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Article

ARTICLE

Potential Benefit of Intra-operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently used in some countries as analgesics in primary cancer surgery. Retrospective studies suggest that NSAIDs could reduce breast cancer recurrences. Because NSAIDs also act on biological mechanisms present in patients with increased adiposity, we aimed at assessing whether the intra-operative administration of ketorolac or diclofenac would be associated with a reduction of recurrence in patients with elevated body mass index (BMI).
Methods: We considered two institutional retrospective series of 827 and 1007 patients evaluating the administration of ketorolac (n = 529 with, n = 298 without) or diclofenac (n = 787 with, n = 220 without). The BMI subgroups were defined as less than 25 kg/m^2 (lean) and 25 or more kg/m^2 (overweight and obese). Cumulative incidence estimation of distant metastases as well as Fine-Gray and Dixon-Simon models was used. These analyses were adjusted for clinico-pathological variables. All statistical tests were two-sided.
Results: The administration of ketorolac was statistically significantly associated with decreased incidence of distant recurrences (adjusted hazard ratio [aHR]= 0.59, 95% confidence interval [CI] = 0.37 to 0.96, $P = .03$). In particular, the association was evident in the high–body mass index (BMI) group of patients (aHR = 0.55, 95% CI = 0.31 to 0.96, $P = .04$). The administration of diclofenac was not statistically significantly associated with decreased incidence of distant recurrences, either in the global population or in the BMI subgroups.
Conclusions: These results show that the intra-operative administration of ketorolac, but not diclofenac, is statistically significantly associated with a reduction of distant recurrences in patients with increased BMI. Altogether, this study points to a potentially important repositioning of ketorolac in the intra-operative treatment of patients with elevated BMI that, if prospectively validated, might be as impactful as and cheaper than adjuvant systemic anticancer therapies.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been evaluated over the last decades in several, mainly retrospective, consecutive or case–control studies for their potential role in preventing breast cancer development and progression (1,2). It should be noted that most of the studies so far, with some exceptions, have investigated the chronic use of NSAIDs globally, without accounting for the pharmacological properties specific to the different drugs. Additionally, NSAIDs, such as diclofenac and ketorolac, both COX-1 and -2 inhibitors, have been introduced over the past decades as effective pain

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relievers in order to reduce the use and dosage of opioids and their associated adverse events (3,4). This has led to the slow introduction of NSAIDs in the anesthetic scene of cancer surgery in some countries. Because no specific guidelines have been proposed as to which specific NSAID should be used, the choice is generally left at the discretion of the anesthesiologists and varies therefore from hospital to hospital.

Surgical removal of the primary tumor is a crucial component of breast cancer treatment. Nevertheless, it has been shown to induce metabolic, neuroendocrine, inflammatory, immunological, and angiogenic changes (5–10). In this context, several retrospectives studies showed that the intra-operative administration of ketorolac was associated with improved cancer outcomes in breast, lung, and ovarian cancer (11,12). These results, although not yet prospectively validated, provocatively suggested that a single intra-operative administration of ketorolac could inhibit the surgery-induced growth of the previously dormant tumor cells.

Over the last decades, obesity has become a worldwide problem, not only because of its association with cardiovascular disease, diabetes mellitus, and hypertension, but also because of its association with the risk of development and progression of several cancers (13). In the United States, according to the latest estimates, 63% of the women are overweight or obese (14). Increased body mass index (BMI), which is the most commonly used surrogate for adiposity, has been recognized as a risk factor for developing breast cancer and has also been associated with adverse survival, and this especially in postmenopausal patients with estrogen receptor (ER)–positive breast cancer (15). Several biological mechanisms have been proposed to explain this adiposity–breast cancer connection, related mainly to hormonal status (estrogens and adipokines), insulin resistance, inflammation, and neo-angiogenesis (16,17). Based on these altered mechanisms, studies have been evaluating, for example, the potential benefit of treating nondiabetic patients with metformin, for which the results of the large randomized adjuvant National Cancer Institute of Canada (NCIC) Clinical Trials Group MA32 trial (NCT01101438) should provide evidence as to whether or not it could provide a survival advantage in early breast cancer patients (18). However, until now, patients are still treated in the same way, independently of their BMI.

