Wound Healing and Infection in Surgery

The Clinical Impact of Smoking and Smoking Cessation: A Systematic Review and Meta-analysis

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Objectives: To clarify the evidence on smoking and postoperative healing complications across surgical specialties and to determine the impact of perioperative smoking cessation intervention.

Data Sources: Cohort studies and randomized controlled trials.

Study Selection: Selected studies were identified through electronic databases (CENTRAL, MEDLINE, and EMBASE) and by hand searching.

Data Extraction: Multiple data on study characteristics were extracted. Risk of bias was assessed by means of the Newcastle-Ottawa Scale and Jadad score. Healing outcome was classified as necrosis, healing delay and dehiscence, surgical site infection, wound complications, hernia, and lack of fistula or bone healing. Mantel-Haenszel and inverse variance methods for meta-analysis (fixed- and random-effects models) were used.

Data Synthesis: Smokers and nonsmokers were compared in 140 cohort studies including 479 150 patients. The pooled adjusted odds ratios (95% CI) were 3.60 (2.62-4.93) for necrosis, 2.07 (1.53-2.81) for healing delay and dehiscence, 1.79 (1.57-2.04) for surgical site infection, 2.27 (1.82-2.84) for wound complications, 2.07 (1.23-3.47) for hernia, and 2.44 (1.66-3.58) for lack of fistula or bone healing. Former smokers and patients who never smoked were compared in 24 studies including 47 764 patients, and former smokers and current smokers were compared in 20 studies including 40 629 patients. The pooled unadjusted odds ratios were 1.30 (1.07-1.59) and 0.69 (0.56-0.85), respectively, for healing complications combined. In 4 randomized controlled trials, smoking cessation intervention reduced surgical site infections (odds ratio, 0.43 [95% CI, 0.21-0.85]), but not other healing complications (0.51 [0.22-1.19]).

Conclusions: Postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. Perioperative smoking cessation intervention reduces surgical site infections, but not other healing complications.

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FOR THE PAST DECADES, A growing amount of literature has shown that smoking has a negative effect on postoperative outcome. A recent study disclosed that postoperative mortality and morbidity in smokers are substantial.[1]

See Invited Critique at end of article

Until now, no general survey on the clinical impact of smoking on postoperative healing has been published, and the literature is dispersed across operations and surgical specialties. The evidence on the impact of smoking cessation on healing complications is sparse, and only a few studies have assessed how long patients must be abstinent from smoking before surgery to reduce the risk. Accordingly, it is not clear if the effort, which is necessary to ensure successful abstinence from smoking, is worthwhile in terms of reducing healing complication rates. Recently published systematic reviews have disclosed that preoperative smoking cessation intervention reduces postoperative complications overall.[2,3] However, these reviews assessed pooled postoperative outcome and did not address healing complications.

The aims of this systematic review were to describe the association between smoking and healing complications across all surgical specialties and to estimate the impact of perioperative smoking cessation on postoperative healing outcomes.

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Table 1. Search Strategy[a]

Strategy	Cohort Studies	Intervention Studies
Short-term outcome (≤30 postoperative days)	Postoperative morbidity OR postoperative complication* OR wound complication* OR wound healing complication* OR surgical wound infection OR surgical site infection OR wound infection OR mesh infection OR delayed healing OR wound dehiscence OR wound rupture OR wound disruption OR wound separation OR wound necrosis OR tissue necrosis OR skin necrosis OR epidermolysis OR flap necrosis OR flap failure OR flap loss OR mesh erosion OR anastomotic leak* OR fistula	Postoperative morbidity OR postoperative complication* OR wound complication* OR wound healing complication* OR surgical wound infection OR surgical site infection OR wound infection OR mesh infection OR delayed healing OR wound dehiscence OR wound rupture OR wound disruption OR wound separation OR wound necrosis OR tissue necrosis OR skin necrosis OR epidermolysis OR flap necrosis OR flap failure OR flap loss OR mesh erosion OR anastomotic leak* OR fistula
Long-term outcome (>30 postoperative days)	Delayed healing OR hernia OR incisional hernia OR hernia recurrence OR pseudarthrosis OR nonunion OR fistula	Delayed healing OR hernia OR incisional hernia OR hernia recurrence OR pseudarthrosis OR nonunion OR fistula
Clinical context	Smoking OR tobacco use OR nicotine	Smoking cessation OR tobacco use cessation OR smoking reduction OR tobacco use reduction OR nicotine drugs OR nicotine replacement therapy
Search filter	None	EMBASE: (1) RCT; (2) randomization; (3) controlled study; (4) multicenter study; (5) phase III clinical trial; (6) phase IV clinical trial; (7) double-blind procedure; (8) single-blind procedure, (9) ([singl* OR doubl* OR trebl* OR tripl*]) adj [blind* OR mask*]).ti,ab; (10) (random* OR cross* over* OR factorial* OR placebo* OR volunteer*).ti,ab; (11) 6 OR 3 OR 7 OR 9 OR 2 OR 8 OR 4 OR 1 OR 10 OR 5; (12) "human*".ti,ab; (13) (animal* OR nonhuman*).ti,ab; (14) 13 AND 12; (15) 13 not 14; (16) 11 not 15 MEDLINE: (1) RCT.pt; (2) controlled clinical trial.pt; (3) randomized.ab; (4) placebo.ab; (5) clinical trial.sh; (6) randomly.ab; (7) trial.ti; (8) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; (9) humans.sh; (10) 8 AND 9
Databases searched	CENTRAL, MEDLINE, and EMBASE. Search terms were applied as MeSH and free text. To validate the search strategy a sampled cross-search strategy with the search terms "risk factor*" AND "postoperative complication*" was applied.	CENTRAL, MEDLINE, and EMBASE. Search terms were applied as MeSH and free text.

