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Smoking as a risk factor for wound healing and infection in breast cancer surgery

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Aim: Clinical studies suggest that smoking is associated with wound necrosis after breast cancer surgery. However, the significance of smoking as a risk factor for wound infection, skin flap necrosis, and epidermolysis when adjusting for other potential risk factors remains to be studied.

Methods: From June 1994 through August 1996, 425 patients underwent breast cancer surgery as simple mastectomy, modified radical mastectomy, or breast conserving surgery. The patients were evaluated postoperatively for wound infection, skin flap necrosis, and epidermolysis. Association between these complications and 17 patient, operative, and postoperative variables were analysed by three separate multiple logistic regression analyses.

Results: When compared to non-smoking, smoking was significantly associated with wound infection after all types of surgery (light smoking (1–14 grams per day): [odds ratio (OR) = 2.95, 95% confidence interval (95% CI) = 1.07–8.16], and heavy smoking (≥15 grams per day): OR = 3.46 (1.52–7.85). A similar significant association was found as regards skin flap necrosis and epidermolysis after simple mastectomy and modified radical mastectomy: both light and heavy smoking were predictive for skin flap necrosis: light smoking: OR = 6.85 (1.96–23.90), heavy smoking: OR = 9.22 (2.91–29.25) and for epidermolysis: light smoking: OR = 3.98 (1.52–10.43) and heavy smoking: OR = 4.28 (1.81–10.13). No significant dose-response relation was disclosed. Other risk factors and confounders associated with complicated wound healing were adjusted for in the analysis: diabetes, obesity, alcohol, NSAIDs, duration of surgery, and surgical experience.

Conclusion: Independent of other risk factors, smoking is predictive for post-mastectomy wound infection, skin flap necrosis, and epidermolysis.

Key words: Postoperative complications; surgical wound infection; life style; smoking; alcohol; diabetes; obesity duration of surgery; non-steroid; anti-inflammatory drugs; surgical experience.

INTRODUCTION

Skin flap necrosis, epidermolysis and surgical wound infection are common and serious complications in breast cancer surgery.[1,2,3] Once such complications are diagnosed, surgical or medical intervention is often required resulting in prolonged hospitalisation, outpatient care and ultimately increase in cost.[4] Postoperative wound hypoxia as a result of tissue injury with disruption of local vascular supply and thrombosis of vessels, is considered to be one of the major causes for impaired wound healing, tissue necrosis and infection.[5] In the mastectomy wound, the risk of hypoxia is even more manifest due to arterial insufficiency of the flap and a large dead space.[6]

A number of risk factors for post-mastectomy wound complications have been identified,[3] including smoking[7–9] which is known to cause reduction in tissue blood flow and low oxygen tension.[10,11] However, the significance of smoking as a risk factor for post-mastectomy wound complications when adjusting for other factors associated with impaired wound healing and infection has not yet been studied.

MATERIAL AND METHODS

From June 1994 through August 1996, two cohorts totalling 425 patients underwent breast cancer surgery in one general surgical department. All patients were women. The type of surgery performed included simple mastectomy, modified radical mastectomy and breast

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conserving surgery. No reconstructive surgery was performed.

The first cohort comprised 313 patients who underwent surgery until March 1996. All patients were prospectively randomised to compressive wound dressing postoperatively versus no compressive dressing. The compression bandage was designed to produce a standardised, uniform, and reproducible pressure over the entire wound area in order to reduce postoperative seroma and haematoma.[12] Furthermore, all patients had 3500 IU of fractioned heparin (Innohep, Leo Pharmaceutical Products Ltd, Denmark) injected subcutaneously once a day as thromboembolic prophylaxis.

The second cohort comprised 112 consecutive patients who were operated on from April 1996 until August 1996. From April 1996 the thromboembolic prophylaxis procedure was replaced by a perioperative application of thigh long graded compression TED-stockings. In this period no compressing wound dressing was applied postoperatively.

Seventeen different variables related to patient characteristics, operation, and postoperative regimen with a possible relation to postoperative complications were assessed. Data regarding patient characteristics (age, gender, body mass index, diabetes, smoking and drinking habits, and current medical therapy) were collected from self-administered questionnaires completed prospectively at referral to the outpatient clinic prior to surgery.

