

# Do Intraoperative Analgesics Influence Breast Cancer Recurrence After Mastectomy? A Retrospective Analysis

Patrice Forget, MD,\* Julie Vandenhende, MD,\* Martine Berliere, MD, PhD,†  
Jean-Pascal Machiels, MD, PhD,‡ Benoit Nussbaum, MD,\* Catherine Legrand, PhD,§  
and Marc De Kock, MD, PhD\*

**BACKGROUND:** Whether intraoperative analgesics have an impact on postoperative cancer recurrence is unknown. Some investigations suggest that the opioids could favor relapse and that regional analgesia and nonsteroidal antiinflammatory drugs could improve cancer prognosis. We retrospectively reviewed our series of breast cancer surgery patients.

**METHODS:** This retrospective study included 327 consecutive women who underwent mastectomy with axillary dissection for breast cancer. The main objective was to compare the incidence of cancer recurrence among patients who received different analgesics during surgery.

**RESULTS:** Perioperative characteristics, cancer prognostic factors, and the length of surgery were comparable regardless of the analgesics administered. Univariate and multivariate analyses showed a lower cancer recurrence rate when ketorolac was given before surgery ( $P = 0.019$ ). Other analgesics (sufentanil, ketamine, and clonidine) were not associated with a significant reduction in cancer recurrence rates in our series.

**CONCLUSION:** This retrospective analysis suggests that intraoperative administration of ketorolac decreases the risk of breast cancer relapse compared with other analgesics. (*Anesth Analg* 2010;110:1630–5)

Surgery remains the keystone in the treatment of solid neoplastic tumors including breast cancer. Paradoxically, the perioperative period represents a high risk of metastases development.<sup>1</sup> Several factors may account for this phenomenon, including profound depression of antitumoral cellular immunity. Depression of this cellular immunity in the postoperative period is at least partially linked to the metabolic and hormonal changes induced by the “stress reaction” to surgery.<sup>2</sup> Analgesics may influence immunity and tumor development either directly by interfering with cellular mechanisms (e.g., cell apoptosis) or indirectly by interacting with the endocrine and sympathetic systems.

In animal models, morphine-based analgesia reduces the number of pulmonary metastases after surgery.<sup>3</sup> However, in humans, recent retrospective data suggest that opioid-based perioperative analgesia is associated with reduced recurrence-free survival, when compared with regional techniques for breast and prostate cancer surgery.<sup>4,5</sup> Very few studies have evaluated the possible immune effect of the other analgesics or antihyperalgesics used for “balanced” perioperative analgesia such as the nonsteroidal antiinflammatory drugs (NSAIDs), ketamine, and clonidine.

Currently, whether perioperative analgesia has an impact on postoperative cancer recurrence remains largely unknown.<sup>1</sup> Therefore, we performed a retrospective analysis of medical records to compare the incidence of local recurrence and metastatic disease after mastectomy in patients with breast cancer who received different intraoperative analgesics (i.e., sufentanil, ketamine, ketorolac, and clonidine).

## METHODS

### Patients and Procedures

After approval from the Ethical Committee of the St-Luc Hospital, Brussels, Belgium, we reviewed the medical records of 327 consecutive patients who underwent mastectomy with axillary dissection between February 2003 and September 2008. The size of this convenience sample was mainly due to logistical reasons (availability of the medical records), but it also maintained the homogeneity in the oncological treatments among the patients. Patients with previous ipsilateral surgery for breast cancer were excluded.

Indications for mastectomy with axillary dissection were defined according to international recommendations and guidelines.<sup>6,7</sup> These indications were discussed every week by the multidisciplinary board of our breast clinic and regularly updated and adjusted with new international recommendations and literature data. All mastectomies were performed by the same surgeon (MB) and jointly followed by the surgeon and the same oncologist (J-PM). Chemotherapy, radiotherapy, and endocrine therapy were performed according to international expert consensus (ninth and 10th St-Gallen consensus).<sup>8–11</sup>

During the first 2 postoperative years, medical consultation occurred every 3 months, then every 6 months for 3 additional years, and then once a year. For all operations,

From the Departments of \*Anesthesiology, †Gynecology, and ‡Oncology, and §Institute of Statistics, Université Catholique de Louvain, Louvain-la-Neuve, Belgium.

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Address correspondence and reprint requests to Patrice Forget, MD, Departments of Anesthesiology, St-Luc Hospital, av. Hippocrate 10-1821, 1200 Brussels, Belgium. Address e-mail to forgetpatrice@yahoo.fr.