Abbreviations: ab, abstract; MeSH, medical subject headings; pt, publication type; RCT, randomized controlled trial; sh, subject heading; ti, title.
[a]Search strategies included the short- or long-term outcomes and clinical context and search filter. An asterisk indicates a truncated search term.

METHODS

SEARCH STRATEGY

Computerized searches in the CENTRAL, MEDLINE, and EMBASE databases were performed under supervision from a Cochrane Collaboration information specialist to identify relevant studies (**Table 1**). In addition, a manual cross-reference search of all potentially eligible articles retrieved for full-text evaluation was undertaken. The searches and study retrieval were performed until May 2010 for cohort studies and January 2011 for randomized controlled trials (RCTs).

STUDY ELIGIBILITY

Cohort studies with 100 patients or more assessing healing complications in smokers and former smokers were included to ensure that a broad range of surgical procedures and healing complications were addressed. Studies assessing multiple operations or healing outcomes from the same patient cohort were included according to each specified operation or healing outcome.

Randomized controlled trials assessing the effect of perioperative smoking cessation on postoperative healing complications were included. This intervention embraced all types of behavioral or motivational counseling with or without pharmacotherapy. Only RCTs with a minimum of 1 week of preoperative intervention and assessment of healing outcome after specified elective surgical procedures were included. Randomized controlled trials with a dropout rate greater than 40% were excluded.

OUTCOME MEASURES

The outcome measures included all types of adverse healing events after surgical procedures with access through a skin incision. Short-term (necrosis of wound and tissue flaps, healing delay and dehiscence of wounds and sutured tissue, surgical site infections, and nonspecified wound complications) and long-term healing outcomes (hernias and lack of fistula or bone healing) were accessed.

DATA EXTRACTION AND STUDY EVALUATION

Data from the cohort studies and RCTs were extracted according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology)[4] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[5] statements, respectively. The methodological quality of the cohort studies was evaluated in a domain-based evaluation process and by the Newcastle-Ottawa Scale, which is a scoring checklist assigning points (maximum, 9 stars) for patient selection characteristics, exposure ascertainment, comparability, and outcome assessment.[6] The methodological quality of the RCTs, including risk of bias assessment, was assessed according to Cochrane Collaboration