Operative data were collected from the descriptions of surgical procedure as noted in the clinical record (type and duration of surgery, size of wound surface, number of removed metastatic axillary lymph nodes, perioperative blood loss and transfusions). Furthermore, histological tumour classification and surgical experience was recorded. Variables related to postoperative regimen embraced compressive wound dressing and thromboembolic prophylaxis. Postoperative wound complications (skin flap necrosis, epidermolysis, and infection) were evaluated at discharge and two weeks after surgery. A wound infection was considered to be present if clinically suspected, microbiologically verified, and treated accordingly.[13] Skin flap necrosis was defined as a substantial necrosis including all layers of the skin and epidermolysis as lack of epidermal wound healing and superficial dermal necrosis, respectively.

The results were analysed by multiple logistic regression (SPSS for Windows 8.0, SPSS Inc., Chicago, Illinois, USA). Three separate explorative analyses were conducted with wound infection, skin flap necrosis, and epidermolysis as the dependent variable. In each case, a univariate analysis was performed and the odds ratio of each variable was estimated. Subsequently, a forward selection procedure was carried out where variables likely to be associated with the dependent variable ($P \leq 0.2$) were included in a multivariate model. Before establishing the final model, all variables not being significant ($P > 0.05$) were discarded by a backward elimination procedure. Finally, tests for linearity and interaction terms between variables were examined. All results were described with odds ratio and 95% confidence interval.

RESULTS

In the pooled cohort, the complication rates were as follows: wound infection 10.2% [95% confidence interval = (7.5–13.5%)], skin flap necrosis 6.1% (4.0–8.8%) and epidermolysis 8.9% (6.4–12.1%). Baseline characteristics for the patients are displayed in Table 1.

With postoperative wound infection as dependent variable, the multivariate logistic regression analysis disclosed that both light and heavy smoking compared to non-smoking were significantly and independently associated with wound infection (Table 2). Furthermore, alcohol consumption over 14 drinks per week compared with abstaining was also associated with wound infection. Diabetic patients compared to non-diabetic patients and patients with increasing body mass index had a higher risk of wound infection. Finally, patients operated by trainees had a higher risk of wound infection compared with patients operated by specialist surgeons.

With skin flap necrosis and epidermolysis as dependent variables, each multivariate logistic regression analysis disclosed that both light and heavy smoking compared to non-smoking was significantly and independently associated with either variable (Tables 3 and 4). Furthermore, increasing duration of surgery was associated with both skin flap necrosis and epidermolysis, whereas daily intake of NSAIDs was associated with epidermolysis (Table 4).

A non-significant dose-response relation between smoking and either outcome variable was observed. No significant interaction between variables in either logistic regression model was found.

DISCUSSION

Independent of confounders and other significant risk factors, smokers have a higher risk of post-mastectomy wound infection, skin flap necrosis, and epidermolysis than non-smokers.

The overall rate of wound healing complications in this study is comparable with reports from other centres.[1,2,3,4,14] Our findings confirm studies of conventional and reconstructive breast cancer surgery, which have shown a higher risk of skin flap necrosis and epidermolysis among smokers.[7,8,9] Smoking has an acute detrimental effect on blood flow and tissue oxygen tension, a mechanism which jeopardises experimental skin flap survival.[10,11,15] More chronically, smoking affects the vascular system and the cellular immune and inflammatory system,[16,17] which play a pivotal role in

