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Original Research Article

Acute and Persistent Postoperative Pain after Breast Surgery

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ABSTRACT

Objectives. This study s primary aim was to determine levels of acute and persistent postoperative pain and the incidence of severe postoperative pain after mastectomy. A secondary aim was to examine factors associated with postoperative pain.

Design. A retrospective cohort study of 196 female breast surgery subjects was conducted. Data were collected on: numerical rating scale (NRS) pain scores in the Post Anesthesia Care Unit (PACU) and at 1 month and 6–12 months postoperative; age; race; insurance; obesity; radiotherapy; chemotherapy; hypertension; anesthesia care time; and intraoperative and PACU opioid use. Severe postoperative pain was de ned as NAS 5. Data were analyzed using chi square, Fisher s exact test or analysis of variance, with $\alpha = 0.05$.

Results. PACU pain and the incidence of severe PACU pain increased with surgical complexity ($P < 0.005$). PACU pain scores averaged 4.71 ± 0.24 and 57.7% of subjects experienced severe pain. Postoperative pain scores at 1 or 6–12 months did not vary by surgical complexity and averaged 2.21 ± 0.32 and 0.74 ± 0.22, respectively. Severe postoperative pain was experienced by 22.1% of subjects at 1 month and 8.2% of subjects at 6–12 months. Older age and systolic hypertension were associated with less PACU pain. Non-White race, obesity, and high PACU opioid use were associated with greater postoperative pain at 1 month. Non-White people also had greater post-operative pain at 6–12 months.

Conclusions. The results suggest that nearly 60% of breast surgery patients experience severe acute postoperative pain, with severe pain persisting for 6–12 months in almost 10% of patients.

Key Words. Acute Pain; Persistent Pain; Postoperative Pain; Mastectomy; Breast Reconstruction

Introduction

Breast cancer is one of the ve most common cancers in the United States. In 2003, the 1-year incidence of breast cancer was 127.6 new cases per 100,000 females and current projections suggest that nearly 213,000 new cases of breast cancer will be diagnosed annually [1]. Treatment for breast cancer consists primarily of surgery (partial or complete mastectomy), with or without chemotherapy, and/or radiotherapy. The 5-year survival after breast cancer diagnosis has been increasing over the past decade and approximately 90% of newly diagnosed patients are now expected to survive 5 years [2].

The tremendous progress that has been made in the early detection and treatment of breast cancer has resulted in greater interest in quality of life

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issues among breast cancer survivors. One area of concern is the development of persistent postoperative pain after breast cancer surgery, although the extent of the problem is unclear [3]. Reported estimates of the incidence of persistent pain after mastectomy vary widely, with some studies nding incidence rates as high as 50% [4–11]. Several risk factors have been suggested, including severe preoperative pain, severe acute postoperative pain, surgical factors such as the number of lymph nodes removed and the complexity of the surgery, prior or concurrent radiotherapy or chemotherapy, obesity, depression or anxiety, and age [6,8–10,12–15].

The primary aim of the present study is to determine levels of acute and persistent postoperative pain, and the incidence of severe postoperative pain, after mastectomy. A secondary aim is to determine the relationship between levels of postoperative pain after breast surgery and demographic, clinical, and anesthesia-related variables hypothesized to be associated with postoperative pain.

Methods

This study was approved by the University of North Carolina Institutional Review Board.

Data Sources, Dataset Generation, and Data Collection

A retrospective cohort design was employed. The data sources were the administrative databases of the Divisions of Surgical Oncology and Plastic and Reconstructive Surgery, electronic patient records, and paper records of the Anesthesia and Post Anesthesia Care Unit (PACU). The administrative databases were queried for data from all patients undergoing breast surgery between January 1, 2003 and December 31, 2005. Data were collected on each patient s date of birth, date of surgery, Current Procedural Terminology (CPT) code and modi er, and CPT text description and diagnostic code(s). The data from each query were downloaded into Microsoft Excel (Microsoft, Seattle, WA) for transfer and then uploaded and merged in SPSS (version 15.0; SPSS Inc., Chicago, IL).

SPSS (v. 15.0) was then used to generate a simple random sample of 100 subjects from each of three breast surgery groups: partial mastectomy; complete mastectomy; and complete mastectomy with immediate reconstruction. The three surgical groups were identi ed by CPT codes. Mastectomies associated with concurrent axillary lymph node dissection or delayed reconstruction were not included.

