Review Article

The association between perioperative opioids and breast cancer recurrence: a narrative review of the literature

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Background and Objective: Opioid use disorder is an evolving crisis, and 17.2% of postsurgical patients continue to fill an opioid prescription one year after surgery. Preclinical studies suggest perioperative opioid use, defined here as opioids used in the setting of operative pain, may be linked to inferior oncologic outcomes. If this were true, opioid minimization strategies for surgical patients may reduce opioid-related deaths in more than one way. This review aims to describe the association between perioperative opioid use and breast cancer recurrence.

Methods: On November 1, 2021, we searched the Ovid and EMBASE databases for the terms "breast neoplasm", "opioid analgesics", "neoplasm recurrence", and "neoplasm metastasis". Of the 350 articles retrieved, 11 met our inclusion criteria. The review was undertaken using the enhancing transparency in reporting the synthesis of qualitative research (ENTREQ) checklist for quality.

Key Content and Findings: Clinical studies report no clear association between perioperative opioid use and local or distant breast cancer recurrence. Mixed results were found when assessing perioperative opioid use and overall survival. Multiple studies paradoxically found opioid use to be associated with lower recurrence rates, despite higher mortality rates. Most studies showed no difference in recurrence or survival in breast cancer surgery patients who did or did not receive opioid-containing analgesia, although most findings were limited by study design and low event rates in patients with breast cancer.

Conclusions: The lack of a clear connection between perioperative opioid use and breast cancer recurrence contradicts some preclinical data, which describes mechanisms through which opioids upregulate tumor proliferation which might worsen oncologic outcomes. Existing clinical literature is limited to mostly retrospective studies in patients with predominantly early-stage breast cancers, with low event rates. Given the worsening opioid epidemic and preclinical study findings, opioid minimization strategies should still be explored. Future work should be prospective and examine cancer recurrence in high-risk patients with more advanced tumor pathologies.

Keywords: Breast cancer recurrence; opioid use; opioid sparing pain management

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Introduction

Background

Opioids have been a cornerstone for perioperative and postoperative pain management in cancer patients for centuries. In the late 1990's, pharmaceutical industries developed extended-release opioids, marketed them as non-addictive, and a rise in opioid use disorder and associated deaths followed (1). The widespread opioid crisis has been an impetus for the development of multimodal analgesia protocols for perioperative pain management, and a culture shift towards more judicious opioid prescribing is underway. However, the coronavirus disease 2019 (COVID-19) pandemic brought obstacles to outpatient care, increasing isolation, and disrupting opioid use disorder treatment, which placed susceptible individuals at greater risk for overdose (2). Additionally, the decrease in non-emergent hospital visits caused a decline in pain management alternatives, pushing the vulnerable towards increased demand for prescription opioids.

Rationale and knowledge gap

According to the American Cancer Society, breast cancer is the most common cancer in women in the United States, accounting for about 30% of all new female cancers yearly (3). Breast cancer surgery, specifically, simple mastectomy with reconstruction, is among the highest-risk surgeries associated with chronic opioid use. Almost 20% of patients continue to fill opioid prescriptions 180 days after surgery and nearly 10% were still filing their prescriptions up to 1 year after surgery (4). The majority of postoperative opioids are prescribed by the operating surgeon or the perioperative care team (5,6). However, most prescribed opioids go unused, creating a reservoir of opioids available for diversion (7). Outside of the well-known untoward effects such as nausea, constipation, sedation, respiratory depression, and risk of dependence, preclinical studies have reported a link between opioids, cancer growth, and metastasis (8). Perioperative opioid minimization strategies can mitigate these risks.

Objective

Our objective is to investigate the association between perioperative and postoperative opioid use and oncologic outcomes. While similar reviews have been published, we aim to delve deeper by creating a distinction between local and distant recurrence, differentiating the timing of opioid and nonopioid analgesia, and the route of administration. With the increasing incidence of breast cancer, the high rate of opioid use disorder after breast cancer surgery, and the potentially tumorigenic effects of these opioids published in the referenced preclinical literature (9), the review will highlight the available evidence of the association between opioid minimization and potential for recurrence. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-6/rc).