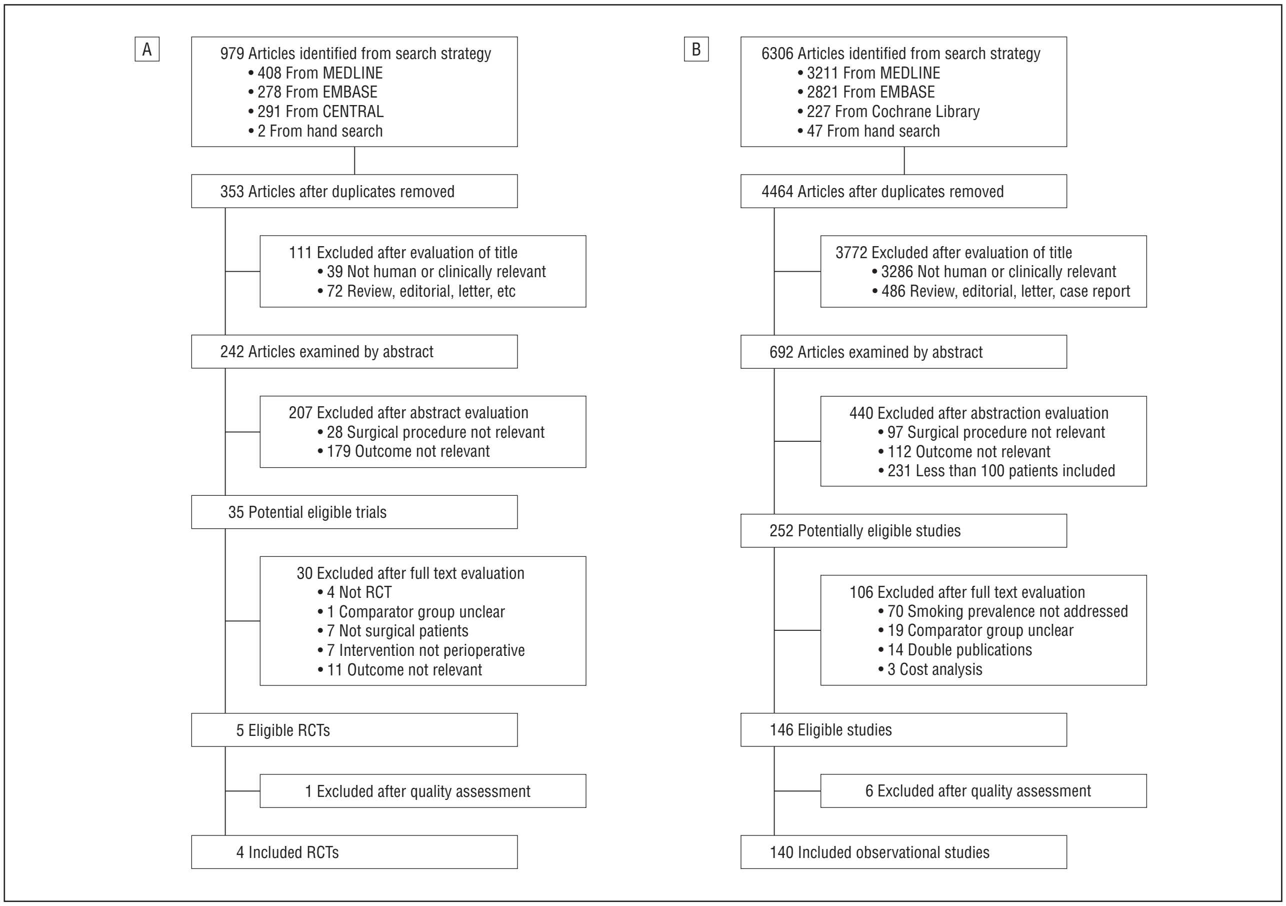

Figure 1. Flowcharts for study selection. A, Randomized controlled trial (RCT) selection. B, Observational study selection.

recommendations[7] and the Jadad score[8] for consideration of random sequence generation, allocation concealment, blinding procedures, address of incomplete outcome data, and unselective reporting. Publication bias was assessed by inspection of funnel plots calculated from meta-analyses including more than 10 studies.[7]

DATA ANALYSIS

From each study crude incidence rates or adjusted odds ratios (ORs) were extracted. Based on these data, unadjusted and adjusted estimates were calculated by means of the Mantel-Haenszel and inverse variance methods, respectively. These estimates were included in separate meta-analyses of the cohort studies according to each type of healing complication measure (smokers compared with nonsmokers) and a combined healing complication measure (former smokers compared with patients who never smoked or current smokers). Unadjusted estimates were included in the meta-analysis of RCTs.

Sensitivity analyses were conducted across complication type and included cohort studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients. Because most of the RCTs assessed outcome by pooling healing complications, sensitivity analyses aimed to estimate the impact of perioperative smoking cessation on different types of healing complications.

The statistical heterogeneity of the studies was reported as an I^2 value in each meta-analysis. Different methods of analysis were applied to assess the pooled treatment effects. In the meta-analyses of cohort studies, the random-effects model was used irrespective of the I^2 value. In the analysis of RCTs, the fixed-effects model was applied in case of an I^2 value of less than 40%.[7] The statistical analysis was performed with the use of the R program meta-analysis package, version 1.6-0.[9] In all analyses, a threshold of $P \leq .05$ was considered statistically significant.

RESULTS

The search for relevant studies yielded 6306 citations for cohort studies and 979 citations for RCTs (**Figure 1**).

CHARACTERISTICS OF COHORT STUDIES

One hundred forty cohort studies compared smokers and nonsmokers. The total number of patients included was 479 150. The studies originated from countries all over the world and embraced operations from all surgical specialties.