Medical records were used to collect additional data on the random sample of subjects. Data were collected only from those subjects whose medical records were complete and whose date of surgery in the electronic health record matched that in the administrative database. This reduced the total number of subjects to 196, with 57 (29.1%) partial mastectomies, 78 (39.8%) complete mastectomies, and 61 (31.1%) complete mastectomies with immediate reconstruction. The following data were abstracted from the medical records and entered into the SPSS dataset: pain scores (numerical rating scale [NRS] of 0 [none]–10 [worst imaginable]) recorded by nurses in the PACU and the clinic at 1 month (median = 11 days) and 6–12 months (median = 247 days) postoperative; race; primary insurance type; history of radiotherapy or chemotherapy (current or prior); height, weight and blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) recorded by nurses in the preoperative appointment; anesthesia start and stop times; and intraoperative and PACU opioid use (drug, dose).

Primary Endpoint Variables

The primary endpoint variables were pain scores (NRS of 0–10) and the incidence of severe postoperative pain measured in the PACU and at 1 month and 6–12 months. Severe postoperative pain was de ned as a NRS score of 5 [13,16–18].

Statistical Analysis

The data were analyzed using SPSS (v. 15.0) and graphed using Sigma Plot (v. 10.0; SPSS, Inc.). Average pain scores and the incidence of severe postoperative pain were calculated for the whole cohort and compared across the three breast surgery groups using chi square, Fisher s exact test or analysis of variance (ANOVA), with $\alpha = 0.05$. The three breast surgery groups were collapsed into a single group to evaluate the relationship between postoperative pain scores and demographic, clinical and anesthesia-related variables using ANOVA, with $\alpha = 0.05$ and type of operation included as a covariate to control for differences between groups in several of these factors (see Table 2). Binary variables were created for this analysis. Age was categorized as <65 years and >65 years, a manner used previously for mastectomy patients [13,19]. Race was categorized as White people (Non-Hispanic) vs Non-White people (77% Black

people) and primary insurance was categorized as Private vs Non-Private. Clinical obesity was de ned as a body mass index 30. Systolic hypertension was de ned as preoperative SBP 140 and diastolic hypertension was de ned as preoperative DBP 90. Total time under anesthesia care was calculated as anesthesia stop time minus anesthesia start time. Total intraoperative and PACU morphine equivalents were calculated using conversion tables [20–21]. A median split was used to categorize anesthesia-related factors into categories of 4 hours vs >4 hours for total time under anesthesia care, 30 mg vs >30 mg for total intraoperative morphine equivalents, and 10 mg vs >10 mg for total PACU morphine equivalents.

Results

The postoperative pain score across all three mastectomy groups was 4.71 ± 0.24 in the PACU, 2.21 ± 0.32 during the rst month and 0.74 ± 0.22 at 6–12 months (Table 1). Severe postoperative pain was experienced by 57.7% of subjects in the PACU, 22.1% of subjects at 1 month, and 8.2% of subjects at 6–12 months (Table 1).

PACU pain scores and intraoperative and PACU opioid use varied by type of surgery (Table 2). PACU pain scores increased with surgical complexity ($P < 0.0005$), ranging from 3.55 ± 0.42 for the partial mastectomy group to 6.27 ± 0.40 for the complete mastectomy with immediate reconstruction group. The incidence of severe PACU pain also increased with surgical complexity ($P < 0.005$), ranging from 43.9% for the partial mastectomy group to 75.4% for the complete mastectomy with immediate reconstruction group. Intraoperative and PACU opioid use was lowest in the partial mastectomy group and highest in the complete mastectomy with immediate reconstruction group ($P < 0.0005$). Surgical complexity did not in uence postoperative pain scores or the incidence of severe postoperative pain at 1 month or 6–12 months (Table 2).