Methods

A narrative review was conducted to identify clinical associations between perioperative opioid use and breast cancer recurrence or metastasis. Due to the broad scope of the clinical and translational components of the concept, a narrative review format was selected to explore the literature. The search strategy is summarized in *Table 1*. From November 1, 2021, to November 30, 2021, the Ovid and EMBASE databases were searched from inception to November 2021 using a combination of the terms: breast neoplasm, opioid analgesics, neoplasm recurrence, and neoplasm metastasis. The initial search resulted in 350 publications. A flowchart of the study selection is provided in *Figure 1*.

The 350 publications were screened by a single reviewer via title and abstract for relevance. Studies that were not clinical and did not address breast cancer, opioid use, and recurrence or metastasis were excluded, as were non-English reports and duplicate articles. Additional included works were identified by a manual search of the reference lists of the retrieved articles that met the inclusion criteria. A single author critically appraised the final 38 studies via a full-text analysis, and the relevance of each article was then discussed with a second reviewer to reach a consensus for inclusion. From this 38, articles were excluded due to duplication or lack of clinical evaluation of human breast cancer metastasis or recurrence with opioids. If no dual consensus was achieved, the article was excluded. A total of 11 clinical studies were included in the present review (*Table 2*).

Results

Clinical studies of opioids' impact on local recurrence demonstrate mixed results

Most of the referenced studies found no strong association

Table 1 The search strategy summary

Items	Specification
Date of search	March 31, 2021 to April 18, 2023
Databases and other sources searched	OVID database, EMBASE database
Search terms used	Breast neoplasm, opioid analgesics, neoplasm recurrence, neoplasm metastasis
Timeframe	2015–2023
Inclusion and exclusion criteria	Inclusion criteria included clinical papers that address breast neoplasm, opioids, and recurrence. Only English language publications were included
Selection process	Single reviewer selection based on title and abstract, followed by single reviewer full text analysis with consensus for inclusion by the author team

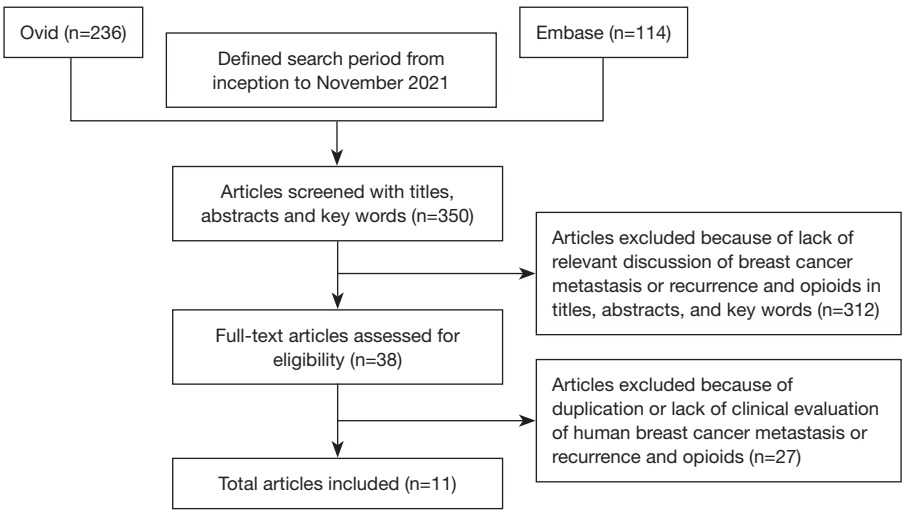

Figure 1 Flow chart of initial articles retrieved and inclusion process.

between opioids and breast cancer recurrence. Three studies paradoxically found lower recurrence in cohorts receiving more opioids. Lee *et al.* compared recurrence-free survival for modified radical mastectomy (MRM) patients between propofol-based total intravenous anesthesia (TIVA) or sevoflurane-based anesthesia. In this study, recurrence sites were bone, brain, lung, chest wall, or liver. TIVA patients had higher intraoperative and postoperative opioid use and lower recurrence risk [hazard ratio (HR) =0.55, 95% confidence interval (CI): 0.311–0.973; P=0.037] (10). A larger study of invasive breast cancer patients by Cronin-Fenton *et al.* analyzed opioid impact on recurrence, defined by the Danish Breast Cancer Cooperative Group (DBCG) as locoregional, distal, or contralateral disease. All opioids excluding tramadol, codeine, and dextropropoxyphene were associated with decreased recurrence (adjusted HR =0.75; 95% CI: 0.57–0.99) but a four-fold increase in all-cause mortality (11).

