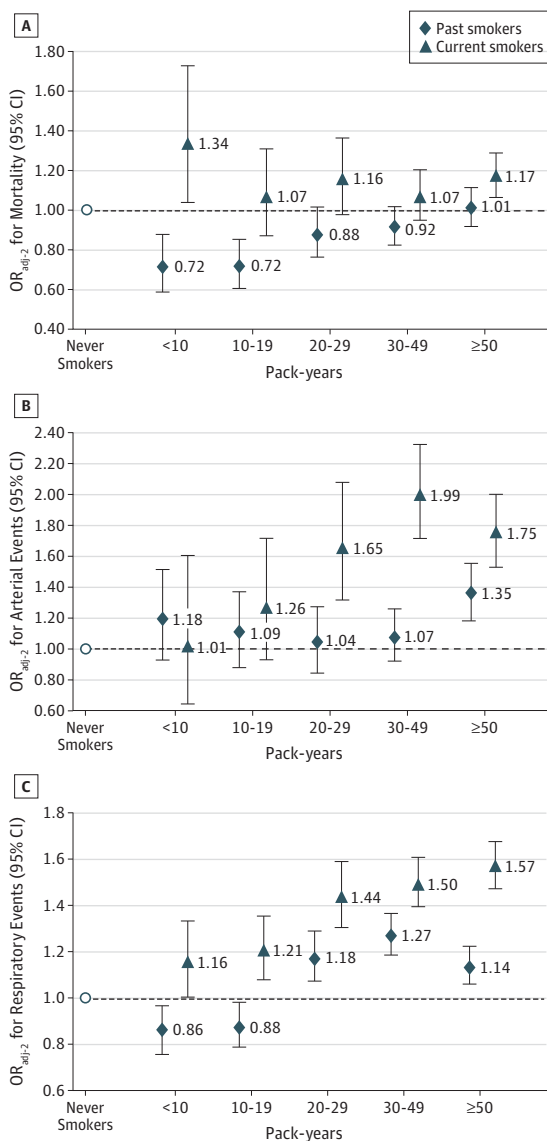
A, Postoperative arterial events depending on different combinations of smoking and history of cardiovascular disease (CVD), defined as any of the following: hypertension (requiring medication), angina (in 30 days prior), dyspnea (at rest, on moderate exertion, or none), congestive heart failure (in 30 days prior), myocardial infarction (in 6 months prior), previous percutaneous coronary intervention, previous cardiac surgery, peripheral vascular disease (requiring revascularization, angioplasty, or amputation), rest pain, transient ischemic attack, or cerebrovascular accident without or with neurologic deficit. No CVD in the never smoker group constituted the reference group. B, Postoperative respiratory events according to different combinations of smoking and history of chronic obstructive pulmonary disease (COPD). No COPD in the never smoker group constituted the reference group.

terial and respiratory events were noted only in past smokers who had smoking histories of at least 50 and at least 20 pack-years, respectively (Figure 2B and C). A similar trend was observed for venous events in current smokers, although the effect estimates remained minimal (eFigure in Supplement).

Discussion

In this large multicenter study, we demonstrated that current but not past smoking is associated with an increased risk of mortality in patients undergoing major surgery. Moreover, although past smokers remain at risk of increased arterial and respiratory events after surgery, the effect is milder than that

Figure 2. Odds Ratios for the Main Study Outcomes in Past and Current Smokers



The odds are adjusted for potential confounders and mediators described in Table 2 (OR_{adj-2}), with never smokers as the reference group. Smoking history is divided into quintiles of pack-years. A, Thirty-day postoperative mortality. B, Arterial events. C, Respiratory events.

observed in current smokers. These findings encourage ongoing efforts to implement smoking cessation programs across various health care systems. Early intervention in heavy smokers is warranted, especially because the effect of smoking on postoperative arterial and respiratory morbidity seems to be dose dependent. However, because smokers with a cigarette smoking history of less than 10 pack-years are also at risk of postoperative death, recent and light smokers should also be targeted.

The prevalence of current smokers presenting for major surgery in our study (approximately 20%) is close to that reported by Turan et al¹³ but lower than that reported by Hawn

et al¹⁴ (approximately 35%), who used data from the Veterans Affairs Surgical Quality Improvement Program involving mostly male veterans. However, the effects of current smoking on mortality and arterial, venous, and respiratory events echoed those reported by both studies, although they used more strict exclusion criteria (eg, excluding patients with the most severe disease, those undergoing cardiac surgery, or emergency cases).^{13,14} We chose to include all patients, apply extensive adjustment, and stratify outcomes per different patient groups. The adverse effects of current smoking were noted across several patient groups and surgical settings, although with varying effect estimates and uncertainties. This study should help to better target subpopulations who may benefit most from smoking cessation intervention trials.