Several demographic, clinical, and anesthesia-related variables were associated with postoperative pain scores (Figures 1 and 2). Older age (Figure 1A) and systolic hypertension (Figure 1E) were associated with lower PACU pain scores ($P < 0.01$). High doses of PACU opioids (Figure 2C) were associated with higher PACU pain scores ($P < 0.0005$). PACU pain scores did not vary by race, insurance type, clinical obesity, diastolic hypertension, history of chemotherapy or radiation, time under anesthesia care, or dosages of intraoperative opioids. Postoperative pain scores at 1 month were higher among subjects who were Non-White people ($P < 0.01$; Figure 1B) and clinically obese ($P < 0.05$; Figure 1D), and received high doses of PACU opioids ($P < 0.01$; Figure 2C). Subjects who experienced severe PACU pain (Figure 2D) tended to have higher

Table 1 Demographics, clinical characteristics, and postoperative pain scores of breast surgery patients*

Total	196
Sex—female	196 (100%)
Age (mean years ± SEM years)	53.62 ± 1.02
Older age (65 years)	44 (22.4%)
Race (%)	
Non-Hispanic White people	139 (71.3)
Black people	44 (22.6)
American Indian/Native Alaskan	1 (0.5)
Hispanic	6 (3.1)
Asian/Pacific Islander	3 (1.5)
Other	3 (1.5)
Health insurance† (%)	
Private	107 (54.6)
Medicare/Medicaid	62 (31.6)
Department of Corrections	2 (1.0)
Tricare	6 (3.1)
Self-pay	18 (9.2)
Clinical obesity (BMI 30; N = 72)	30 (41.7%)
Systolic hypertension (SBP 140)	64 (32.7%)
Diastolic hypertension (DBP 90)	25 (12.8%)
Radiotherapy history—Yes	98 (51.0%)
Chemotherapy history—Yes	136 (70.8%)
Type of operation‡ (%)	
Partial mastectomy	57 (29.1)
Complete mastectomy	78 (39.8)
Immediate reconstruction	61 (31.1)
Total time under anesthesia care (mean min ± SEM)	278.44 ± 12.12
Intraoperative morphine equivalents (mean mg ± SEM)	34.34 ± 1.79
PACU morphine equivalents (mean mg ± SEM)	12.00 ± 0.91
PACU pain score (mean ± SEM)§	4.71 ± 0.24
Severe PACU pain (NAS 5)	113 (57.7%)
Pain score first postoperative month (mean ± SEM; N = 77)	2.21 ± 0.32
Severe pain first postoperative month (NAS 5)	17 (22.1%)
Pain score 6–12 months postoperative (mean ± SEM; N = 85)	0.74 ± 0.22
Severe pain 6–12 months postoperative (NAS 5)	7 (8.2%)

* The table provides demographical information, clinical characteristics, anesthesia-related data, and postoperative pain data for patients that underwent breast surgery between January 1, 2003 and December 31, 2005. Sample sizes for BMI and postoperative pain scores in the first month or 6–12 months after surgery were adjusted for missing data points.
† Health insurance group was based on patient's primary health insurance plan.
‡ Type of operation was categorized by CPT codes.
§ Pain scores are based on a NRS of 0–10 and are presented as averages (mean ± SEM) and as categories (none/mild [NRS < 5] or severe [NRS 5]). PACU pain scores re ect the maximum pain score recorded in the PACU.
BMI = body mass index; CPT = Current Procedural Terminology; DBP = diastolic blood pressure; NAS = numerical analog scale; PACU = Post Anesthesia Care Unit; SBP = systolic blood pressure; SEM = standard error of the mean.

Table 2 Demographics, clinical characteristics, and postoperative pain scores of breast surgery patients by type of operation*