All retrospective studies used multivariate regression models to account for confounding variables. Among the retrospective studies, tramadol correlated with a 0.71-fold decreased recurrence risk, which was attributed to its action on 5-HT receptors and low affinity for mu opioid receptors. Postoperative recurrence was lower in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) with tramadol than NSAIDs alone. The investigators concluded tramadol as rescue analgesia may improve oncologic outcomes through proliferation inhibition and promotion of apoptosis (12).

In a retrospective analysis of 1,143 triple-negative breast cancer patients, intraoperative opioid use correlated with greater recurrence-free survival and tumor cell upregulation of tumor-suppressive opioid receptors. Variations in cancer

Table 2 Summary of included studies (10-20)

Author [year]	Study type	Comparison	No. of subjects	Years follow-up	Primary outcome	Results	Conclusion	Limitations
Lee *et al*. [2015] (10)	Retrospective cohort	Patients undergoing MRM received either: A. Propofol-based TIVA; B. SEVO	325	5	(I) RFS (II) OS	(I) TIVA group had significantly greater postoperative opioid use: (A) TIVA had lower rate of cancer recurrence (HR =0.55, 95% CI: 0.311–0.973, P=0.037); (B) no difference in OS	Propofol-based TIVA group associated with greater opioid use and reduced risk of recurrence	Retrospective study design
Cata *et al.* [2016] (14)	Retrospective cohort	Patients undergoing MRM received either: A. PVB; B. Opioid-based pain management	792	6	(I) RFS (II) OS	(I) RFS was 89.9% *vs.* 93.77% (II) OS was 93.43% *vs.* 94.95%	No statistically significant difference in RFS or OS between pain management strategies	Retrospective study design
Cronin-Fenton *et al.* [2016] (11)	Prospective cohort	Patients with breast cancer: A. No opioid use; B. Weak opioids; C. Strong opioids; D. Strong and weak opioids	34,188	10	(I) Recurrence	(I) Decreased rate of recurrence in C (II) No difference in rate of recurrence between A and B, or D	Strongly immunosuppressive opioids are associated with decreased recurrence but greater all-cause mortality	Does not include opioid use while still hospitalized
Karmakar *et al.* [2017] (15)	Randomized controlled trial	Patients undergoing MRM received GA with either: A. No PVB; B. Single PVB; C. Continuous PVB	180	5	(I) LRR (II) DRR (III) OS	(I) No difference in local recurrence among groups (II) No difference in distant recurrence among groups (III) No difference in OS among groups	No difference in recurrence or overall survival between groups	Potentially too underpowered to evaluate long-term cancer outcomes
Cho *et al.* [2017] (17)	Prospective randomized trial	Patients undergoing breast cancer surgery received either: A. Propofol-remifentanil anesthesia with PRK; B. SRF	50	2	(I) Natural killer cell cytotoxicity (II) 48 h pain scores and inflammatory responses measured by WBC, neutrophil, and lymphocyte counts (III) LRR (IV) DRR	(I) Natural killer cell cytotoxicity was significantly increased in the PRK group (P=0.048) and decreased in the SRF (P=0.032) (II) Pain scores were comparable in both groups (III) No patients had local recurrence (IV) No patients had distant recurrence One patient in the SRF group had new primary cancer in the contralateral breast	PRK group with postoperative NSAID instead of opioid produced less immunosuppression as measured by NK cell function	Insufficient local or distant recurrences
Yan *et al.* [2018] (18)	Randomized controlled trial	Breast cancer resection patients received either: A. SEVO or B. Propofol-remifentanil-based TIVA	80	2	(I) Change in serum VEGF-C (II) Change in TGF-β (III) RFS	(I) VEGF-C increased from 105 to 174 pg/mL in SEVO group (P=0.009), unchanged in TIVA (II) No significant changes in TGF-b (III) RFS was 78% (SEVO) and 95% (TIVA) (NS)	TIVA is associated with less derangements in VEGF-C and TGF-b. No difference in RFS between groups	Both groups received propofol and fentanyl for anesthesia induction
Yoo *et al.* [2019] (19)	Retrospective cohort	Breast cancer surgery patients received either: A. TIVA with intraoperative opioids; B. Inhalation anesthesia without intraoperative opioids	5,331	5	(I) RFS (II) OS	(I) RFS was 93.2% for A and 93.8% for B (NS) (II) OS was 94.2% for A and 94.5% for B (NS)	No difference in RFS or OS between arms	Retrospective study design
Kim *et al.* [2019] (12)	Retrospective cohort	Patients undergoing breast cancer surgery received either: A. Postoperative tramadol; B. NSAIDs alone	2,588	5.8	(I) RFS (II) OS	(I) Recurrence was 92.7% in A and 90.6% in B (HR =0.714; 95% CI: 0.512–0.995; P=0.046) (II) Overall survival was 95.3% in A and 91.9% in B (HR =0.565; 95% CI: 0.380–0.841; P=0.005) (III) Tramadol cohort had a 0.71-fold decreased risk of recurrence and a 0.56-fold decrease in mortality	Cohort that received tramadol had decreased rate of recurrence and breast cancer-specific mortality	Retrospective study design
Boudreau *et al.* [2019] (20)	Retrospective cohort	Women with early-stage breast cancer after surgical treatment: A. Non-chronic opioid users; B. Chronic opioid users	4,216	5	(I) SBCE, including ipsilateral recurrence and second primary breast cancer	(I) 9.7% of women were chronic opioid users. This group had more extensive surgery, comorbidities, and a higher SBCE rate (HR =1.20; 95% CI: 0.85–1.70) SBCE rate (per 1,000-person year)	Chronic opioid use associated with non-significant increased risk of SBCE, study was underpowered to detect difference in breast cancer events	Retrospective study design
Sessler *et al.* [2019] (16)	Randomized controlled trial	Patients undergoing surgery for breast cancer received either: A. PVB + propofol; B. GA (SEVO) and opioids	2132	3	(I) LRR (II) RFS	(I) LRR 10% (PVB) *vs.* 10% (GA) (adjusted HR =0.97, 95% CI: 0.74–1.28, P=0.84) (II) RFS 15 months in PVB (IQR, 7–26 months) *vs.* 17 months in GA (IQR, 7–24 months)	LRR and RFS similar in both PVB and GA cohorts	Majority early-stage and estrogen receptor-positive cancers with lower recurrence and metastasis risk
Montagna *et al.* [2020] (13)	Retrospective cohort	Patients with TNBC undergoing breast cancer surgery were analyzed with respect to quantity of perioperative opioids received	1143	3	(I) RFS (II) OS (III) Patterns of opioid receptor expression in tumor samples	(I) RFS was associated with greater RFS (HR =0.93, 95% CI: 0.88–0.99) per 10 OME (P=0.028) (II) OS was not associated with OMEs received (III) OGFR, OPRK1, and OPRD1, upregulated TLR4 was downregulated in the tumor tissue, compared to normal tissue from a separate cohort	Study found a protective effect of intraoperative opioids on TNBC recurrence	Retrospective study design