NSAIDs are acting on biological processes altered both by primary tumor surgery, as described above, and by adiposity. For instance, it has been suggested that adiposity could induce COX-2 expression by the macrophages and tumor cells (19) and promote angiogenesis (20–22). We therefore hypothesized that breast cancer patients with an elevated BMI would have an increased benefit from intra-operative NSAIDs. To test this, we assessed, using two large retrospective institutional cohorts, whether the intra-operative administration of ketorolac or diclofenac would be associated with a reduction of distant recurrences in patients with elevated BMI.

Methods

Study Populations

The institutional retrospective and consecutive "ketorolac" series of breast cancer patients treated with primary tumor surgery between February 2003 and December 2008 at the Université Catholique de Louvain, Brussels, has already been reported elsewhere (11,23). Previous publications reported a protective effect on disease recurrence and survival for the use of NSAIDs (11,23). Of note, no association with cancer outcome was seen for the other investigated analgesics (sufentanil, ketamine, and clonidine). This study was approved by the respective ethics committee (REF 2010/15MAR/085, No. B40320108384). Given the different pharmacological properties, we excluded from this series the few patients who received diclofenac, as well as those without BMI information available. We considered 827 patients, 529 treated with and 298 without a single dose (typically 20 mg in patients <60 kg and 30 mg in patients ≥60 kg) of intra-operative ketorolac (Supplementary Figure 1A and Supplementary Table 1, available online).

The institutional retrospective and consecutive "diclofenac" series of breast cancer patients treated with primary tumor surgery between January 2008 and December 2010 at the Institut Jules Bordet, Brussels, was also considered. Similar to the previous cohort, the eligibility criteria were diagnosis of invasive breast cancer, older than age 18 years at diagnosis, no cancer in the past five years, and no chronic use of an NSAID. This study was approved by the respective ethics committee (REF AS14/07/2016, No. 2572). After excluding the patients who did not meet the eligibility criteria or those without available BMI, 1007 patients remained, 787 treated with intra-operative diclofenac (75 mg) and 220 without (Supplementary Figure 1B and Supplementary Table 2, available online).

In both series, distant recurrence was defined as clinical evidence of the development of distant metastases confirmed by radiological examination(s). BMI was calculated as the weight in kilograms divided by the square of the height in meters, and categorized using the World Health Organization classification (24), and for both cohorts, the BMI at the time of primary surgery was considered. The BMI subgroups were defined as less than 25 kg/m^2 (lean) and 25 or more kg/m^2 (overweight and obese).

Statistical Methods

The associations between the NSAID administration and the clinico-pathological variables were assessed using the Fisher exact test. Competing risk analysis of distant recurrences was done by crude cumulative incidence curves to be interpreted as the cumulative probability of distant metastases as first event (25) and consistently by Fine and Gray semiparametric models on subdistribution hazards (26). These analyses were adjusted for standard clinico-pathological variables: age (<50 or ≥50 years), tumor size (<2 or ≥2 cm), nodal status (negative or positive), grade (1–2 or 3), ER status (negative or positive), human epidermal growth factor receptor 2 (HER2; negative or positive), adjuvant chemotherapy (yes or no), adjuvant endocrine therapy (yes or no), and BMI (<25 or ≥25 kg/m^2).

Analyses for the effect of ketorolac, accounting for the continuous measurements of age and BMI and their interactions, were also performed adjusting for the above clinical-pathological variables, through generalized additive models on distant metastasis cause-specific hazard.

The Dixon and Simon model for subgroup analysis was also adopted for the assessment of NSAID effects, following a Bayesian approach under a skeptical prior hypothesis of no difference of the effects between the considered subgroups (27). The median follow-up times of the ketorolac and diclofenac cohort were 5.7 and 7.0 years, respectively, as estimated by the reverse Kaplan-Meier method. The distant recurrence dynamics were represented by cause-specific hazard curves, that is, the rates of recurrence of a specific event at a certain follow-up time on a monthly basis, estimated by the flexible bshazard

Table 1. Patient and tumor characteristics of the ketorolac and diclofenac series according to the administration of the respective NSAID