	Partial Mastectomy (N = 57)	Complete Mastectomy (N = 78)	Immediate Reconstruction (N = 61)	Statistic, *P* Value†
Age (mean years ± SEM years)	58.77 ± 1.95	55.90 ± 1.57	45.90 ± 1.42	$F = 15.60$, $P < 0.0005$
Older age (65 years)	17 (29.8%)	24 (30.8%)	3 (4.9%)	$\chi^2 = 15.65$, $P < 0.0005$
Race—Non-Hispanic White people	41 (71.9%)	52 (66.7%)	46 (76.7%)	N.S.
Private health insurance‡	26 (45.6%)	42 (53.8%)	39 (65.0%)	N.S.
Clinical obesity (BMI 30)	9 (42.9%)	15 (50.0%)	6 (28.6%)	N.S.
Systolic hypertension (SBP 140)	22 (38.6%)	33 (42.3%)	9 (14.8%)	$\chi^2 = 13.11$, $P < 0.001$
Diastolic hypertension (DBP 90)	9 (15.8%)	11 (14.1%)	5 (8.2%)	N.S.
Radiotherapy history—Yes	50 (87.7%)	34 (43.6%)	14 (24.6%)	$\chi^2 = 48.41$, $P < 0.0005$
Chemotherapy history—Yes	45 (78.9%)	60 (76.9%)	31 (54.4%)	$\chi^2 = 10.68$, $P < 0.005$
Total time under anesthesia care (mean min ± SEM)	160.39 ± 8.53	243.43 ± 14.5	429.55 ± 19.08	$F = 76.91$, $P < 0.0005$
Intraoperative morphine equivalents (mean mg ± SEM)	19.93 ± 1.38	32.87 ± 1.79	49.87 ± 4.33	$F = 27.67$, $P < 0.0005$
PACU morphine equivalents (mean mg ± SEM)	6.86 ± 1.04	11.63 ± 1.23	17.37 ± 2.09	$F = 11.14$, $P < 0.0005$
PACU pain score (mean ± SEM)§	3.55 ± 0.42	4.33 ± 0.36	6.27 ± 0.40	$F = 11.70$, $P < 0.0005$
Severe PACU pain (NAS 5)	25 (43.9%)	42 (53.8%)	46 (75.4%)	$\chi^2 = 12.78$, $P < 0.005$
Pain score first postoperative month (mean ± SEM)	2.28 ± 0.65	1.95 ± 0.39	2.79 ± 0.83	N.S.
Severe pain first postoperative month (NAS 5)	7 (28.0%)	5 (13.2%)	5 (35.7%)	N.S.
Pain score 6–12 months postoperative (mean ± SEM)	0.70 ± 0.44	0.71 ± 0.34	0.83 ± 0.40	N.S.
Severe pain 6–12 months postoperative (NAS 5)	2 (8.7%)	3 (7.9%)	2 (8.3%)	N.S.

* The table provides demographical data, clinical data, anesthesia-related data, and postoperative pain data for breast surgery patients who underwent surgery between January 1, 2003 and December 31, 2005.
† *P* values are derived from the analysis of variance for continuous variables and chi square or Fisher's exact test for categorical variables comparing differences across surgical procedure type.
‡ Health insurance group was based on patient's primary health insurance plan.
§ Pain scores are based on a NRS of 0–10 and are presented as averages (mean ± SEM) and as categories (none/mild [NAS < 5] or severe [NAS 5]). PACU pain scores re ect the maximum pain score recorded in the PACU.
BMI = body mass index; DBP = diastolic blood pressure; NAS = numerical analog scale; N.S. = not significant; PACU = Post Anesthesia Care Unit; SBP = systolic blood pressure; SEM = standard error of the mean.

levels of pain 1 month after surgery ($P < 0.07$). Postoperative pain scores at 1 month did not vary by age, insurance type, systolic or diastolic hypertension, chemotherapy or radiation history, time under anesthesia care, or doses of intraoperative opioids. Postoperative pain scores at 6–12 months varied only by race, with Non-White people having higher pain scores than White people ($P < 0.01$; Figure 1B).

Discussion

The present results suggest that nearly 60% of breast surgery patients experience severe acute postoperative pain, with incidence rates increasing with surgical complexity. The average acute postoperative pain score is about 5 on a NRS of 0–10 and this also increases with surgical complexity. The incidence and degree of acute postoperative pain after breast surgery in this study is almost identical to that reported by another group after partial or complete mastectomy [13]. Unlike acute pain, postoperative pain scores and the incidence of severe postoperative pain did not vary among the three breast surgery groups. Within the rst postoperative month, the incidence of severe pain was 22.1%. Six to twelve months after breast surgery, the incidence of severe pain was 8.2%. Early studies suggested that 13–43% of breast cancer patients experience surgery-related pain a year or more after mastectomy [10,14,15]. Although surgical techniques have been re ned since these earlier studies were conducted [19], more recent studies support the earlier ndings, with one study nding that 48% of women experienced clinically meaningful pain 3 months after partial or complete mastectomy [6]. In another study, 25% of women who underwent complete mastectomy with immediate reconstruction reported persistent pain 3–4 years after surgery [5]. The estimated incidence of persistent postoperative pain in the present study is lower than recently published rates, perhaps because subjects who underwent concurrent axillary lymph node dissection, a known risk factor for persistent pain [5], were not included.