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general anesthesia was induced with sufentanil ( $0\text{--}0.2 \mu\text{g} \cdot \text{kg}^{-1}$ ) and a hypnotic, sodium thiopental ( $4 \text{ mg} \cdot \text{kg}^{-1}$ ) or propofol ( $2\text{--}3 \text{ mg} \cdot \text{kg}^{-1}$ ). After insertion of a laryngeal mask airway, anesthesia was maintained with continuous infusion of propofol, plus sevoflurane or desflurane in an oxygen/air mixture. The type, dosage, and combination of intraoperative analgesic therapy were left to the discretion of the 2 anesthesiologists in charge. Total doses administered were as follows: sufentanil ( $0\text{--}0.5 \mu\text{g} \cdot \text{kg}^{-1}$ ); preincisional clonidine ( $0\text{--}6 \mu\text{g} \cdot \text{kg}^{-1}$ ); and preincisional ketamine ( $0\text{--}0.5 \text{ mg} \cdot \text{kg}^{-1}$ ). Ketorolac, when administered before the incision, was used in IV doses of 20 mg in patients  $<60 \text{ kg}$  body weight and 30 mg in patients  $>60 \text{ kg}$ .

In the postanesthesia care unit, postoperative analgesia consisted of IV piritramide titrated until the visual analog scale scores were lower than 4 on a scale anchored with 0 as "no pain" and 10 as "the worst pain ever experienced." During the first 48 postoperative hours, all patients received acetaminophen, 3 to 4 g/d. Oral diclofenac 50 mg was administered 3 times a day for 3 days as necessary, in the absence of contraindication (gastric, renal, or advanced age). No additional opioid was administered.

### Primary End Point

The main objective of this study was to determine the effect, if any, of the administration of different intraoperative analgesics (sufentanil, ketamine, clonidine, and ketorolac) on cancer recurrence. Consequently, our primary end point for this analysis was the length of recurrence-free survival through February 2009. Recurrence-free survival was measured from the date of surgery to the date of first recurrence, death due to oncological cause, or to the date of last follow-up, whichever occurred first. Recurrence was defined as clinical evidence of local recurrence or development of metastases confirmed by radiological examination(s). Patients lost to follow-up or those remaining disease free at the time of analysis were censored in the statistical model at the date of the last follow-up (administrative censoring). Patients who died of nononcological causes were censored at the date of death (assuming noninformative censoring).

### Data Collection

The following data were obtained from the medical records: perioperative (demographic) characteristics, tumor size, histological tumor grade, histopathological type, estrogen and progesterone receptor status, epidermal growth factor receptor type 2 (HER-2) expression, extent of axillary node disease, and administration of perioperative or postoperative adjuvant chemotherapy, radiotherapy, or endocrine therapy. The patient's current status was determined by the most recent follow-up in our breast cancer clinic through February 2009. Lost to follow-up was defined as patients who lacked follow-up for  $>3$  months after the last clinic visit attended date. The Nottingham Prognostic Index was calculated based on the histological findings: 0.2 (tumor size) + histological grade (1 = grade 1, least aggressive tumor appearance; 2 = grade 2, intermediate appearance; and 3 = grade 3, most aggressive appearance) + axillary lymph node involvement (1 = no axillary lymph nodes involved, 2 = up to 3 axillary lymph nodes involved, and 3 =  $>3$  axillary lymph nodes involved).<sup>4</sup> The type and total dose of the analgesics administered intraoperatively

were obtained by reviewing the electronic intraoperative and postoperative records. The duration of the surgical procedure, and type and doses of hypnotic administered were also noted.

### Statistical Analysis

Patient baseline characteristics are presented as mean  $\pm$  SD, median (interquartile 25–75), or numbers (percentage). Univariate Cox model and log-rank test were used to assess the potential effect of these baseline characteristics and to investigate an eventual effect of the administration of the analgesics on recurrence-free survival probability. Kaplan-Meier analyses were used to estimate recurrence-free survival probabilities. Variables considered for the univariate analyses were tumor size, histological grade and lymph node involvement,<sup>12</sup> age, height, weight, length of surgery, Nottingham Prognostic Index, hormonal receptor status (estrogen and/or progesterone positive), HER-2 expression, hypnotics (propofol, sevoflurane, or desflurane), and postoperative analgesics (synthetic opioid piritramide and diclofenac).