Characteristics	Ketorolac series				Diclofenac series			
	All No. (%)	No K No. (%)	K No. (%)	P*	All No. (%)	No D No. (%)	D No. (%)	P*
Age, y								
<50	197 (23.8)	52 (17.4)	145 (27.4)	.001	290 (28.8)	36 (16.4)	254 (32.3)	<.001
≥50	630 (76.2)	246 (82.6)	384 (72.6)		717 (71)	184 (83.6)	533 (67.7)	
BMI, kg/m^2								
<25	446 (53.9)	130 (43.6)	316 (59.7)	<.001	531 (52.7)	110 (50.0)	421 (53.5)	.36
≥25	381 (46.1)	168 (56.4)	213 (40.3)		476 (47.3)	110 (50.0)	366 (46.5)	
Tumor size, cm								
<2	466 (56.4)	153 (51.3)	313 (59.3)	.03	634 (63.5)	136 (62.4)	498 (63.8)	.69
≥2	360 (43.6)	145 (48.7)	215 (40.7)		364 (36.5)	82 (37.6)	282 (36.2)	
Unknown	1	–	1		9	2	7	
Grade								
1	129 (16.9)	46 (16.7)	83 (17.0)	.97	192 (19.1)	48 (21.9)	144 (18.3)	.37
2	281 (36.8)	100 (36.4)	181 (37.0)		518 (51.5)	113 (51.6)	405 (51.5)	
3	354 (46.3)	129 (46.9)	225 (46.0)		295 (29.4)	58 (26.5)	237 (30.2)	
Unknown	63	23	40		2	1	1	
Nodal status								
Negative	505 (65.8)	173 (63.1)	332 (67.2)	.27	699 (69.4)	168 (76.4)	531 (67.5)	.01
Positive	263 (34.2)	101 (36.9)	162 (32.8)		308 (30.6)	52 (23.6)	256 (32.5)	
Unknown	59	24	35		–	–	–	
ER status								
Negative	141 (17.4)	50 (17.1)	91 (17.6)	.92	161 (16.0)	27 (12.3)	134 (17.1)	.10
Positive	670 (82.6)	243 (82.9)	427 (82.4)		843 (84.0)	192 (87.7)	651 (82.9)	
Unknown	16	5	11		3	1	2	
HER2 status								
Negative	577 (76.7)	210 (78.1)	367 (76.0)	.53	802 (79.6)	180 (81.8)	622 (79.0)	.39
Positive	175 (23.3)	59 (21.9)	116 (24.0)		205 (20.4)	40 (18.2)	165 (21.0)	
Unknown	75	29	46		–	–	–	

*Two-sided Fisher exact test P values. BMI = body mass index; D = diclofenac; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; K = ketorolac; NSAID = nonsteroidal anti-inflammatory drug.

estimator (28). All statistical tests were two-sided at the .05 statistical significance level. Statistical analyses were performed with R v.3.4.1 and its packages cmprsk, mgcv, DSBayes, and bshazard (29).

Results

Association of BMI and Clinico-pathological Variables in the Ketorolac and Diclofenac Study Populations

Consistent with previous reports (30), we observed in both cohorts a statistically significant association between age at diagnosis and the administration of the NSAID (Table 1). This can be explained by the fact that advanced age is a contraindication for use of NSAIDs. Some additional associations with the administration of the respective NSAID were private to one of the cohorts. These marginal associations can possibly be explained by the effect of age.

The proportion of overweight and obese patients was comparable in the two cohorts, 46.1% and 47.3% in the ketorolac and diclofenac series, respectively (Table 1), and in line with the proportion of patients with an elevated BMI in Belgium during the past decade (14). When assessing the associations within the predefined BMI subgroups (Table 2), the only residual associations that we observed were the ones with age at diagnosis in the lean subgroup of the ketorolac cohort and in the two BMI subgroups of the diclofenac cohort.