A secondary aim of the present study is to examine the relationship between levels of postoperative pain after breast surgery and a variety of demographic, clinical and anesthesia-related factors that were hypothesized, on the basis of experimental and clinical pain literature, to be related to postoperative pain. Older age and systolic hypertension were found to be associated

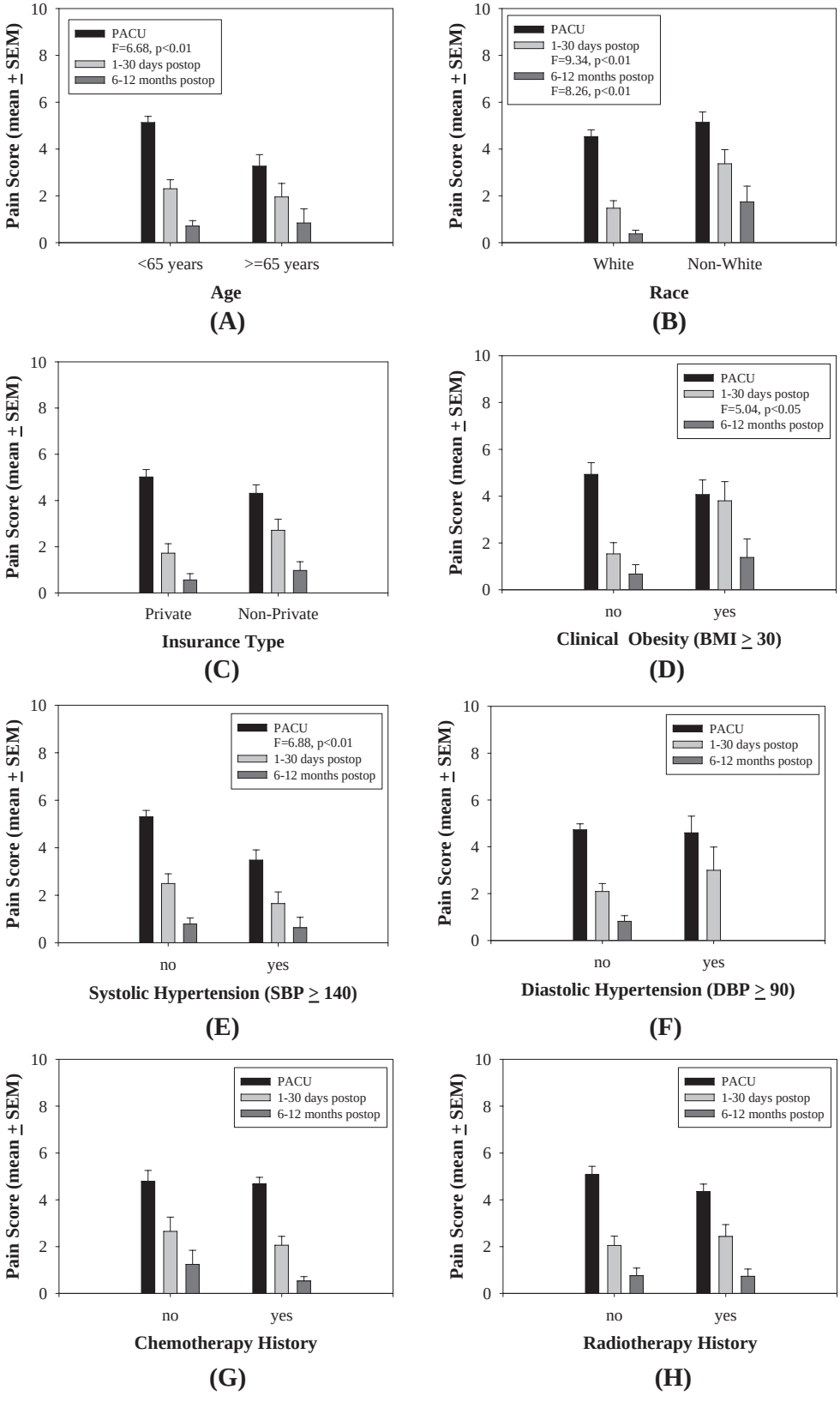

Figure 1 The association between postoperative pain scores after breast surgery and age (A), race (B), insurance type (C), clinical obesity (D), systolic hypertension (E), diastolic hypertension (F), and history of chemotherapy (G) or radiotherapy (H). Each panel shows the relationship between demographic and clinical risk factors, indicated on the x-axis, and average (mean ± standard error of the mean [SEM]) pain scores (numerical rating scale, 0–10 scale), on the y-axis, reported by breast surgery patients in the Post Anesthesia Care Unit (PACU), within the first postoperative month and within 6–12 months after surgery, as indicated in the figure legends. Significant associations are noted. BMI = body mass index; DBP = diastolic blood; SBP = systolic blood pressure.

with lower levels of acute postoperative pain, whereas Non-White race, clinical obesity, and PACU opiate use were associated with greater levels of long-term postoperative pain.

Several studies suggest that older patients are at reduced risk for acute and persistent postoperative pain [6,9,13,15,22], although one other study does not support this association [14]. The present study found that older age was associated with lower levels of pain in the PACU, but not at 1 month or 6–12 months after surgery, suggesting that the relationship between age and postoperative pain is perhaps stronger for acute than persistent pain.

Elevated blood pressure is associated with decreased experimental pain sensitivity [23,24], and a recent prospective study indicates that a genetic variant of the beta-adrenergic receptor is associated