Twenty-six cohort studies assessed healing complications in former smokers. In 18 of these studies, former smokers were compared with current smokers and patients who never smoked. The studies originated from multiple countries and embraced general, thoracic, orthopedic, and plastic and reconstructive surgery. Half the studies defined former smokers as being abstinent from smoking for a median of 4 (range, 2-52) weeks before surgery,[10-21] whereas the other half did not address the period of preoperative abstinence.[22-35] In 2 studies, smok-

Table 2. Meta-analyses of Observational Studies on Healing Complications in Smokers Compared With Nonsmokers

	Studies Reporting Crude Data			Studies Reporting Adjusted Values			
Complication Category	No. of Studies[a]	OR (95% CI)[b]	*P* Value	No. of Studies[a]	OR (95% CI)[b]	*P* Value	eTable No.
Necrosis of wound and tissue	15	3.61 (2.78-4.68)	<.001	9	3.60 (2.62-4.93)	<.001	1
Healing delay and dehiscence	9	2.86 (1.49-5.49)	.002	12	2.07 (1.53-2.81)	<.001	2
Surgical site infection	25	2.12 (1.56-2.88)	<.001	32	1.79 (1.57-2.04)	<.001	3
Wound complications, nonspecified	20	2.06 (1.60-2.65)	<.001	17	2.27 (1.82-2.84)	<.001	4
Hernia	2	2.21 (0.71-6.84)	.17	7	2.07 (1.23-3.47)	.006	5
Lack of healing	6	2.21 (1.60-3.05)	<.001	4	2.44 (1.66-3.58)	<.001	6
Sensitivity analysis[c]	...	...	...	24	1.52 (1.36-1.69)	<.001	...

Abbreviations: ellipses, not applicable; OR, odds ratio.
[a] Indicates combined studies.
[b] Pooled treatment effects (OR [95% CI]) are calculated by means of the random-effects model. Forest plots and funnel plots on the meta-analysis and sensitivity analysis can be obtained from the author by request.
[c] Includes studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients (smokers and nonsmokers).

ers were requested to quit smoking 4 weeks before the operation and then were compared with current smokers and patients who never smoked.[19,21]

CHARACTERISTICS OF RCTs

Four RCTs assessed the impact of perioperative smoking cessation intervention. The trials originated from Denmark and Sweden.[36-39] The operations were elective orthopedic operations (hip and knee arthroplasty) and general surgical operations (herniotomy, cholecystectomy, and colorectal resection). The studies complied with the similar criteria for inclusion (ie, daily smoking, patients older than 18 years) and exclusion (ie, alcohol or other drug abuse, dementia, and lack of language proficiency). All studies reported the number of eligible patients, accounted for missing data, and discarded data from dropouts from the intention-to-treat analyses.

The intervention periods ranged from 2 to 3 weeks to 6 to 8 weeks before surgery until the day of skin suture removal or 30 days after surgery. Apart from 1 study,[37] the intervention was tailored individually and offered by study nurses professionally trained in smoking cessation therapy. The intensity ranged from brief advice with a follow-up telephone or outpatient reminder to multiple sessions of individual face-to-face counseling and unlimited hotline service access. Free-of-charge nicotine replacement drugs were offered by all but 1 study.[37] The control interventions ranged from standard advice about smoking and surgical outcome to a request to maintain daily smoking habits during the perioperative period.[38]

All studies assessed self-reported smoking or abstinence at the day before surgery and at the day of outcome assessment. Biochemical validation was assessed by measurement of cotinine levels in saliva or carbon monoxide levels in expired air. Compliance to abstinence varied from 23% to 64%.

ASSESSMENT OF RISK OF BIAS

The clinical heterogeneity was considerable in the cohort studies, and a variety of methodological flaws were present across studies. These flaws included retrospective data collection, no report of missing data, detection bias due to inadequate outcome definition, attrition bias due to inadequate postdischarge follow-up reporting, and inadequate confounder control. All RCTs had a low risk of bias, and they achieved a maximum Jadad score.

Inspection of funnel plot symmetry disclosed that the publication bias of the cohort studies was generally low (data not shown). In the cohort studies assessing surgical site infection and wound complications, a discrepancy was found between studies reporting crude incidence rates and adjusted ORs, indicating that some degree of publication bias was present in these studies.

SHORT-TERM HEALING COMPLICATIONS

Necrosis of wounds and tissue flaps was assessed in 19 unique studies including 7616 (number of subjects per study, 111-1177) smokers and nonsmokers (eTable 1; http://www.archsurg.com). Both meta-analyses disclosed a significantly higher incidence of necrosis in smokers (crude OR, 3.61 [95% CI, 2.78-4.68]) and adjusted OR, 3.60 [95% CI, 2.62-4.93]) (**Table 2**).