Distant Recurrences According to the Administration of Ketorolac or Diclofenac and BMI

In the ketorolac cohort, 73 distant metastases occurred as the first event, of which 48 were in the high-BMI group (Figure 1). The administration of ketorolac was associated with decreased incidence of distant recurrences both in the unadjusted and adjusted analysis (hazard ratio [HR]$_{unadjusted}$ = 0.55, 95% confidence interval [CI] = 0.35 to 0.86, Fine and Gray regression two-sided Wald test P = .01; HR$_{adjusted}$ = 0.59, 95% CI = 0.37 to 0.96, P = .03) (Table 3), after accounting for the effect of age, tumor size, grade, nodal status, ER status, HER2 status, treatment, and BMI.

Subgroup analyses in patients within the predefined BMI subgroups (<25 and ≥25 kg/m^2) showed that the effect of ketorolac was limited to the high-BMI group of patients, both from the incidence curves and the unadjusted and adjusted regression analyses (HR$_{unadjusted}$ = 0.51, 95% CI = 0.29 to 0.90, Fine and Gray regression two-sided Wald test P = .02; HR$_{adjusted}$ = 0.55, 95% CI = 0.31 to 0.96, P = .04) (Table 3). Given the known limitations of subgroup analyses, an additional evaluation was provided according to the Dixon and Simon model, which provides estimates of the ketorolac effect, following a Bayesian approach under a skeptical assumption of no difference between the subgroups defined by BMI. Even after a major shrinkage of the effect of ketorolac in the low-BMI group toward a protective association, there is still no evidence from the interval estimates for this group, whereas this association of ketorolac is still evident in the high-BMI group (Supplementary Table 3, available online). Exploratory analyses on local recurrences did

Table 2. Patient and tumor characteristics according to the administration of the respective NSAID and BMI category

Characteristics	All No. (%)	No K No. (%)	K No. (%)	P*	All No. (%)	No D No. (%)	D No. (%)	P*
Patients with BMI <25 kg/m^2								
Age, y								
<50	128 (28.7)	28 (21.5)	100 (31.6)	.04	192 (36.2)	24 (21.8)	168 (39.9)	<.001
≥50	318 (71.3)	102 (78.5)	216 (68.4)		339 (63.8)	86 (78.2)	253 (60.1)	
Tumor size, cm								