In the study by Hawn et al,¹⁴ the authors found that past smokers remain at increased risk of mortality compared with never smokers and have similar or sometimes even higher odds of certain morbidities (eg, myocardial infarction) than current smokers when compared with never smokers. However, the authors in that study did not adjust the association for mediators, and the reported effect also includes that attributed to smoking-related disease. Moreover, only minimal adjustment for confounding was undertaken, which excluded some clinical conditions (not smoking related) that could cause the patient to stop smoking, while leaving him or her at higher risk of adverse outcomes (eg, obesity and diabetes mellitus). The key strengths of our study lie in the large number of patients and the reliable and comprehensive data collection tool of the ACS NSQIP, which provides more than 60 demographic and preoperative variables available for adjustment. Our study established that past smoking does not increase the risk of postoperative mortality and poses lower risks of arterial and respiratory events compared with those found in current smokers, which is in agreement with smaller studies on select populations.^{6,19}

Our study demonstrates that smoking is associated with adverse postoperative outcomes irrespective of the presence of smoking-related disease (eg, cardiovascular disease, chronic obstructive pulmonary disease, and cancer). The effect of smoking on adverse postoperative outcomes mediated by smoking-related disease (the difference between OR_{adj-2} and OR_{adj-1}) was minimal. This finding suggests that smoking may exert its effect on adverse postoperative outcomes through acute or subclinical chronic vascular and respiratory pathologic mechanisms. Smoking has acute exposure and chronic cumulative effects on pulmonary function. Toxins and particles in tobacco smoke activate the inflammatory system, ultimately leading to the destruction of alveoli and reduction of the surface area for gas exchange.²⁰ Smoking impairs mucus transport, provokes goblet cell hyperplasia and thus causes stimulation of mucus overproduction,²¹ impairs pulmonary macrophage function,²² and increases bronchial reactivity by stimulation of airway inflammation.²³ Moreover, animal studies show that exposure to tobacco smoke leads to an increased bacterial load and delayed bacterial clearance, demonstrating that cigarette smoke suppresses the respiratory antibacterial host defense and potentially increases the risk for pneumonia.²⁴ The effects of smoking on vessel wall patho-

logic changes, progression of atherosclerosis, and thrombosis potential are numerous. Smoking increases oxidative stress and inflammation; promotes endothelial activation, dysfunction, and damage; alters the endothelium-mediated vascular tone control; increases hypercoagulability and platelet activation; and reduces fibrinolysis. A direct necrotic action on cardiomyocytes is also believed to exist.²⁵ The contribution of smoking to venous thrombosis is still a matter of debate, and studies with a positive association reported effects smaller than those consistently observed in arterial thrombosis.^{26,27} Many of the smoking-induced effects on respiratory and vascular pathologic changes are at least partially reversible on cessation of exposure, usually within 1 year.²⁸⁻³¹

One limitation in our study is that we could identify only past smokers who quit smoking less than 1 year before surgery (otherwise considered current smokers in the ACS NSQIP). This limitation will not permit any conclusions regarding the effects of smoking cessation when implemented closer to surgery (eg, at the time of the decision to undergo an elective procedure), but it does show that the benefits of smoking cessation on surgical outcomes may start appearing as soon as 1 year after cessation. This difference may have little importance in the individual setting but has relevance in the public health perspective. Studies in this direction had mixed results and depended on the surgical population and the timing and intensity of the intervention.^{19,32-39} In our multivariate analyses, we considered preoperative medical diseases that could be caused by smoking as mediators. However, these conditions may be confounders rather than mediators in some patients if smoking did not contribute to their causation but influenced the decision of the patient to continue or quit smoking. However, this confounding does not affect the main estimate in our study, OR_{adj-2}, which represents the true and nonmediated effect of smoking.