Table 1 Characteristics of the patients

	*n**
Baseline	
Median age (range)	64 (29–90)
Female gender	425 (100)
Mean body mass index (S.D.)	25.0 (4.9)
Smokers	
Light smokers (1–14 grams per day) †	118 (28.0)
Heavy smokers (≥15 grams per day) †	78 (18.5)
Alcohol consumers	
Light consumers (1–14 drinks per week) ‡	176 (41.8)
Heavy consumers (≥15 drinks per week) ‡	40 (9.5)
Diabetics	
Patients in current medical therapy	21 (4.9)
Cardiovascular drugs §	117 (27.5)
Hormone drugs **	87 (20.5)
Anti-inflammatory drugs	79 (18.6)
Histological tumour classification	
Non malignant	1 (0.2)
Carcinoma *in situ*	15 (3.5)
Ductal carcinoma	327 (77.1)
Lobular carcinoma	44 (10.4)
Mucinous carcinoma	12 (2.8)
Other types of cancer	25 (5.9)
Operative	
Surgical procedure	
Mastectomy	105 (24.7)
Mastectomy with axillery dissection	214 (50.4)
Breast-conserving surgery	106 (24.9)
Surgery performed by specialised surgeon ‡‡	213 (50.1)
Median duration of surgery (interquartile range)	145 (110–195)
Median excised axillary lymph nodes	12 (7–16)
Median wound area (cm^2) (interquartile range)	336 (142–480)
Median bloodloss (ml) (interquartile range)	300 (200–500)
Perioperative transfusions	38 (15.3)
Postoperative	
Thromboembolic prophylaxis	
Graded TED-stockings	103 (24.2)
Fractionated heparine	314 (73.9)
Compressive wound dressing	
No compression	300 (70.6)
6 hours compression	63 (14.8)
24 hours compression	62 (14.6)

* Values are number of patients (with percentages in parentheses) unless stated otherwise.
† Defined as the sum of tobacco content in a cigarerette (1 gr) and a cheroot (2 gr) (present habit recorded).
‡ Defined as the sum of a bottled beer, a glass of wine, and a measure of spirits (9–13 grams of alcohol) (present habit recorded).
§ Digoxin, diuretics, blood pressure medicine, anticoagulants.
** Estrogens and contraceptive agents.
¶ Acetylsalicylic acid and non-steroid anti-inflammatory drugs.
‡‡ Supervised operations are credited to the specialised surgeon.

Table 2 Variables associated with infection analysed by multiple logistic regression – the final model

	Univariate odds ratio		Multivariate odds ratio	
Smoking habits				
Non-smoker	1	—	1	—
Light smoker (1–14 grams per day)	1.60	(0.65–3.93)	2.95	(1.07–8.16)
Heavy smoker (≥15 grams per day)	2.89	(1.42–5.88)	3.46	(1.52–7.85)
Alcohol consumption				
Abstainer	1	—	1	—
Light consumers (1–14 drinks per week)	0.61	(0.29–1.26)	0.76	(0.34–1.71)
Heavy consumers (≥15 drinks per week)	2.48	(1.04–5.90)	3.08	(1.11–8.84)
Diabetes				
None	1	—	1	—
IDDM or NIDDM	2.99	(1.04–8.60)	4.22	(1.10–16.16)
Body mass index				
Continuous variable	1.14	(1.07–1.22)	1.15	(1.07–1.24)
Surgical experience				
Specialist surgeon*	1	—	1	—
Trainee	2.90	(1.45–5.81)	2.88	(1.35–6.17)

Values in parenthesis are 95 per cent confidence intervals.
Number of patients included in the analysis: 423 (minus cases with missing data).
Introduction of epidermolysis as covariate in the model did not change the estimates, but when skin flap necrosis was introduced as covariate, diabetes and surgical experience lost their significant association with wound infection.
*Supervised operations are credited to the specialist surgeon.

Table 3 Variables associated with necrosis analysed by multiple logistic regression – the final model

	Univariate odds ratio		Multivariate odds ratio	
Smoking habits				
Non-smoker	1	—	1	—
Light smoker (1–14 grams per day)	6.49	(1.88–22.38)	6.85	(1.96–23.90)
Heavy smoker (≥15 grams per day)	9.41	(2.98–29.61)	9.22	(2.91–29.25)
Duration of surgery (per 15 min)				
Continuous variable	1.12	(1.06–1.16)	1.12	(1.07–1.18)

Values in parenthesis are 95 per cent confidence intervals.
Number of patients included in the analysis: 313 (minus cases with missing data).
Patients undergoing breast conserving surgery were excluded from the analysis as none experienced skin flap necrosis.