<2	276 (61.9)	77 (59.2)	199 (63.0)	.52	353 (67.1)	67 (61.5)	286 (68.6)	.17
≥2	170 (38.1)	53 (40.8)	117 (37.0)		173 (32.9)	42 (38.5)	131 (31.4)	
Unknown	–	–	–		5	1	4	
Grade								
1	78 (18.8)	24 (20.5)	54 (18.2)	.62	116 (21.9)	29 (26.4)	87 (20.7)	.34
2	156 (37.7)	40 (34.2)	116 (39.1)		266 (50.2)	55 (50.0)	211 (50.2)	
3	180 (43.5)	53 (45.3)	127 (42.8)		148 (27.9)	26 (23.6)	122 (29.0)	
Unknown	32	13	19		1	–	1	
Nodal status								
Negative	291 (70.0)	86 (72.3)	205 (69.0)	.56	371 (69.9)	84 (76.4)	287 (68.2)	.10
Positive	125 (30.0)	33 (27.7)	92 (31.0)		160 (30.1)	26 (23.6)	134 (31.8)	
Unknown	30	11	19		–	–	–	
ER status								
Negative	81 (18.6)	26 (20.5)	55 (17.8)	.50	98 (18.5)	17 (15.6)	81 (19.3)	.41
Positive	355 (81.4)	101 (79.5)	254 (82.2)		431 (81.5)	92 (84.4)	339 (80.7)	
Unknown	10	3	7		2	1	1	
HER2 status								
Negative	297 (74.2)	87 (77.7)	209 (72.8)	.37	427 (80.4)	95 (86.4)	332 (78.9)	.08
Positive	103 (25.8)	25 (22.3)	78 (27.2)		104 (19.6)	15 (13.6)	89 (21.1)	
Unknown	47	18	29		–	–	–	
Patients with BMI ≥25 kg/m^2								
Age, y								
<50	69 (18.1)	24 (14.3)	45 (21.1)	.11	98 (20.6)	12 (10.9)	86 (23.5)	.004
≥50	312 (81.9)	144 (85.7)	168 (78.9)		378 (79.4)	98 (89.1)	280 (76.5)	
Tumor size, cm								
<2	190 (50.0)	76 (45.2)	114 (53.8)	.12	281 (59.5)	69 (63.3)	212 (58.4)	.38
≥2	190 (50.0)	92 (54.8)	98 (46.2)		191 (40.5)	40 (36.7)	151 (41.6)	
Unknown	1	–	1		4	1	3	
Grade								
1	51 (14.6)	22 (13.9)	29 (15.1)	.74	76 (16.0)	19 (17.4)	57 (15.6)	.85
2	125 (35.7)	60 (38.0)	65 (33.9)		253 (53.1)	58 (53.2)	194 (53.0)	
3	174 (49.7)	76 (48.1)	98 (51.0)		147 (30.9)	32 (29.4)	115 (31.4)	
Unknown	31	10	21		1	1	–	
Nodal status								
Negative	214 (60.8)	87 (56.1)	127 (64.5)	.12	328 (68.9)	84 (76.4)	244 (66.7)	.06
Positive	138 (39.2)	68 (43.9)	70 (35.5)		149 (31.1)	26 (23.6)	122 (33.3)	
Unknown	29	13	16		–	–	–	
ER status								
Negative	60 (16.0)	24 (14.5)	36 (17.2)	.48	63 (13.3)	10 (9.1)	53 (14.5)	.15
Positive	315 (84.0)	142 (85.5)	173 (82.8)		412 (86.7)	100 (90.9)	312 (85.5)	
Unknown	6	2	4		1	–	1	
HER2 status								
Negative	281 (79.6)	123 (78.3)	158 (80.6)	.60	375 (78.8)	85 (77.3)	290 (79.2)	.69
Positive	72 (20.4)	34 (21.7)	38 (19.4)		101 (21.2)	25 (22.7)	76 (20.8)	
Unknown	28	11	17		–	–	–	