Another potential limitation of this study was that we were unable to control for hospital effects owing to the absence of hospital identifiers in our data. Variability in hospital quality or in surgical strategy may have confounded the association

between risk factors and outcome. Last, the OR_{adj} of outcomes that we reported attributable to smoking might be regarded as of modest clinical significance because the crude 30-day outcome rates (cumulative incidence) in never smokers are low (eg, 0.3% for myocardial infarction). However, such adjusted increase in outcome rates in a large sample still means that a considerable number of patients could have acute adverse postoperative outcomes solely from the subclinical damaging effects of smoking (eg, 675 myocardial infarctions during the 2 years of the study). Moreover, our data included a wide variety of patients and surgical procedures from various surgical subspecialties with different crude outcome rates in never smokers (eTable 4 in Supplement), and the adjusted estimates of increased morbidity and mortality may be of higher clinical significance in certain patient populations or surgical procedures. Similarly, we reported adverse outcome rates applicable in a population with a case mix similar to that generated by the ACS NSQIP sampling strategy. If our findings are to be extrapolated to settings with higher adverse outcome rates, such relative increases would be of more apparent clinical significance.

Studies show that hospitals do not consistently provide smoking cessation services to their hospitalized patients, and in most cases these services are restricted to adults admitted for acute myocardial infarction, congestive heart failure, or pneumonia.¹ Our study should increase awareness of the detrimental effects of smoking—and the benefits of its cessation—on morbidity and mortality in the surgical setting. Surgical teams should thus be more involved in the ongoing efforts to optimize measures for smoking control. Surgery provides a teachable environment for smoking cessation. Unlike the long-term consequences of smoking, the acute consequences of smoking on patients' postoperative outcomes can provide a strong motive for quitting.⁴⁰ The cost-effectiveness of such interventions warrants further study. Finally, the effects of other forms of tobacco smoking, such as cigars, pipers, and water pipes, on surgical outcomes merit evaluation.

ARTICLE INFORMATION

Accepted for Publication: January 9, 2013.

Published Online: June 19, 2013.

doi:10.1001/jamasurg.2013.2360.

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Conflict of Interest Disclosures: None reported.

Disclaimer: The ACS NSQIP and the participating hospitals are the source of data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

REFERENCES

1. Fiore MC, Goplerud E, Schroeder SA. The Joint Commission's new tobacco-cessation measures: will hospitals do the right thing? *N Engl J Med*. 2012;366(13):1172-1174.
2. Al-Sarraf N, Thalib L, Hughes A, Tolan M, Young V, McGovern E. Effect of smoking on short-term outcome of patients undergoing coronary artery bypass surgery. *Ann Thorac Surg*. 2008;86(2):517-523.