MRM, modified radical mastectomy; TIVA, total intravenous anesthesia; SEVO, sevoflurane-based anesthesia; RFS, recurrence free-survival; OS, overall survival; PVB, paravertebral block; LRR, local recurrence rate; DRR, distant recurrence rate; PRK, postoperative ketorolac; SRF, sevoflurane-remifentanil with postoperative fentanyl; NSAIDs, nonsteroidal anti-inflammatory drugs; VEGF-C, vascular endothelial growth factor C; NS, non-significant; GA, general anesthesia; PCA, patient-controlled analgesia; EA, epidural anesthesia; TNBC, triple negative breast cancer; RFS, recurrence-free survival; OME, oral morphine equivalent; SBCE, secondary breast cancer event.

cell genetic profiles are one proposed mechanism (13).

Most studies found no association between opioids and recurrence, although universally low breast cancer recurrence rates limited prospective studies. Three studies utilized paravertebral block (PVB) anesthetic strategies. Cata *et al.* retrospectively compared PVB versus opioid-based analgesia in non-metastatic mastectomy patients. In this study, recurrence was defined as breast cancer confirmed via biopsy in cases of local, regional, or distant metastasis. PVB reduced opioid use but did not change recurrence-free survival (14). Karmakar *et al.* randomized MRM patients to general anesthesia with morphine, one-shot PVB without morphine, or continuous PVB without morphine. Five-year local recurrence rates were similar amongst groups (15). Recurrence in this study was defined as local disease. Sessler *et al.*'s study randomized 2,132 women to either regional anesthesia with PVB and propofol or general anesthesia with sevoflurane and opioids. Local recurrence rates were similar between groups (adjusted HR =0.97, 95% CI: 0.74–1.28; P=0.84) (16).