*Two-sided Fisher exact test P values. BMI = body mass index; D = diclofenac; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; K = ketorolac; NSAID = nonsteroidal anti-inflammatory drug.

not support any association of ketorolac in the global population or in the BMI subgroups. However, these latter analyses were limited by the small number of events and should therefore be taken with caution (data not shown). In addition, the exploratory analysis of the modifying role of age and BMI, both considered as continuous variables, on the effect of ketorolac was consistent with the above results, showing major evidence in the group of overweight patients with older than age 50 years (Supplementary Figure 2 and Supplementary Table 4, available online).

To evaluate the potential confounding effect of the other drugs administered in the operative setting, especially opioids such as sufentanil and piritramide, we conducted exploratory adjusted analyses including each of these drugs for the subset of patients for which this information had been recorded (n = 272 for sufentanil, clonidine, and ketamine and 251 for piritramide). The administration of ketorolac was associated with a decrease in the administration of sufentanil (odds ratio [OR] = 0.30, 95% CI = 0.15 to 0.56, two-sided Fisher exact test $P < .001$)

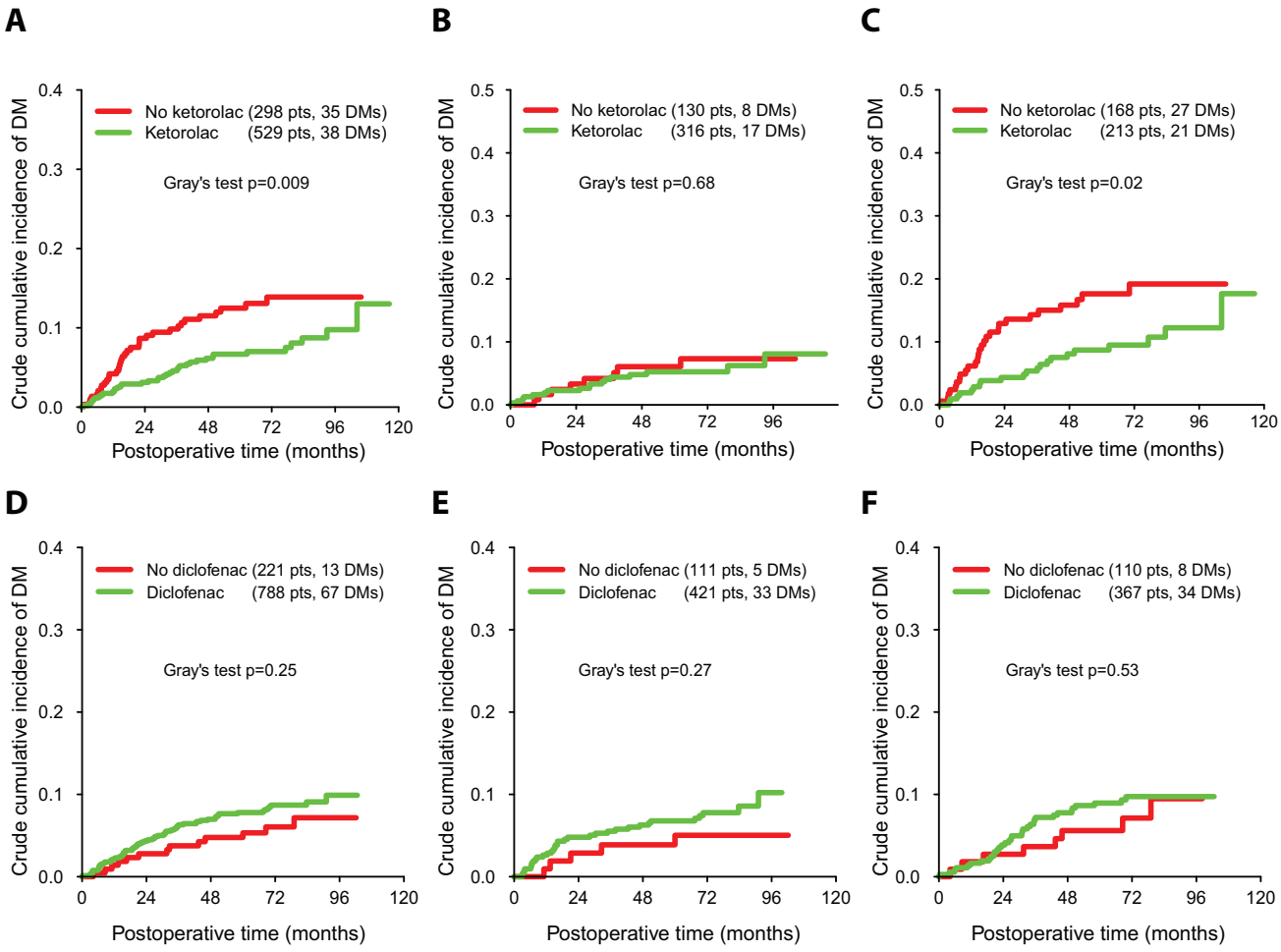

Figure 1. Crude cumulative incidence of distant metastases according treatment. Ketorolac **(A–C)** and diclofenac **(D–F)** administration in all patients **(A, D)**, in patients with BMI <25kg/m^2 **(B, E)** and BMI ≥25kg/m^2 **(C, F)**. Two-sided Gray's test *P* values are reported. BMI = body mass index; DM = distant metastasis.