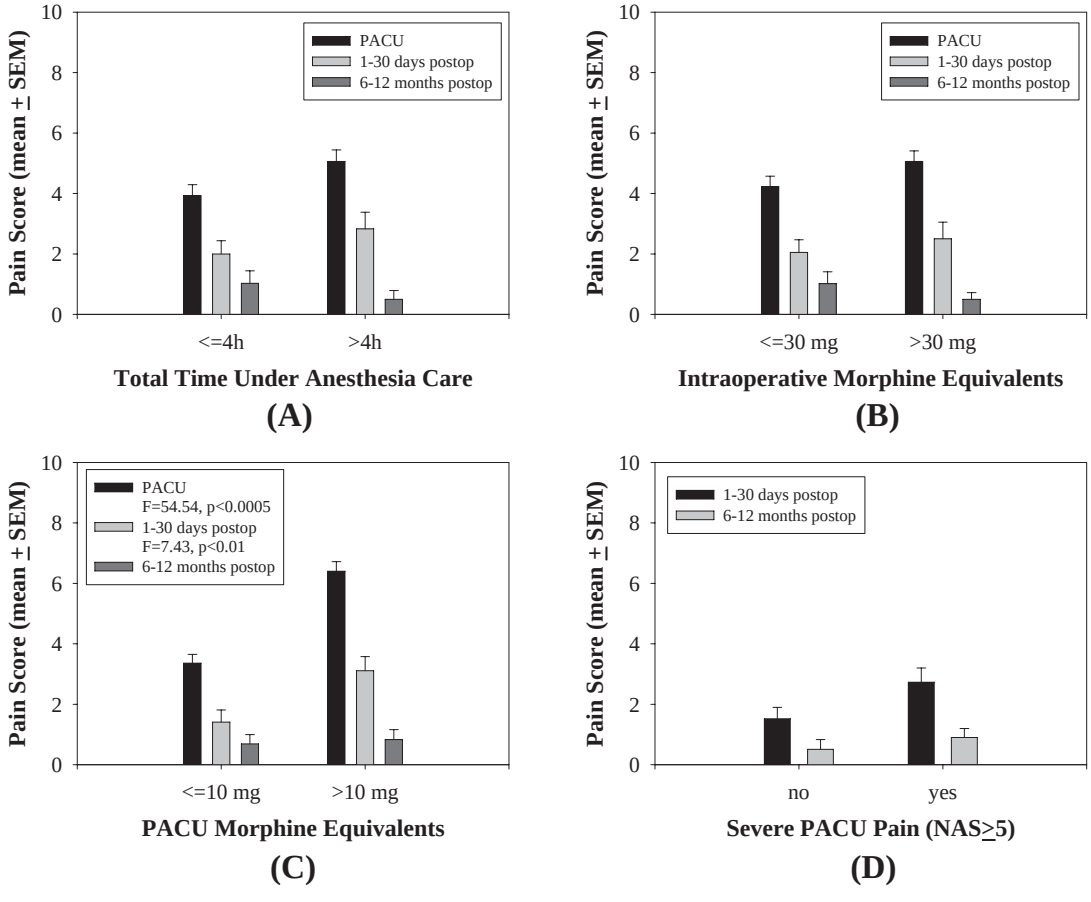

Figure 2 The association between postoperative pain scores after breast surgery and total time under anesthesia care (A), intraoperative morphine equivalents (B), Post Anesthesia Care Unit (PACU) morphine equivalents (C), and severe PACU pain (D). Each panel shows the relationship between anesthesia-related factors, indicated on the x-axis, and average (mean ± standard error of the mean [SEM]) pain scores (numerical rating scale [NRS], 0–10 scale), on the y-axis, reported by breast surgery patients in the PACU, within the first postoperative month and within 6–12 months after surgery, as indicated in the figure legends. Significant associations are noted.

with both elevated blood pressure and a decreased risk for developing temporomandibular disorder, a common chronic pain condition [25]. In the current study, preoperative systolic hypertension, but not diastolic hypertension, was associated with lower pain scores in the PACU, in agreement with studies on experimental pain. However, neither systolic nor diastolic hypertension was associated with postoperative pain at later time points.

Black people show greater experimental pain sensitivity than non-Hispanic White people [24]. The present study did not find a difference in PACU pain between non-Hispanic White people and Non-White people (77% Black people), but Non-White people had increased pain during the first postoperative month and 6–12 months after surgery. The current findings suggest that acute postoperative pain sensitivity, as opposed to experimental pain sensitivity, is not greater among Non-White people than White people, but levels of persistent pain are.

Clinical obesity was identified as a risk factor for persistent pain after breast surgery by another group [15]. In the present study, clinically obese subjects had higher levels of pain during the first postoperative month and a trend toward higher levels at 6–12 months postoperative, suggesting that persistent postoperative pain represents yet another health problem associated with obesity.

Several studies suggest that prior or concurrent radiotherapy and chemotherapy increase acute postoperative pain and the likelihood of developing persistent pain after breast surgery [6,8,9], although at least one study did not find an association [14]. The present study did not find a relationship between history of radiotherapy or chemotherapy and postoperative pain levels. However, the timing of the radiotherapy and chemotherapy was not evaluated.