Most studies compared recurrence between cohorts receiving varied general anesthesia strategies and opioids. Cho *et al.* measured recurrence by randomly assigning patients to receive propofol-remifentanil anesthesia with postoperative ketorolac (PRK) or sevoflurane-remifentanil with postoperative fentanyl (SRF). Recurrence in this study was diagnosed via breast and abdominal ultrasound. Insufficient local or distant recurrences limited the analysis (17). Yan *et al.*'s randomized study compared recurrence-free survival and perioperative opioid use in patients receiving propofol-remifentanil-based TIVA or sevoflurane-based anesthesia. Recurrence in this study was categorized as short-term return of disease. Serum vascular endothelial growth factor C (VEGF-C) and transforming growth factor beta (TGF-β) levels were compared, assessing tumor cell angiogenesis and metastatic potential. TIVA patients required more opioids but had lower postoperative VEGF-C concentrations. The recurrence risk was similar (18). A large retrospective study by Yoo *et al.* analyzed recurrence-free survival in patients receiving TIVA with propofol-remifentanil versus inhalational anesthesia without opioids and found no difference in recurrence, defined as locoregional or systemic disease confirmed by radiology or histology (19). Lastly, one study analyzed local recurrence with long-term oral opioid receipt. Boudreau *et al.* retrospectively studied second breast cancer events (SBCE) after curative-intent surgery and categorized patients as either non-chronic or chronic opioid users. They defined recurrence as ipsilateral invasive cancer. Chronic users had more extensive surgery and comorbidities. There was no significant difference in SBCE rates between groups (HR =1.20; 95% CI: 0.85–1.70) (20).

Clinical studies show no association between opioid receipt and distant recurrence

Prospective randomized studies reported neutral or negative associations between perioperative opioids and distant recurrence. Cho *et al.* found similar disease-free survival rates between patients receiving postoperative ketorolac versus fentanyl (17). Karmakar *et al.* found no significant difference in distant recurrence between those receiving general anesthesia with intraoperative morphine versus PVB without morphine (15). Cata *et al.*'s retrospective study of PVB versus opioid-based analgesia in MRM patients found no significant difference in distant recurrence rates (14). Three additional studies also yielded no difference (10,16,19). Conversely, Kim *et al.*'s work found lower recurrence in patients receiving tramadol versus NSAIDs (12). They defined recurrence as tumor in the ipsilateral breast, regional lymph nodes, and/or chest wall.

Clinical studies of opioids' impact on overall survival demonstrate mixed results

All studies reporting overall survival were retrospective. Both studies comparing general anesthesia strategies found similar survival rates (10,19). Similar survival outcomes were also reported when comparing PVB *vs.* opioid analgesia (12). Two studies utilizing oral opioids found contradictory differences in survival. Strongly immunosuppressive opioids correlated with higher all-cause mortality in one study (11). Another found tramadol correlated with a 0.56-fold decreased mortality, and tramadol with NSAIDs was associated with improved survival compared to NSAIDs alone (12). Lastly, varying intraoperative morphine doses did not affect overall survival in Montagna *et al.*'s retrospective study (HR =0.96 per 10 morphine milligram equivalents increase; 95% CI: 0.89–1.02; P=0.2) (13). Parameters for recurrence were not defined in this study.

Discussion

A review of preclinical works excluded from the present narrative review reveals potential mechanisms for opioids to worsen cancer outcomes. These include altered nitric oxide

synthesis, cyclooxygenase (COX)-2 activation, prostaglandin E2 production, signal transduction and activation of transcription 3 (STAT3), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAP-kinase) and Akt signaling pathways (21). Cross-activation of epidermal growth factor receptor and vascular endothelial growth factor receptor 2 (VEGFR2), substance P, and mast cell activation also increase tumor angiogenesis, progression, and distant metastasis (22-29). Farooqui *et al.* found mice with breast cancer tumors treated with morphine had worse survival compared to mice not treated with morphine but adding a COX-2 inhibitor attenuated this effect (28). Gupta *et al.* found that opioids stimulated VEGF receptors, nitric oxide and intracellular calcium expression, and vascular proliferation *in vitro* for human cells and *in vivo* for rat models. While the opioid receptor antagonist naloxone could not reverse these effects (25), other studies show naloxone alone is sufficient to inhibit morphine-induced tumor progression, suggesting an opioid receptor-mediated mechanism (24).