Table 4 Variables associated with epidermolysis analysed by multiple logistic regression – the final model

	Univariate odds ratio		Multivariate odds ratio	
Smoking habits				
Non-smoker	1	—	1	—
Light smoker (1–14 grams per day)	3.25	(1.28–8.25)	3.98	(1.52–10.43)
Heavy smoker (≥15 grams per day)	4.28	(1.84–9.93)	4.28	(1.81–10.13)
Duration of surgery (per 15 min)				
Continuous variable	1.08	(1.03–1.13)	1.18	(1.13–1.23)
Anti-inflammatory medicine				
No	1	—	1	—
Yes*	2.23	(1.06–4.67)	3.30	(1.46–7.43)

* Includes acetyl salicylic acid and non-steroid anti-inflammatory drugs.
Values in parenthesis are 95 per cent confidence intervals.
Number of patients included in the analysis: 313 (minus cases with missing data).
Patients undergoing breast conserving surgery were excluded from the analysis as only two experienced epidermolysis.

normal wound healing and defence against surgical pathogens.

Despite the fact that skin flap necrosis and epidermolysis were significant predictors of wound infection in this study, smoking was still independently associated with this complication. This finding is confirmed by studies showing wound infection rate as inversely proportional to tissue oxygen tension,[18] presumably due to inadequate bactericidal killing capacity of neutrophils as a result of low oxygen partial pressure in the wound.[19,20] This hypothesis has recently been supported by a study demonstrating that postoperative supplemental oxygen providing an arterial oxygen tension beyond that required to saturate blood reduces the incidence of wound infection.[21]

The significance of smoking as predictor of wound infection may, however, depend of the nature of the tissue. In lower extremity amputation wounds which are at risk for low oxygen tension,[22] a significantly higher wound infection rate in smokers has been demonstrated.[23] Mastectomy wounds seem to be even more vulnerable to hypoxia, as the blood supply to the flap is compromised by arterial insufficiency and a large dead space of the wound.[24] Consequently, impeded wound blood supply in smokers as well as presence of microvascular disease and alterations in the cellular and inflammatory system, may explain the association between smoking and complicated wound healing as demonstrated in this study.

The presence of diabetes was the most significant factor for wound infection. This finding confirms well accepted evidence that diabetics are at higher risk for surgical wound infections than non-diabetics.[25,26] The suggested pathogenesis is facilitation of Gram-positive bacteria growth in a hyperglycaemic environment[27] and neutrophil dysfunction, i.e. impaired chemotaxis and phagocytosis.[28]

Other risk factors related to life style such as obesity and alcohol intake over 14 drinks per week were independent risk factors for wound infection. Like a previous report showing significantly more post-mastectomy wound infections in obese patients,[3] we found that increasing body mass index was directly proportional to the risk of wound infection. In contrast, the effect of alcohol intake has not previously been evaluated in mastectomy patients. However, our results confirm a study of postoperative morbidity after hysterectomy.[29] Moreover, our finding is in accordance with epidemiological evidence indicating an increased risk of morbidity among women who consume more than 14 drinks per week.[30]

Conflicting results about the significance of patient age as a predictor for wound healing complication has been reported.[3,9,14,31,32] When adjusting for other significant risk factors, we did not find patient age to be associated with complicated wound healing.

The effect of surgical experience on post-mastectomy wound complications is not clear. Contrary to a previous report,[33] we find a significant association between limited surgical experience and wound infection. A similar finding being independent of type of surgery performed has not been reported, although a higher incidence of skin flap necrosis in trainees compared to specialist surgeons has been shown.[34]

Duration of surgery has been suggested as a risk factor for surgical wound infection,[25] but the reports regarding post-mastectomy wound infections show conflicting results.[31,35] Our study shows that the risk of both epidermolysis and skin necrosis is directly proportional with the duration of surgery, but we do not find this risk factor to be associated with wound infection.

Finally, this study discloses that medication with non-steroid anti-inflammatory drugs is associated with epidermolysis. This coincidental finding confirms experimental evidence showing that prostaglandin inhibitors like indomethacin and acetylsalicylic acid impede growth stimulation of the epidermis when applied topically.[36]

In conclusion, the risk of wound infection, skin flap necrosis, and epidermolysis in breast cancer surgery is increased in smokers independent of other significant factors like diabetes, obesity, alcohol consumption, surgical experience, duration of surgery and non-steroid anti-inflammatory drugs. This finding may imply that surgeons would be justified to advise patients to change life style and quit smoking before breast cancer surgery. However, as the time from diagnosis of breast cancer to surgery is limited, further research is warranted to determine when patients should quit smoking prior to surgery to neutralize this factor as a risk for post-operative wound complications.

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