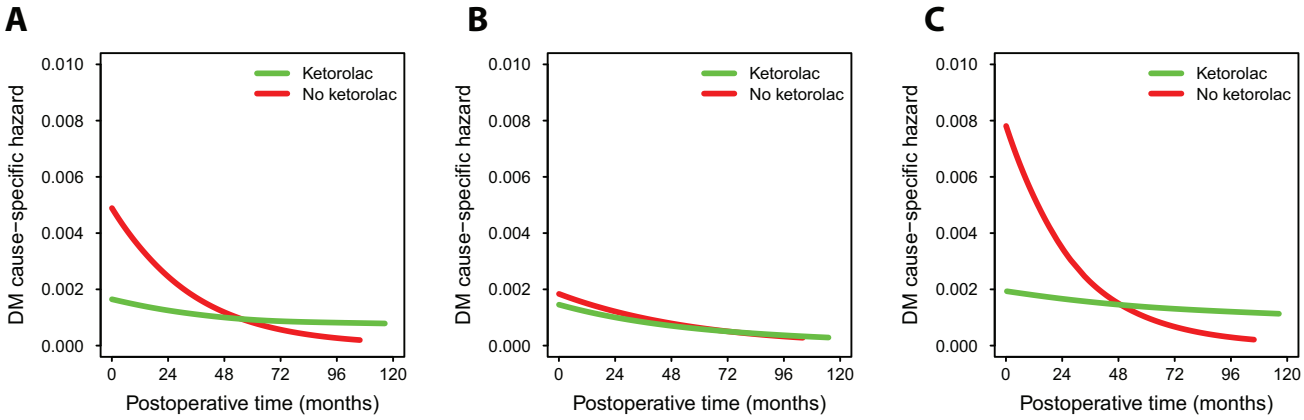

Figure 2. Cause-specific hazard estimates for distant metastases over time according to BMI in the ketorolac cohort. All patients **(A)**, BMI <25 kg/m^2 **(B)**, and BMI ≥25 kg/m^2 **(C)**. Estimates were obtained by the bshazard method. BMI = body mass index; DM = distant metastasis.

but not piritramide (OR = 0.75, 95% CI = 0.43 to 1.31, *P* = .30; data not shown). In all models, ketorolac remained statistically significantly associated with a reduction of distant disease recurrences, therefore, against a possible confounding effect of the other drugs (Supplementary Figure 3, available online).

We further evaluated the recurrence patterns over time for the two BMI subgroups. These analyses revealed that the administration of ketorolac was clearly associated with a reduction of the early metastases in all patients and in the high-BMI subgroup (Figure 2).

Table 3. Results from Fine and Gray regression model, with estimated distant metastasis hazard ratios for those receiving vs not receiving NSAIDs, in all patients and in the two BMI subgroups*

	All		BMI < 25		BMI ≥ 25	
NSAID	HR (95% CI)	P†	HR (95% CI)	P†	HR (95% CI)	P†
Ketorolac						
Unadjusted	0.55 (0.35 to 0.86)	.01	0.84 (0.37 to 1.94)	.68	0.51 (0.29 to 0.90)	.02
Adjusted	0.59 (0.37 to 0.96)	.03	0.78 (0.29 to 2.05)	.61	0.55 (0.31 to 0.96)	.04
Diclofenac						
Unadjusted	1.39 (0.77 to 2.51)	.28	1.66 (0.65 to 4.24)	.29	1.24 (0.58 to 2.69)	.58
Adjusted	1.04 (0.58 to 1.87)	.88	1.29 (0.53 to 3.12)	.57	0.89 (0.39 to 2.02)	.77

*Adjusted model includes age (<50 or ≥50 years), tumor size (<2 or ≥2 cm), nodal status (negative or positive), grade (1–2 or 3), estrogen receptor status (negative or positive), human epidermal growth factor receptor 2 status (negative or positive), adjuvant chemotherapy (no or yes), adjuvant endocrine therapy (no or yes) and BMI (<25 or ≥25 kg/m^2). BMI = body mass index; CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.
†Two-sided Wald test P values.

In the diclofenac cohort, 79 distant metastases occurred as the first event, of which 41 were in the high-BMI group. The administration of diclofenac was not associated with decreased incidence of distant recurrences in the global population, neither in the unadjusted or adjusted analyses ($HR_{unadjusted}$ = 1.39, 95% CI = 0.77 to 2.51, Fine and Gray regression two-sided Wald test $P = .28$; $HR_{adjusted}$ = 1.04, 95% CI = 0.58 to 1.87, $P = .88$) (Table 3). We also did not observe any association with distant events in the BMI subgroups (Table 3).

Discussion

So far, few treatment modalities focusing on the biological characteristics of breast cancer patients with increased BMI have been evaluated. In this study, we explored the impact of two different nonselective NSAIDs administered intra-operatively on disease recurrence after primary tumor surgery. Our results showed that ketorolac was mainly associated with a reduction in disease recurrence in the group of patients with increased BMI, but without excluding, so far, an effect also in normal BMI patients. The exploratory analyses that considered age and BMI as continuous variables suggested that this association could be more pronounced for overweight patients older than age 50 years.