Studying the association between opioids and recurrence in higher-risk cancers could show a larger effect size. Most patients in Karmakar *et al.*'s randomized trial had early-stage and estrogen receptor-positive cancers, which have lower metastasis or recurrence risk than advanced-stage or triple-negative cancers (15). Opioid users in the Cronin-Fenton study had more early-stage disease and comorbidities than nonusers. This may have been attributed to lower recurrence but higher mortality. These opioid users also had greater concurrent NSAID use (11,30). A retrospective study found patients receiving intravenous ketorolac before incision had a lower recurrence risk (31). This benefit was greater in overweight patients, making it a promising adjunct for overweight patients meriting further research (32).

Different mechanisms across opioid classes may also contribute to mixed results. Tramadol stimulates serotonergic and noradrenergic nociceptors with opioid receptors, inhibiting proliferation and inducing apoptosis in human breast adenocarcinoma cells through 5-hydroxytryptamine (HT)2B receptors (21). This contextualizes the lower recurrence in the tramadol cohort in Kim *et al.*'s study. An animal-model immunoassay ascribed tramadol's immunostimulant properties to its serotonergic properties, not its mu receptor effects. The immune effects of tramadol, despite its classification among opioids, is a relevant subject for future research.

Strengths and limitations

The present review found contradictions in available clinical and preclinical study findings, consistent with that by Lucia *et al.* (14,33,34). Our review builds upon the previous literature by stratifying studies between local and distant recurrence. Mixed results in the rates of local recurrence suggest a need for a more in-depth review of patients with higher risk of recurrence. Study design and low recurrence in contemporary breast cancer populations limit the existing literature (35). Four studies found lower recurrence in cohorts receiving more opioids but were limited by bias inherent to retrospective study design (10-13). Comparison groups were often unequal in the retrospective studies. Variations in opioid dose, type, and other factors influencing cancer outcomes, including patient characteristics, cancer staging, and adjuvant therapy were difficult to assess.

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Since the inception of this review, several trials studying the effects of opioids on cancer recurrence are underway. While outside the scope of the present review, these studies analyze incorporate additional patient and tumor covariates that may influence the association between opioids and breast cancer recurrence and include mu-opioid receptor polymorphisms, other genetic biomarkers (36,37), immunological processes (38). and hormone receptor-specific responses to opioids (39).

Despite the mixed results in this review, limiting superfluous opioid prescribing can change the opioid epidemic surge seen during the COVID-19 pandemic (40). Surgeons prescribe approximately 70% of opioids in the US, and one in five mastectomy patients use opioids one year after surgery (5,41). Multimodal analgesia protocols, including local anesthetics, regional blocks, and NSAIDs, can effectively decrease perioperative pain and limit prescription

opioid diversion (42-47). Ongoing clinical trials in the US, Austria, China, Sweden, Canada, Spain, and South Korea are investigating the feasibility and sequelae of breast cancer surgery with minimal to no utilization of opioid anesthesia and analgesia (48).

Conclusions

Future work investigating the association between opioids and cancer outcomes should be prospective in nature with balanced comparison groups, limited to one non-immunosuppressive opioid type, with long-term follow-up. Focusing on high-risk patients with greater risk of recurrence, such as those with node-positive triple-negative breast cancer, could be considered. To our knowledge, this review is the first to summarize clinical studies examining the association between opioids and breast cancer outcomes stratified by local and distant recurrence. Despite the mixed results of the available clinical data, most of which is retrospective in nature, some preclinical works have described potential mechanisms for adverse oncologic outcomes with the receipt of opioids. These should provide further impetus to continue to investigate opioid-sparing pain management options for patients undergoing surgery for breast cancer.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-6/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health 2009;99:221-7.
2. Ghose R, Forati AM, Mantsch JR. Impact of the COVID-19 Pandemic on Opioid Overdose Deaths: a Spatiotemporal Analysis. J Urban Health 2022;99:316-27.
3. Breast cancer statistics | how common is breast cancer? Available online: https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html. Accessed Apr 18, 2023.
4. Shen C, Thornton JD, Gu D, et al. Prolonged Opioid Use After Surgery for Early-Stage Breast Cancer. Oncologist 2020;25:e1574-82.
5. Klueh MP, Hu HM, Howard RA, et al. Transitions of Care for Postoperative Opioid Prescribing in Previously Opioid-Naïve Patients in the USA: a Retrospective Review. J Gen Intern Med 2018;33:1685-91.
6. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ 2018;360:j5790.
7. Park KU, Kyrish K, Yi M, et al. Opioid Use after Breast-Conserving Surgery: Prospective Evaluation of Risk Factors for High Opioid Use. Ann Surg Oncol 2020;27:730-5.
8. Sethi V, Kurtom S, Ferrantella A, et al. Opioids modulate carcinogenesis via the gut microbiome: A potential role in cancer immunotherapy. J Am Coll Surg 2019;229:S270.
9. Kashyap D, Pal D, Sharma R, et al. Global Increase in