Most of the studies were conducted in patients undergoing breast surgery. Wound necrosis after mastectomy was 4-fold more frequent in smokers.[40,41] Three studies assessing a dose-effect relationship between the intensity of smoking and necrosis found conflicting results.[13,20,42] Two studies reported a dose-effect relationship between lifelong smoking intensity (in pack-years) and necrosis.[17,43]

In breast reconstructive surgery ranging from breast reduction to postmastectomy reconstruction, all studies demonstrated a high incidence of necrotic complications.[13,44-50] Small retrospective studies of flap transposition or free-flap reconstruction after head and neck surgery found conflicting results.[35,51-53] After lung cancer surgery and pelvic organ prolapse repair, fistulas caused by necrotic suture or mesh erosion were more frequent in smokers.[17,43,54,55]

Healing delay and dehiscence of wounds and tissue were assessed in 18 unique studies including 26 297 (number of subjects per study, 111-24 192) smokers and

Table 3. Meta-analyses of Observational Studies on Healing Complications in Former Smokers Compared With Patients Who Never Smoked or Smokers

	Studies Reporting Crude Data			Studies Reporting Adjusted Values			
Healing Complications Combined	No. of Studies[a]	OR (95% CI)[b]	P Value	No. of Studies[a]	OR (95% CI)[b]	P Value	eTable No.
Former smokers compared with those who never smoked	22	1.30 (1.07-1.59)	<.001	15	1.31 (1.10-1.56)	.006	7
Former smokers compared with current smokers	26	0.69 (0.56-0.85)	.002	2	0.28 (0.12-0.72)	.008	8
Sensitivity analysis[c]	...	...	...	5	1.23 (0.99-1.51)	.06	...

Abbreviations: ellipses, not applicable; OR, odds ratio.
[a] Indicates combined studies.
[b] Pooled treatment effects (OR [95% CI]) are calculated by means of the random-effects model. Forest plots and funnel plots on the meta-analysis and sensitivity analysis can be obtained from the author by request.
[c] Includes studies with a maximum Newcastle-Ottawa Scale score and more than 1000 patients (former smokers and those who never smoked).

nonsmokers (eTable 2). Both meta-analyses disclosed a significantly higher incidence of healing delay and dehiscence of wounds and tissue in smokers (crude OR, 2.86 [95% CI, 1.49-5.49] and adjusted OR, 2.07 [95% CI, 1.53-2.81]) (Table 2).

Most studies assessing dehiscence of wounds, fascia, and sutured tissue, including anastomotic leakage, found a higher incidence in smokers.[24,26,56-63] Postoperative healing delay as an outcome measure was assessed in a few older cohort studies. In orthopedic surgery, the reamputation rate owing to failed healing showed conflicting results[34,64-66]; in breast reconstructive surgery, more recent studies did not find postoperative healing delay to be more frequent in smokers.[16,67]

Surgical site infection was assessed in 51 unique studies including 408 428 (number of subjects per study, 100-163 824) smokers and nonsmokers (eTable 3). Both meta-analyses disclosed significantly more surgical site infections in smokers (crude OR, 2.12 [95% CI, 1.56-2.88] and adjusted OR, 1.79 [95% CI, 1.57-2.04]) (Table 2).

In general surgery, most of the studies found a higher surgical site infection in smokers.* In 1 study,[80] smokers had more surgical site infections after intestinal and colon surgery, but not after gastrectomy. After coronary bypass surgery, sternal wound infection after coronary bypass surgery was more frequent in smokers compared with nonsmokers in most studies.[10-12,33,81-92] In orthopedic and reconstructive surgery, all major studies found surgical site infection to be more frequent in smokers,[13,16,29,44,46,66,93-95] contrary to a few small studies.[96-98] In gynecologic and obstetric surgery, conflicting results were found.[99-101]

Wound complications (nonspecified) were assessed in 31 unique studies including 22 516 (number of subjects per study, 102-6676) smokers and nonsmokers (eTable 4). Both meta-analyses disclosed significantly more wound complications in smokers (crude OR, 2.06 [95% CI, 1.60-2.65] and adjusted OR, 2.27 [95% CI, 1.82-2.84]) (Table 2).

All major studies in breast reconstructive surgery found smoking to predict wound complications.[13,19,20,102,103] A number of smaller studies assessing wound complications after reconstructive surgery showed conflicting results.† Similar conflicting results were found in larger and smaller cohort studies after orthopedic, obstetric, gastrointestinal tract, and head and neck surgery.[23,25,94,118-124]

LONG-TERM HEALING COMPLICATIONS

Incisional or recurrent inguinal hernia was assessed in 9 unique studies including 2296 (number of subjects per study, 114-544) smokers and nonsmokers (eTable 5). The meta-analysis from studies[30,125-130] reporting adjusted estimates found hernia to be more frequent in smokers (OR, 2.07 [95% CI, 1.23-3.47]), contrary to the meta-analysis based on studies[27,131] reporting crude incidence rates (OR, 2.21 [95% CI, 0.71-6.84]) (Table 2).