As opposed to ketorolac, no association with disease recurrence was observed for diclofenac. Actually, this difference might be explained by an important additional pharmacological property recently uncovered for ketorolac. Indeed, besides the selective activity of the S-enantiomer against COX-1 and -2, which is the basis of the US Food and Drug Administration approval for pain management, an unexpected GTPase inhibitor activity against RAC1 and CDC42 has recently been attributed to the R-enantiomer (30–32). RAC1 and CDC42 are members of the Ras-homologous (Rho) family of small GTPases, involved in cell motility, adhesion, and invasion (33). Importantly, RAC1 and CDC42 have been shown to be upregulated by leptin, one of the two adipokines abnormally secreted in case of overweight and obesity, in colorectal and ovarian cancer (34,35). Specifically, the authors demonstrated that leptin was capable of inducing new focal adhesion complexes by activating the RhoA signaling pathway (35). Therefore, the fact that only ketorolac but not diclofenac was associated with a statistically significant reduction of distant recurrences in patients with elevated BMI could possibly be explained by the specific Rho GTPase inhibitory effect of the R-enantiomer of ketorolac, which is absent in diclofenac (Supplementary Figure 4, available online). Also of interest is the demonstration that the half-life of the R-enantiomer is twice that of the S-enantiomer of ketorolac, and it has consequently been shown that the R-enantiomer is enriched in serum (30,36). It is, however, unclear whether the anti-inflammatory pharmacological property of the S-enantiomer is still playing a role in preventing distant recurrences or whether the effect is fully played by the R-enantiomer. This should be explored using the enantiopure drugs. Of note, the only other NSAID for which the Rho GTPase inhibitory effect of the R-enantiomer has been demonstrated is naproxen (12). The effect seen with ketorolac could also potentially and partially be linked to the fact that the intra-operative administration of ketorolac is less immunosuppressive than the administration of other analgesics, as recently demonstrated by Bakr et al. (37).

While it might appear surprising that a single dose of ketorolac is associated with a reduction of distant disease recurrence, this is most probably due to the timing of the administration, the intra-operative setting at the initiation of surgery. Indeed, the surgical removal of the primary tumor has been shown to disturb the homeostasis of the disease at the systemic level and to possibly trigger the development of early recurrences (38,39). Indeed, the "primary metastases–host" combination should be viewed as a complex system, where the focalized action of primary tumor surgical removal is able to prompt a long-lasting effect on the course of the disease by disrupting the homeostatic stability (38,39). It is therefore reasonable that impinging on destabilizing processes right in this time may have definite consequences. Complex system dynamics are exquisitely sensitive on initial conditions, and, therefore, changes occurring in critical early times may be able to cause major changes in system evolution (40). In this context, it is worth reporting the old Scandinavian randomized clinical trial where one single course of peri-operative cyclophosphamide resulted in a statistically significant improvement in disease-free survival at 17.1 years of follow-up, while the same course given two to four weeks after mastectomy did not provide any benefit (41).

The time-dependent analyses revealed that ketorolac was specifically associated with a reduction of early recurrences, suggesting that it could exert an excellent distant control on the surgically induced awakening of already disseminated subclinical metastatic foci. These data therefore emphasize that anesthesia can have in addition to its expected immediate effects, also consequences on disease evolution. Consequently, this approach could be extremely appealing for parts of the globe where obesity has been strongly increasing during the last decade and where resources for cancer treatment are scarce. Of

interest, as previously reported for breast cancer (11,23), the intra-operative role of ketorolac had also been demonstrated in lung and ovarian cancer patients (42,43). Forget et al. reported an independent beneficial effect of NSAID administration (mainly ketorolac) at the beginning of surgery on distant disease–free survival in an institutional series of 255 lung cancer patients (42). Guo et al. further showed in their retrospective study, which included 123 ovarian cancer patients, that the peri-operative use of ketorolac was associated with a statistically significant reduction of ovarian cancer–specific mortality (43). We may therefore hypothesize that also in other cancer types ketorolac may play a role in reducing disease recurrence specifically in patients with increased adiposity.

To conclude, while this study is limited by its retrospective nature and many questions regarding the intra-operative use of ketorolac still need to be answered, such as the optimal timing, duration, dose, and combination with other analgesics, it suggests a potentially important repositioning of ketorolac in the intra-operative treatment of breast cancer patients with elevated BMI and points to the need for a prospective confirmatory randomized trial.

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