Breast Cancer Incidence: Risk Factors and Preventive Measures. Biomed Res Int 2022;2022:9605439.
10. Lee JH, Kang SH, Kim Y, et al. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: a retrospective study. Korean J Anesthesiol 2016;69:126-32.
11. Cronin-Fenton DP, Heide-Jørgensen U, Ahern TP, et al. Low-dose Aspirin, Nonsteroidal Anti-inflammatory Drugs, Selective COX-2 Inhibitors and Breast Cancer Recurrence. Epidemiology 2016;27:586-93.
12. Kim MH, Oh JE, Park S, et al. Tramadol use is associated with enhanced postoperative outcomes in breast cancer patients: a retrospective clinical study with in vitro confirmation. Br J Anaesth 2019;123:865-76.
13. Montagna G, Gupta HV, Hannum M, et al. Intraoperative opioids are associated with improved recurrence-free survival in triple-negative breast cancer. Br J Anaesth 2021;126:367-76.
14. Cata JP, Chavez-MacGregor M, Valero V, et al. The Impact of Paravertebral Block Analgesia on Breast Cancer Survival After Surgery. Reg Anesth Pain Med 2016;41:696-703.
15. Karmakar MK, Samy W, Lee A, et al. Survival analysis of patients with breast cancer undergoing a modified radical mastectomy with or without a thoracic paravertebral block: A 5-year follow-up of a randomized controlled trial. Anticancer Res 2017;37:5813-20.
16. Sessler DI, Pei L, Huang Y, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet 2019;394:1807-15.
17. Cho JS, Lee MH, Kim SI, et al. The Effects of Perioperative Anesthesia and Analgesia on Immune Function in Patients Undergoing Breast Cancer Resection: A Prospective Randomized Study. Int J Med Sci 2017;14:970-6.
18. Yan T, Zhang GH, Wang BN, et al. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: a prospective, randomized and controlled study. BMC Anesthesiol 2018;18:131.
19. Yoo S, Lee HB, Han W, et al. Total Intravenous Anesthesia versus Inhalation Anesthesia for Breast Cancer Surgery: A Retrospective Cohort Study. Anesthesiology 2019;130:31-40.
20. Boudreau DM, Chen L, Yu O, et al. Risk of second breast cancer events with chronic opioid use in breast cancer survivors. Pharmacoepidemiol Drug Saf 2019;28:740-53.
21. Novy DM, Nelson DV, Koyyalagunta D, et al. Pain, opioid therapy, and survival: a needed discussion. Pain 2020;161:496-501.
22. Sacerdote P, Bianchi M, Gaspani L, et al. Effects of tramadol and its enantiomers on Concanavalin-A induced-proliferation and NK activity of mouse splenocytes: involvement of serotonin. Int J Immunopharmacol 1999;21:727-34.
23. Nguyen J, Luk K, Vang D, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer. Br J Anaesth 2014;113 Suppl 1:i4-13.
24. Lam CF, Liu YC, Tseng FL, et al. High-dose morphine impairs vascular endothelial function by increased production of superoxide anions. Anesthesiology 2007;106:532-7.
25. Gupta K, Kshirsagar S, Chang L, et al. Morphine stimulates angiogenesis by activating proangiogenic and survival-promoting signaling and promotes breast tumor growth. Cancer Res 2002;62:4491-8.
26. Gong L, Qin Q, Zhou L, et al. Effects of fentanyl anesthesia and sufentanil anesthesia on regulatory T cells frequencies. Int J Clin Exp Pathol 2014;7:7708-16.
27. Ecimovic P, Murray D, Doran P, et al. Direct effect of morphine on breast cancer cell function in vitro: role of the NET1 gene. Br J Anaesth 2011;107:916-23.
28. Farooqui M, Li Y, Rogers T, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer 2007;97:1523-31.
29. Afsharimani B, Cabot P, Parat MO. Morphine and tumor growth and metastasis. Cancer Metastasis Rev 2011;30:225-38.
30. Cronin-Fenton D, Lash TL, Ahern TP, et al. Concurrent new drug prescriptions and prognosis of early breast cancer: studies using the Danish Breast Cancer Group clinical database. Acta Oncol 2018;57:120-8.
31. Forget P, Vandenhende J, Berliere M, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. Anesth Analg 2010;110:1630-5.
32. Desmedt C, Demicheli R, Fornili M, et al. Potential Benefit of Intra-operative Administration of Ketorolac on Breast Cancer Recurrence According to the Patient's Body Mass Index. J Natl Cancer Inst 2018;110:1115-22.
33. Lucia M, Luca T, Federica DP, et al. Opioids and Breast Cancer Recurrence: A Systematic Review. Cancers (Basel)