After univariate analyses, the Cox regression model was used for multivariate analysis while adjusting for any baseline factors and intraoperative or oncological factors related to the outcome in the univariate analyses ( $P < 0.05$ ). A single model was conducted including all the analgesics simultaneously to assess the effect of each analgesic while adjusting for taking one and not another analgesic. We then used stepwise manual backward regression, and all significant factors at a value of  $P < 0.05$  were retained in the final model. STATISTICA (data analysis software system, 2004) version 7 (StatSoft, Tulsa, OK) was used for all analyses.

## RESULTS

### Patients and Procedure Characteristics: Histopathological Findings

The data from 327 consecutive patients who underwent mastectomy with axillary dissection were reviewed. Eight patients were excluded because of intrathoracic tumor expansion, incomplete surgical resection, and/or perioperative metastases. The data from the 319 remaining patients were analyzed. Patients, histological findings, and duration of the surgery are summarized in Table 1. Postoperative complications included wound infection in 13 patients (4%) and significant hemorrhage requiring transfusion and reoperation in 1 patient (0.3%).

The median follow-up time was 27.3 months (13–44 months). Recurrence was noted in 35 patients (11%), and 17 patients (5%) died of oncological causes during the follow-up period. Deaths from nononcological causes were rare (3 patients, 0.9%), distributed equally according to the type of treatment, and not related to treatment (2 due to pneumonia and 1 due to cardiovascular disease). Sixteen patients (5%) were lost to follow-up.

### Intraoperative and Postoperative Analgesics

The intraoperative analgesics included sufentanil, ketorolac, clonidine, and ketamine. Table 2 summarizes the proportion of patients receiving the various drugs. Clonidine and ketamine were often combined for their opioid-sparing effects and were associated with smaller doses of sufentanil. Half of the patients who received

**Table 1. Patient Characteristics**

Patients and procedure characteristics: histologic findings (N = 319)	
Age (y)	59 ± 14
Weight (kg)	68 ± 15
Height (cm)	163 ± 9
Tumor size (mm)	34 ± 24
Histologic grade	
1	30 (9%)
2	111 (35%)
3	178 (56%)
Lymph node invasion	
1 (none)	151 (47%)
2 (1–3 positive lymph nodes)	99 (31%)
3 (>3 positive lymph nodes)	69 (22%)
Nottingham Prognostic Index	11 ± 5
Hormonal receptor status	
Estrogen positive	262 (82%)
Progesterone positive	280 (88%)
HER-2 expression	172 (54%)
Duration of surgery (min)	90 ± 26

Data are presented as mean ± SD or as numbers (percentage).

**Table 2. Number of Patients Receiving Intra- and Postoperative Analgesics and the Doses Administered**

	Number of patients	Doses
Ketorolac	175 (55)	20 mg [0–25]
Sufentanil	227 (71)	15 µg [0–18]
Clonidine	184 (58)	150 µg [0–185]
Ketamine	166 (52)	10 mg [0–20]
Piritramide	159 (50)	2 mg [0–4]
Diclofenac	223 (70)	50 mg [0–50]

Intravenous ketorolac, sufentanil, clonidine, and ketamine were administered intraoperatively. Intravenous piritramide was administered in the postanesthesia care unit until visual analog scale score <4. Diclofenac was administered if necessary during the first 48 postoperative hours. Data are presented as numbers (percentage) and median [interquartile 25–75].

sufentanil also received ketorolac. All postoperative analgesics (except acetaminophen) are also listed in Table 2.

**Association Between Use of Analgesics and Cancer Recurrence: Univariate and Multivariate Analyses**

Potential confounders, including perioperative patient characteristics, cancer prognostic factors, and length of surgery, were equally distributed over the groups of patients treated with the different analgesics (data not shown). One exception is the younger age of the patients receiving ketorolac (56 ± 12 vs 63 ± 14 years) (P = 0.02).

In univariate analysis, intraoperative administration of ketorolac was associated with longer recurrence-free survival (P = 0.019). Cancer recurrence was more frequent in patients who did not receive intraoperative ketorolac (17%, n = 25 of 145 vs 6%, n = 10 of 174; P = 0.001). No significant change in the rate of cancer recurrence was found in the patients who received sufentanil, clonidine, ketamine, and other drugs (P > 0.05) (Table 3, Fig. 1). Univariate analysis also showed that age (P = 0.004), histological grade (P = 0.006), lymph node invasion (P < 0.001), and Nottingham Prognostic Index (P = 0.048) were significantly associated with recurrence-free survival (Table 3).