3. Rock P, Rich PB. Postoperative pulmonary complications. *Curr Opin Anaesthesiol*. 2003;16(2):123-131.
4. Myles PS, Iacono GA, Hunt JO, et al. Risk of respiratory complications and wound infection in patients undergoing ambulatory surgery: smokers versus nonsmokers. *Anesthesiology*. 2002;97(4):842-847.
5. Al-Sarraf N, Thalib L, Hughes A, Tolan M, Young V, McGovern E. Lack of correlation between smoking status and early postoperative outcome following valve surgery. *Thorac Cardiovasc Surg*. 2008;56(8):449-455.
6. Delgado-Rodriguez M, Medina-Cuadros M, Martínez-Gallego G, et al. A prospective study of tobacco smoking as a predictor of complications in general surgery. *Infect Control Hosp Epidemiol*. 2003;24(1):37-43.
7. Finan KR, Vick CC, Kiefe CI, Neumayer L, Hawn MT. Predictors of wound infection in ventral hernia repair. *Am J Surg*. 2005;190(5):676-681.
8. Johnson RG, Arozullah AM, Neumayer L, Henderson WG, Hosokawa P, Khuri SF. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the Patient Safety in Surgery study. *J Am Coll Surg*. 2007;204(6):1188-1198.
9. Livingston EH, Arterburn D, Schifftner TL, Henderson WG, DePalma RG. National Surgical Quality Improvement Program analysis of bariatric operations: modifiable risk factors contribute to bariatric surgical adverse outcomes. *J Am Coll Surg*. 2006;203(5):625-633.
10. Arabaci U, Akdur H, Yiğit Z. Effects of smoking on pulmonary functions and arterial blood gases following coronary artery surgery in Turkish patients. *Jpn Heart J*. 2003;44(1):61-72.
11. 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(6):377-386.
12. Hollenberg M, Mangano DT, Browner WS, London MJ, Tubau JF, Tateo IM; Study of Perioperative Ischemia Research Group. Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. *JAMA*. 1992;268(2):205-209.
13. Turan A, Mascha EJ, Roberman D, et al. Smoking and perioperative outcomes. *Anesthesiology*. 2011;114(4):837-846.
14. Hawn MT, Houston TK, Campagna EJ, et al. The attributable risk of smoking on surgical complications. *Ann Surg*. 2011;254(6):914-920.
15. Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet*. 2011;378(9800):1396-1407.
16. Khuri SF, Henderson WG, Daley J, et al; Principal Site Investigators of the Patient Safety in Surgery Study. The Patient Safety in Surgery Study: background, study design, and patient populations. *J Am Coll Surg*. 2007;204(6):1089-1102.
17. Fink AS, Campbell DA Jr, Mentzer RM Jr, et al. The National Surgical Quality Improvement Program in non-Veterans Administration hospitals: initial demonstration of feasibility. *Ann Surg*. 2002;236(3):344-354.
18. American College of Surgeons. *ACS NSQIP User Guide for the 2008 Participant Use Data File*. Chicago, IL: American College of Surgeons; 2009.
19. Mason DP, Subramanian S, Nowicki ER, et al. Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. *Ann Thorac Surg*. 2009;88(2):362-371.
20. Mattison S, Christensen M. The pathophysiology of emphysema: considerations for critical care nursing practice. *Intensive Crit Care Nurs*. 2006;22(6):329-337.
21. 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(3, pt 1):1016-1021.
22. Dhillon NK, Murphy WJ, Filla MB, Crespo AJ, Latham HA, O'Brien-Ladner A. Down modulation of IFN- γ signaling in alveolar macrophages isolated from smokers. *Toxicol Appl Pharmacol*. 2009;237(1):22-28.
23. Garey KW, Neuhauser MM, Robbins RA, Danziger LH, Rubinstein I. Markers of inflammation in exhaled breath condensate of young healthy smokers. *Chest*. 2004;125(1):22-26.
24. Drannik AG, Pouladi MA, Robbins CS, Goncharova SI, Kianpour S, Stämpfli MR. Impact of cigarette smoke on clearance and inflammation after *Pseudomonas aeruginosa* infection. *Am J Respir Crit Care Med*. 2004;170(11):1164-1171.
25. Varela-Carver A, Parker H, Kleinert C, Rimoldi O. Adverse effects of cigarette smoke and induction of oxidative stress in cardiomyocytes and vascular endothelium. *Curr Pharm Des*. 2010;16(23):2551-2558.
26. Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am J Hematol*. 2008;83(2):97-102.
27. Tapson VF. The role of smoking in coagulation and thromboembolism in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2(1):71-77.
28. Godtfredsen NS, Prescott E. Benefits of smoking cessation with focus on cardiovascular and respiratory comorbidities. *Clin Respir J*. 2011;5(4):187-194.
29. Caponnetto P, Russo C, Di Maria A, et al. Circulating endothelial-coagulative activation markers after smoking cessation: a 12-month observational study. *Eur J Clin Invest*. 2011;41(6):616-626.
30. Johnson HM, Gossett LK, Piper ME, et al. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. *J Am Coll Cardiol*. 2010;55(18):1988-1995.
31. Celermajer DS, Adams MR, Clarkson P, et al. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. *N Engl J Med*. 1996;334(3):150-154.
32. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. *Ann Surg*. 2003;238(1):1-5.
33. Sørensen LT, Hemmingsen U, Jørgensen T. Strategies of smoking cessation intervention before hernia surgery: effect on perioperative smoking behavior. *Hernia*. 2007;11(4):327-333.
34. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. *Ann Surg*. 2008;248(5):739-745.
35. Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet*. 2002;359(9301):114-117.
36. Sørensen LT, Jørgensen T. Short-term pre-operative smoking cessation intervention does not affect postoperative complications in colorectal surgery: a randomised clinical trial. *Colorectal Dis*. 2003;5(4):347-352.
37. Kuri M, Nakagawa M, Tanaka H, Hasuo S, Kishi Y. Determination of the duration of preoperative smoking cessation to improve wound healing after head and neck surgery. *Anesthesiology*. 2005;102(5):892-896.
38. Mastracci TM, Carli F, Finley RJ, Muccio S, Warner DO; Members of the Evidence-Based Reviews in Surgery Group. Effect of preoperative smoking cessation interventions on postoperative complications. *J Am Coll Surg*. 2011;212(6):1094-1096.
39. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. *Cochrane Database Syst Rev*. 2010;(7):CD002294.
40. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. *Anesthesiology*. 2010;112(1):102-107.