2021;13:5499.
34. Looney M, Doran P, Buggy DJ. Effect of anesthetic technique on serum vascular endothelial growth factor C and transforming growth factor β in women undergoing anesthesia and surgery for breast cancer. Anesthesiology 2010;113:1118-25.
35. Enlund M, Berglund A, Ahlstrand R, et al. Survival after primary breast cancer surgery following propofol or sevoflurane general anesthesia-A retrospective, multicenter, database analysis of 6305 Swedish patients. Acta Anaesthesiol Scand 2020;64:1048-54.
36. Lee YJ, Oh CS, Choi JM, et al. mu-Opioid Receptor Polymorphisms and Breast Cancer Recurrence in Adult Korean Women Undergoing Breast Cancer Surgery: A Retrospective Study. Int J Med Sci 2020;17:2941-6.
37. Raigon Ponferrada A, Guerrero Orriach JL, Molina Ruiz JC, et al. Breast Cancer and Anaesthesia: Genetic Influence. Int J Mol Sci 2021;22:7653.
38. Aghamelu O, Buggy P, Smith G, et al. Serum NETosis expression and recurrence risk after regional or volatile anaesthesia during breast cancer surgery: A pilot, prospective, randomised single-blind clinical trial. Acta Anaesthesiol Scand 2021;65:313-9.
39. Li M, Zhang Y, Pei L, et al. Potential Influence of Anesthetic Interventions on Breast Cancer Early Recurrence According to Estrogen Receptor Expression: A Sub-Study of a Randomized Trial. Front Oncol 2022;12:837959.
40. Huynh V, Rojas K, Ahrendt G, et al. Reassessing Opioid Use in Breast Surgery. J Surg Res 2020;254:232-41.
41. Cogan JC, Raghunathan RR, Beauchemin MP, et al. New and persistent controlled substance use among patients undergoing mastectomy and reconstructive surgery. Breast Cancer Res Treat 2021;189:445-54.
42. Deegan CA, Murray D, Doran P, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. Reg Anesth Pain Med 2010;35:490-5.
43. Zhang J, Chang CL, Lu CY, et al. Paravertebral block in regional anesthesia with propofol sedation reduces locoregional recurrence in patients with breast cancer receiving breast conservative surgery compared with volatile inhalational without propofol in general anesthesia. Biomed Pharmacother 2021;142:111991.
44. Patel AR, Vuong B, Kuehner GE, et al. Adoption of Opioid-Sparing and Non-Opioid Regimens After Breast Surgery in a Large, Integrated Health Care Delivery System. Ann Surg Oncol 2020;27:4835-43.
45. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg 2012;114:424-33.
46. Gayraud G, Le Graverend S, Beguinot M, et al. Analgesic and opioid-sparing effects of single-shot preoperative paravertebral block for radical mastectomy with immediate reconstruction: A retrospective study with propensity-adjusted analysis. Surg Oncol 2020;34:103-8.
47. Rojas KE, Manasseh DM, Flom PL, et al. A pilot study of a breast surgery Enhanced Recovery After Surgery (ERAS) protocol to eliminate narcotic prescription at discharge. Breast Cancer Res Treat 2018;171:621-6.
48. Opioids+recurrence: Breast+cancer - list results. Home - ClinicalTrials.gov. (n.d.). Retrieved April 18, 2023, Available online: https://clinicaltrials.gov/ct2/results?cond=breast%2Bcancer&term=opioids%2C%2Brecurrence&cntry=&state=&city=&dist=

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