**Table 3. Univariate Analyses of Demographic Characteristics, Cancer Prognostic Factors, Length of Surgery, and Intraoperative Analgesics for Breast Cancer Surgery**

	Beta	Hazard ratio	95% CI	P
Age	0.04	1.04	1.02–1.42	0.004
Height	0.02	1.02	1–1.03	0.054
Weight	0.26	1.03	0.98–1.07	0.31
Tumor size	0.006	1	1–1.1	0.36
Histologic grade	0.96	2.62	1.92–3.32	0.006
Lymph node invasion	0.95	2.6	2.16–3.04	<0.001
Nottingham Prognostic Index	0.05	1.05	1–1.1	0.048
Hormonal receptor status				
Estrogen positive	–0.81	0.44	0–1.15	0.25
Progesterone positive	–0.36	0.69	0–1.39	0.45
HER-2 expression	–0.02	0.98	0.33–1.63	0.94
Duration of surgery	–0.001	0.99	1–1.01	0.94
Hypnotics				
Thiopental	0.002	1	1–1.1	0.19
Propofol	0.15	1.17	0.87–1.47	0.59
Desflurane	0.36	1.44	0.69–2.2	0.36
Sevoflurane	–0.54	0.58	0–1.33	0.16
Ketorolac	–0.89	0.41	0–1.19	0.019
Sufentanil	–0.31	0.73	0–1.83	0.57
Clonidine	0.77	2.17	0.33–3.01	0.63
Ketamine	–0.056	0.57	0–1.49	0.23
Postoperative analgesics				
Piritramide	–0.49	0.61	0–1.31	0.16
Diclofenac	–0.03	0.97	0.85–1.19	0.57

Data are presented as factor effect (beta) estimated from univariate Cox regression model, hazard ratio (HR) and associated 95% confidence intervals (CIs), and log-rank P value.

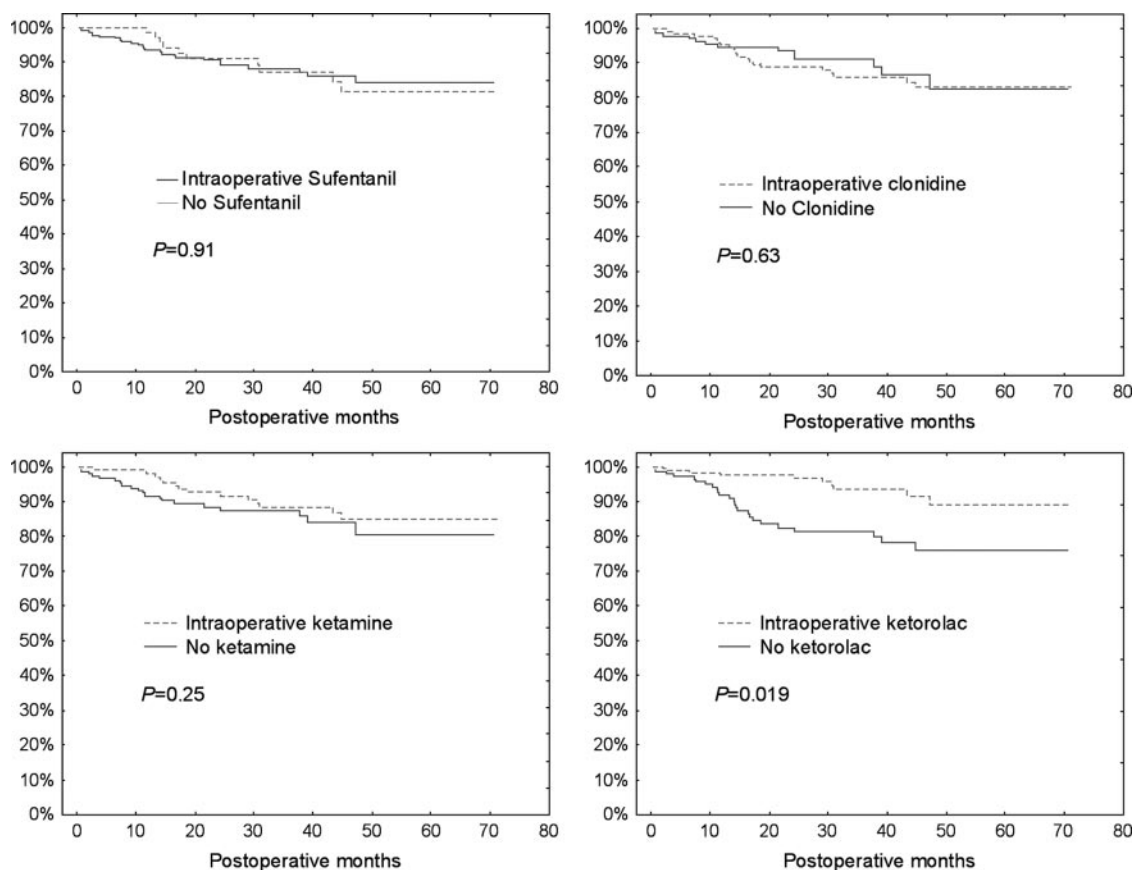
The Cox regression model was used for multivariate analysis while adjusting for these factors. Using stepwise manual backward selection, age, histological grade, and lymph node invasion were retained as risk factors in our multivariate analysis model (Table 4).