In general surgery and urology, most studies found hernia to be more frequent in smokers,[27,30,127,130] contrary to studies of aortic reconstructive surgery, which showed conflicting results.[125,126,128,129,131]

Lack of fistula and bone healing was assessed in 10 unique studies including 14 293 (number of subjects per study, 105-12 297) smokers and nonsmokers (eTable 6). Both meta-analyses disclosed a significantly higher incidence of lack of fistula and bone healing in smokers (crude OR, 2.21 [95% CI, 1.60-3.05] and adjusted OR, 2.44 [95% CI, 1.66-3.58]) (Table 2).

In a study of open tibial fracture repair, Adams et al[132] found that smokers' fractures healed slower. All studies assessing long-term outcome after spinal surgery, except one,[133] found failed bone union to be more frequent in smokers.[21,31,134-136] In addition, unhealed sternocutaneous fistula and anal fistula were more frequent in smokers.[137,138]

HEALING COMPLICATIONS IN FORMER SMOKERS

Twenty-four unique studies reporting the outcome of 47 764 (number of subjects per study, 177-10 897) former smokers and patients who never smoked were included (eTable 7). Both meta-analyses disclosed significantly more combined healing complications in former

*References 18, 27, 28, 32, 42, 60, 63, 68-79.

†References 15, 16, 19, 45, 67, 102, 104-117.

Table 4. Randomized Controlled Trials Assessing the Effect of Preoperative Smoking Cessation Intervention on Postoperative Healing Complications

Source/ Country	No. of Patients Included/ Completed	Intervention (Control)	Duration	Intensity	Abstinence Validation	Operation	Healing Outcome	No./Total No. (%) With Outcome	Jadad Score
Lindström et al,[36] 2008/Sweden	117/102	Nurse provided counseling, weekly FU, NRT offer, telephone hotline, and inpatient contacts (standard care)	4 wk before surgery through 4 wk after	Intermediate	Measurement of CO levels	Herniotomy, cholecystectomy, hip, or knee Arthroplasty	Wound complication	Intervention, 6/48 (13); control, 14/54 (26); $P > .05$; OR, 0.48 (95% CI, 0.2-1.2)	6
Møller et al,[39] 2002/Denmark	120/108	Nurse provided counseling, weekly FU, NRT offer, and inpatient contacts (standard care)	6-8 wk before surgery through 10 d after	High	Measurement of CO levels	Hip or knee Arthroplasty	Wound complication	Intervention, 3/56 (5); control, 16/52 (31); $P < .001$; RR, 0.16 (95% CI, 0.05-0.52)	6
Sørensen and Jørgensen,[38] 2003/Denmark	60/57	Surgeon provided counseling, telephone contacts with nurse, NRT offer, and inpatient contacts (standard care)	2-3 wk before surgery through 10 d after	Intermediate	Measurement of CO and cotinine levels	Colorectal resection	SSI, wound or fascial dehiscence, anastomotic leakage	Intervention, 9/27 (33); control, 8/30 (27); $P > .05$	6
Sørensen et al,[37] 2007/Denmark	180/149	Surgeon provided advice, counseling by telephone or outpatient talk with nurse, and NRT sample (surgeon provided advice)	4 wk before surgery through 10 d after	Low	Measurement of CO and cotinine levels	Inguinal or incisional herniotomy	SSI	Intervention, 6/101 (6); control, 4/48 (8); $P > .05$	6

Abbreviations: CO, carbon monoxide; FU, follow-up; NRT, nicotine replacement therapy; OR, odds ratio; RR, relative risk; SSI, surgical site infection.

smokers than in those who never smoked (crude OR, 1.30 [95% CI, 1.07-1.59] and adjusted OR, 1.31 [95% CI, 1.10-1.56]) (**Table 3**).

Twenty unique studies reporting the outcome of 40 629 (number of subjects per study, 177-10 897) former smokers and current smokers were included (eTable 8). Both meta-analyses disclosed significantly fewer healing complications in former smokers than in current smokers (crude OR, 0.69 [95% CI, 0.56-0.85]; adjusted OR, 0.28 [95% CI, 0.12-0.72]) (Table 3). Some of these studies assessed the effect of pack-years on healing complications in former smokers, but the results were conflicting.[13,17,20,23,25,32]

SENSITIVITY ANALYSES OF COHORT STUDIES

The sensitivity analyses confirmed that smokers had significantly more healing complications than did nonsmokers across complication types (Table 2), contrary to former smokers compared with patients who never smoked, which disclosed a nonsignificant trend (Table 3).