Psychological traits, particularly depression and anxiety, have been linked to the development of persistent pain after breast surgery [10,13]. Insurance type was used as a surrogate marker for psychosocioeconomic risk in the present study. An association between insurance type and postoperative pain was not found, but the contribution of psychological, social, and/or economic factors to postoperative pain cannot be ruled out.

Anesthesia-related factors that were examined included total time under anesthesia care, intraoperative opioid use, PACU opioid use, and PACU pain. Of these factors, only PACU opioid use was associated with pain during the first postoperative month, with high opioid use associated with greater pain. This finding likely reflects the documented relationship between severe acute pain and increased likelihood of persistent pain [3]. However, opioid-induced hyperalgesia is another explanation [26].

Limitations

Our study has several limitations that should be considered when interpreting the results. First, this was a retrospective study and as such, it is vulnerable to several types of bias, including self-selection bias and misclassification bias, particularly with respect to pain scores. Second, our primary data source was nursing records taken preoperatively, in the PACU and at postoperative appointments. The nurses taking the pain scores were not specifically trained to collect data for research purposes and so measurement error is possible. Third, height data and postoperative pain scores at 1 month and 6–12 months were missing for a subset of subjects, which could introduce confounding. Confounding also is possible with respect to comorbidities and variations in the surgical technique, which were not controlled for.

Conclusions

Overall, our findings suggest that severe acute postoperative pain is problematic for more than half of all breast surgery patients and that severe postoperative pain persists for 1 month in nearly 25% of breast surgery patients and 6–12 months in close to 10% of breast surgery patients. Our findings further suggest that Non-White race, clinical obesity, and high PACU opioid use are factors associated with increased postoperative pain, whereas older age and systolic hypertension are factors associated with less postoperative pain. These findings should help guide the design of future prospective studies to fully evaluate these factors.