When adjusting for age (P = 0.02), histological grade (P = 0.015), and lymph node involvement (P < 0.001), the risk of cancer recurrence remains significantly lower after the intraoperative administration of ketorolac (P = 0.019). No significant effect was found with sufentanil, clonidine, and ketamine (P > 0.05) (Table 4). A single model was constructed to test all the analgesics simultaneously, to assess the effect of each analgesic while adjusting for the others, and to consider the risk of potential confounder effects in the case of drug combinations.

**DISCUSSION**

This retrospective analysis suggests an association between a reduced risk of breast cancer recurrence after surgery and the perioperative administration of ketorolac. This reduced risk was not observed when other intraoperative analgesics were administered. In contrast with previous data suggesting a negative influence of opioids on cancer-related immunity,<sup>13</sup> sufentanil had no deleterious effect on cancer recurrence. One reason may be the doses used in our patients, which are relatively small in comparison with those in other series.<sup>14</sup> This is consistent with the fact that opioid-induced immunosuppression is dose dependent.<sup>13</sup>

The α2-agonist clonidine enhances hypnotics, optimizes postoperative analgesia, and stabilizes intraoperative hemodynamic variables. This drug potentially interferes with



**Figure 1.** Kaplan-Meier recurrence-free survival estimated for 319 patients receiving (or not receiving) intraoperative analgesics (sufentanil, clonidine, ketorolac, and ketamine). Univariate analysis by log-rank tests.

**Table 4. Multivariate Association with Cancer Recurrence After Mastectomy: Cox Regression Model**

	Beta	Hazard ratio	95% CI	P
Age	0.03	1.03	1–1.06	0.02
Histologic grade	0.85	2.34	1.67–3.01	0.015
Lymph node invasion	0.83	2.28	1.87–2.69	<0.001
Ketorolac	–0.98	0.37	0–0.79	0.019
Sufentanil	–0.31	0.73	0–1.83	0.57
Clonidine	0.77	2.15	0.74–3.56	0.08
Ketamine	–0.56	0.57	0–1.49	0.23

Data are presented as factor effect (beta) estimated from multivariate Cox regression model, hazard ratio (HR) and associated 95% confidence interval (CI), and P value.

immunity via adrenergic antiinflammatory pathways and by a central analgesic effect that reduces sympathetic tone<sup>15</sup>; these effects are immunosuppressive in the perioperative period.<sup>2</sup> The doses administered were chosen based on the patients' physical conditions and the fact that mastectomy is classically considered a minor surgery<sup>14</sup> that induces a relatively limited "stress reaction."<sup>1</sup>

Ketamine is a drug widely used in the perioperative period. At subanesthetic doses, it prevents hyperalgesia and enhances analgesia.<sup>16</sup> Ketamine, similar to the other analgesics, interferes with natural killer (NK) cell activity. It

possesses antiinflammatory properties in humans during the postoperative period<sup>17</sup> or in severe sepsis.<sup>18</sup> In our series, ketamine was not associated with improved oncological outcome.