IMPACT OF SMOKING CESSATION ON HEALING COMPLICATIONS

Four RCTs reporting the outcome of 416 patients (number of subjects per study, 57-149) were included and healing complications were found in 15.9% (66 of 416) (**Table 4**). The meta-analysis disclosed that perioperative smoking cessation did not significantly reduce healing complications combined (**Figure 2**). In contrast, surgical site infections were significantly reduced by perioperative smoking cessation as shown by a sensitivity analysis (**Figure 3**).

COMMENT

This systematic review shows that smokers compared with nonsmokers and former smokers compared with those who never smoked have more postoperative healing complications. Former smokers (compared with current smokers) have fewer healing complications. Perioperative smoking cessation reduces surgical site infections, but not other healing complications.

Across cohort studies, necrosis was 4 times more frequent in smokers than nonsmokers, whereas surgical site infection, dehiscence, healing delay, hernia, and lack of fistula and bone healing occurred 2 times more frequently in smokers. The following pathophysiological mechanisms for defective healing in smokers appear to be involved: (1) an acute detrimental vasoactive effect of smoking leads to postoperative necrosis in tissues with fragile blood supply, such as reconstructive tissue flaps and colorectal anastomoses; (2) attenuation

Study	Smoking Cessation No. of Events	Smoking Cessation Total	Control No. of Events	Control Total	OR	(95% CI)	W(Random)
Lindström et al,[36] 2008	6	48	14	54	0.41	(0.14-1.17)	27.5%
Møller et al,[39] 2002	3	56	16	52	0.13	(0.03-0.47)	23.3%
Sørensen and Jorgensen,[38] 2003	9	27	8	30	1.38	(0.44-4.29)	26.0%
Sørensen et al,[37] 2007	6	101	4	48	0.69	(0.19-2.59)	23.1%
Random-effects model	**24**	**232**	**42**	**184**	**0.48**	**(0.19-1.25)**	**100%**

Heterogeneity: $I^2 = 61.1\%$, $\tau^2 = 0.5817$, $P = .0524$

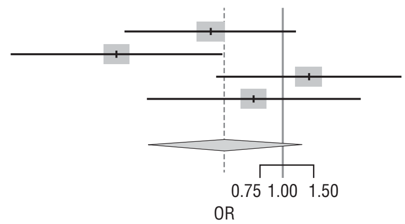

Figure 2. Meta-analysis of the effect of perioperative smoking cessation intervention on postoperative healing complications. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models. OR indicates odds ratio; W, weighted.

Study	Smoking Cessation No. of Events	Smoking Cessation Total	Control No. of Events	Control Total	OR	(95% CI)	W(Random)
Lindström et al,[36] 2008	2	48	4	54	0.54	(0.10-3.11)	15.0%
Møller et al,[39] 2002	2	56	12	52	0.12	(0.03-0.58)	49.8%
Sørensen and Jorgensen,[38] 2003	3	27	4	30	0.81	(0.16-4.01)	14.0%
Sørensen et al,[37] 2007	6	101	4	48	0.69	(0.19-2.59)	21.2%
Fixed-effect model	**13**	**232**	**24**	**184**	**0.40**	**(0.20-0.83)**	**100%**

Heterogeneity: $I^2 = 19.8\%$, $\tau^2 = 0.1527$, $P = .29$

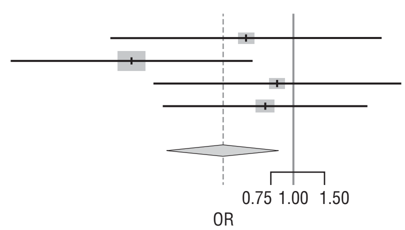

Figure 3. Meta-analysis (sensitivity analysis) of the effect of perioperative smoking cessation intervention on surgical site infection. The size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models. OR indicates odds ratio; W, weighted.

of the inflammatory healing response and impairment of oxidative bacterial killing mechanisms lead to surgical site infection; and (3) delay of the proliferative healing response and alteration of collagen metabolism lead to dehiscence, incisional hernia, and lack of fistula or bone healing.[139-144]

Former smokers had a one-third higher incidence of healing complications than did patients who never smoked, although the sensitivity analysis did not confirm the significance of this finding. The difference in complication rate probably reflects a sustained detrimental effect of previous smoking on postoperative healing, implying that former smokers seem to have a lifelong higher risk of healing complications than those who never smoked. The lower incidence of complications in former smokers compared with current smokers suggests that a beneficial effect of abstinence from smoking on healing mechanisms exists. The finding, however, should be interpreted carefully owing to methodological flaws and bias in the cohort studies.