References

1 National Cancer Institute, National Institutes of Health. Cancer Trends Progress Report – 2005 Update. 2005. Available at: http://www.progressreport.cancer.gov (accessed February 23, 2007).

2 American Cancer Society, Inc. Breast Cancer Facts & Figures 2005–2006. Available at http://www.cancer.org/docroot/stt/stt_0.asp (accessed February 23, 2007).

3 Kehlet H, Jensen TS, Woolf C. Persistent postsurgical pain: Risk factors and prevention. Lancet 2006;367:1617–25.
4 Carpenter JS, Andrykowski MA, Sloan P, et al. Postmastectomy/postlumpectomy pain in breast cancer survivors. J Clin Epidemiol 1998;51:1285–92.
5 Legeby M, Segerdahl M, Sandelin K, et al. Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain. Breast 2002;11:156–62.
6 Poleshuck EL, Katz J, Andrus CH, et al. Risk factors for chronic pain following breast cancer surgery: A prospective study. J Pain 2006;7:626–34.
7 Roth RS, Lowery JC, Davis J, Wilkins EG. Persistent pain following postmastectomy breast reconstruction: Long-term effects of type and timing of surgery. Ann Plast Surg 2007;58:371–6.
8 Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E. Treatment-related factors predisposing to chronic pain in patients with breast cancer–A multivariate approach. Acta Oncol 1997;36:625–30.
9 Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. Ann Oncol 1995;6:453–9.
10 Tasmuth T, Estlanderb A-M, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain 1996;68:343–7.
11 Wallace MS, Wallace AM, Lee J, Dobke MK. Pain after breast surgery: A survey of 282 women. Pain 1996;66:195–205.
12 Iohom G, Abdalla H, O Brien J, et al. The associations between severity of early postoperative pain, chronic postsurgical pain and plasma concentration of stable nitric oxide products after breast surgery. Anesth Analg 2006;103:995–1000.
13 Katz J, Poleshuck EL, Andrus CH, et al. Risk factors for acute pain and its persistence following breast cancer surgery. Pain 2005;119:16–25.
14 Krøner K, Knudsen UB, Lundby L, Hvid H. Long-term phantom breast syndrome after mastectomy. Clin J Pain 1992;8:346–50.
15 Smith WCS, Bourne D, Squair J, Phillips DO, Chambers WA. A retrospective cohort study of post mastectomy pain syndrome. Pain 1999;83:91–5.
16 Anderson KO. Role of cutpoints: Why grade pain intensity? Pain 2005;113:5–6.
17 Paul SM, Zelman DC, Smith M, Miaskowski C. Categorizing the severity of cancer pain: Further exploration of the establishment of cutpoints. Pain 2005;113:37–44.
18 Serlin RC, Mendoza RT, Nakamua Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995;61:277–84.
19 Bloom JR, Stewart SL, Chang S, Banks PJ. Then and now: Quality of life of young breast cancer survivors. Psychooncology 2004;13:147–60.
20 Gutstein HB, Akil H. Chapter 23: Opioid Analgesics. In: Hardman JG, Limbird LE, Gilman AG, eds. Goodman & Gilman s The Pharmacological Basis of Therapeutics, 10th edn. New York: The McGraw-Hill Companies, Inc.; 2001:569–620.
21 Tollison CD, Satterthwaite JR, Tollison JW. Practical Pain Management, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.
22 Mattila K, Toivonen J, Janhunen L, Rosenberg PH, Hynyen M. Postdischarge symptoms after ambulatory surgery: First-week incidence, intensity, and risk factors. Anesth Analg 2005;101:1643–50.
23 Maixner W, Fillingim R, Kincaid S, et al. Relationship between pain sensitivity and resting arterial blood pressure in patients with painful temporomandibular disorders. Psychosom Med 1997;59:503–11.
24 Campbell TS, Hughes JW, Girdler SS, Maixner W, Sherwood A. Relationship of ethnicity, gender, and ambulatory blood pressure to pain sensitivity: Effects of individualized pain rating scales. J Pain 2004;5:183–91.
25 Diatchenko L, Anderson AD, Slade GD, et al. Three major haplotypes of the β2 adrenergic receptor de ne psychological pro le, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet Part B 2006;141B:449–62.
26 Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. Anesthesiol 2006; 104:570–87.