When considering the administration of ketorolac, these results suggest that, given just before the surgery, it was associated with a lower risk of breast cancer relapse. By multivariate analysis, age was identified as a potential confounder. Indeed, advanced age was considered a relative contraindication for NSAIDs and was consequently associated with a lower use of NSAIDs. After adjustment for the significant oncological predictors (histological grade and lymph node invasion) and the potential confounder (age), the association between ketorolac administration and the lower risk of cancer recurrence remained significant. Our observation is consistent with the results obtained in previous studies that investigated the influence of NSAIDs on antitumoral immunity. These studies identified the role of prostaglandins in immunity and inflammation,<sup>19,20</sup> and the positive effect of NSAIDs on immunity and against cancer progression in both animals and humans.<sup>21–26</sup> Indeed, cyclooxygenase-2 (COX-2) inhibitors are active in some models of breast cancer, and COX-2 could play a role in tumor development.<sup>24</sup> In fact, overexpression of COX-2 in breast cancer leads to stimulation of epithelial cell proliferation, inhibition of apoptosis, stimulation of angiogenesis, immune suppression, and increases the production of mutagens.<sup>23</sup> This favors breast tumor growth and

increases the risk of cancer relapse. These effects are mostly mediated by prostaglandins and specifically prostaglandin E<sub>2</sub> (PGE<sub>2</sub>).<sup>19,24</sup> PGE<sub>2</sub> is released by monocytes and dendritic cells to regulate the inflammatory cascade and profoundly depresses cellular antitumoral immunity, i.e., NK cell activity.<sup>24</sup> The PGE<sub>2</sub>-induced suppression of NK cell activity is carried via membrane receptors that trigger the synthesis of cyclic adenosine monophosphate, which interferes with the cytotoxicity of NK cells. This suppression of NK cell activity dissipates quickly after removal of prostaglandins. The time course of postoperative immunosuppression extends from the first postoperative hours to a few days. As a consequence, the optimal window for administration of a drug that acts on NK cells may be very short, ideally just before surgery. This time-specific effect may explain the effect of intraoperative ketorolac and the absence of effect of postoperative diclofenac in our retrospective study.

Another explanation is a specific effect of ketorolac. Indeed, inhibition of COX-2 is necessary to counteract the deleterious effects of PGE<sub>2</sub>,<sup>25</sup> but, although all NSAIDs act against the growth of tumors, they are probably not equivalent in their antitumor effects. Alternative targets, such as the tumor-associated reduced nicotinamide adenine dinucleotide oxidase (tNOX), are possibly involved in this anticancer effect. The existence of tNOX explains the fact that some cancer cell lines lacking COX-2 respond to certain NSAIDs but not to others, suggestive of additional COX-2-independent antitumor activities.<sup>26</sup> Further studies are required to explore the differences between the NSAIDs and their antitumor effects in this context.

When analyzing the timing of cancer recurrence, the greatest difference between patients receiving ketorolac and those not receiving it appears between 9 and 18 months. This early cancer recurrence confirms our observation that intraoperative administration of ketorolac improves the control of residual neoplastic disease. Cancer relapse is a consequence of intraoperative spread of tumor cells in the bloodstream, local recurrence, or previously disseminated micrometastatic dormant cells.<sup>27</sup> Inducing or maintaining dormancy in these neoplastic cells is a major goal for the adjuvant therapeutics, e.g., endocrine therapy. The control of residual disease limits the risk of early recurrence. It explains why recurrences occur gradually during the first 10 to 15 years in women treated with endocrine therapy, whereas in women not treated with endocrine therapy (i.e., with estrogen receptor-negative tumors), the majority of cancer relapses occur in the first 2 years.<sup>27</sup>

Our study is potentially limited by the retrospective design and the exploratory nature of our analyses. Uncontrolled and unrecognized biases are frequent in retrospective studies. All known variables that influence cancer outcome were analyzed, but this does not exclude unrecognized bias. Overfitting, i.e., having poor predictive performance or exaggerating minor fluctuations in the data, is also a well-known problem of prognostic factor analyses, and validation against an external database is always advisable. The collection of data was systematic and the investigators (PF, JV, BN, and MDK) used the same methodology. The quality of the follow-up (MB and J-PM) and

the accessibility of data permitted us to ascertain all variables. Nevertheless, to confirm these data, prospective well-conducted and multicenter studies are required. Although never reported as immunosuppressive, we did not investigate the effect of acetaminophen, because it was prescribed systematically during the postoperative period.

In conclusion, our data support a positive effect of ketorolac administered preoperatively for breast cancer surgery. These data are consistent with previous animal and human preclinical studies that suggested an anticancer effect of preoperatively administered NSAIDs.

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