The meta-analysis of the RCTs disclosed that perioperative smoking cessation intervention did not reduce pooled healing complications. This finding contrasts with 2 recent meta-analyses that disclosed that smoking cessation reduced postoperative complications overall.[2,3] Most likely the reason is methodological because 3 of the 4 RCTs included clinically heterogeneous adverse healing events in a pooled healing complication measure.[36,38,39] Wound hematomas, seromas, and subfascial collections after hip and knee arthroplasty were included as healing outcome, although none of these complications have been individually proven to be associated with smoking.[13,145]

Perioperative smoking cessation intervention including 4 to 8 weeks of preoperative abstinence from smoking significantly reduced surgical site infections. This finding suggests that the primary impact of smoking cessation on healing is a reduction in infectious healing complications as shown by Møller et al.[39] This finding was confirmed by a randomized study of healthy volunteers, which disclosed that 4 weeks of abstinence from smoking significantly reduced incisional wound infection.[146] However, in 2 of the included RCTs, 4 weeks of preoperative abstinence did not reduce surgical site infections significantly, most probably because the RCTs were underpowered.[36,37] In one of the RCTs, 2 to 3 weeks of preoperative abstinence did not affect healing complications.[38]

This is the first systematic review to examine the impact of smoking and smoking cessation on healing complications. Strengths of this methodological approach include an extensive search complying with validated search strategies and a systematic scoring of methodological quality and risk of bias assessment. The following limitations are related to methodological issues of the cohort studies: differences in design, inconsistent definitions of smoking, underreporting of smoking habits and lack of biochemical validation, inconsistent definitions of healing outcome, and unclear outcome assessment and follow-up. In addition, the lack of addressing missing data, including former smokers' recall bias for the exact time of smoking cessation, and conflicting clinical confounders to be considered restrict the validity of the cohort studies.[147-150] Although homogeneous and with a low risk of bias, the included RCTs were small. Apart from 1 study[37] that studied healing complications as a secondary outcome measure, the actual patient number included in the other RCTs appeared to be smaller than that specified in the protocol. Consequently, the included RCTs seem to have been underpowered to show a difference in healing complications by smoking cessation.

CONCLUSIONS

Smokers have a higher incidence of infectious and noninfectious healing complications after surgery compared with nonsmokers across all surgical specialties. Former smokers appear to have a lifetime higher risk of healing complications compared with patients who never smoked. Smoking cessation for at least 4 weeks before surgery reduces surgical site infections, but not other healing complications. Patients should be encouraged to stop smoking at least 4 weeks before surgery to reduce the risk of surgical site infections.

Further cohort studies are needed to clarify the risk of former smokers for postoperative healing complications. Accordingly, valid data from a detailed smoking history including the period of abstinence from smoking should be included in future clinical database studies on surgical outcome.

Additional RCTs assessing the impact of perioperative smoking cessation on healing outcome are needed for definite confirmation. Because interventions on lifestyle changes afford a number of challenges, multicenter and large-scale RCTs using cluster randomization should be considered.

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INVITED CRITIQUE

Kicking Society's Tobacco Habit

Does the Butt Stop Here?

An astonishing 1 in 5 US adults are current smokers (≥100 lifetime cigarettes and regular consumption).[1] Although this figure has declined a little recently, the overhanging health issues will persist for some time. The current findings of adverse effects on surgical site infections and reparative processes are less surprising.[2] However, can we confidently determine inhaled tobacco smoke as an isolated risk factor with the current study design? There are far too many covariables to digest. Smokers tend to be in lower socioeconomic groups, be more sedentary, drink more alcohol, and have more comorbidities than current nonsmokers (ex-smokers) and never (life-long tobacco-free) smokers. The inadequate power of the studies, the well-recognized inaccuracy with which patients report their smoking habits, and the haziness of wound-healing definition (eg, rate of healing, time to complete closure, patient satisfaction, self-assessed or surgical scores?) are prohibitive impediments to present data interpretation and the call for future trials.

A more pragmatic position for the surgical community to maintain is a consistent antitobacco attitude, encouraging and strongly recommending cessation (whether or not it is in advance of an operation). This moral imperative helps reduce direct and related health care costs and so benefits the patient and society as a whole. Sustained comprehensive tobacco control programs that include patient information, support programs, health warnings, media campaigns, and smoke-free policies work. California, Washington, Maine, and New York saw their smoking prevalence fall by 40% or more in the past decade by implementing these programs. The question is not at what cost this is achieved. Federal and state government must support health care reform that embraces tobacco control or risk being the butt of society's smoke.

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