

## Peer Review File

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### Reviewer Comments

**Comment 1:** Line 24 “Opioid use disorder is an evolving crisis, and 20% of patients undergoing mastectomy continue to fill an opioid prescription one year after surgery”. I could not find a reference to this statement.

**Reply 1:** Thank you for your suggestion. This sentence and the reference have been amended for clarity.

**Comment 2:** Line 27 “by surgeons”. Patients postoperative care and opioid prescription is usually managed, at least in our European experience, by a multidisciplinary medical team including surgeons, anesthesiologists and general practitioners. May I suggest to reformulate the sentence including all of the components aforementioned.

**Reply 2:** Thank you for this comment. This sentence has been amended as suggested for inclusivity and clarity.

**Comment 3:** Line 83 “Simple mastectomy is among the highest-risk surgeries associated with chronic opioid use, and 70% of prescribed opioids come from a surgeon”. The sentence refers to the article published by Klueh et al.; in this article the surgeons actually account for 70% of the prescribed opioids, but only in the first three months of postoperative care. Please specify.

**Reply 3:** Thank you for this suggestion. The time frame of surgeon prescription of opioids has been amended to be more specific.

**Comment 4:** Line 85 “Outside of the known untoward effects of opioids such as nausea, constipation, sedation, and risk of dependence, preclinical studies have reported a link between opioids, cancer growth, and metastasis.” Please consider to include rare but fearsome side effects such as respiratory depression due to the opioid-related deaths. I suggest to mitigate the statement regarding the correlation between opioids, cancer growth and metastasis as many preclinical studies have shown no correlation.

**Reply 4:** Thank you for this suggestion. This sentence has been amended to include respiratory depression as a side effect. Additionally, the statement about correlations between opioids, cancer growth, and metastasis has been mitigated for accuracy.

**Comment 5:** Line 124 “A larger study of invasive breast cancer patients 124 analyzed opioid impact on recurrence. All opioids excluding tramadol, codeine, and 125 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.” The sentence refers to the article published by Cronin-Fenton et al which doesn’t take into account opioid drugs.

**Reply 5:** Thank you for the correction. Reference #7 has been updated to reflect the appropriate article by Cronin-Fenton.

**Comment 6:** Line 223 “This may have attributed to lower recurrence but higher mortality. These opioid users also had greater concurrent NSAID use”. The statement cites reference #7, which doesn’t take into account opioid drugs, and reference #29, which states that opioids do not appear to modify cancer recurrence and that “an observed decreased recurrence, but increased mortality, likely attributable to channeling bias, is observed among patients who used strongly immunosuppressive drugs”. Please reformulate the sentence.

**Reply 6:** Thank you for the correction. Reference #7 has been updated to reflect the appropriate article by Cronin-Fenton.

**Comment 7:** Line 251 “Despite the mixed results of the available clinical data, most of which is retrospective in nature, preclinical works suggest potential mechanisms for adverse oncologic outcomes with the receipt of opioids, which should provide further impetus to continue to investigate opioid-sparing pain management options for patients undergoing surgery for breast cancer.” Both preclinical and clinical studies have shown mixed results regarding the association of opioid use and cancer progression/recurrence. I suggest to highlight the importance of reducing opioid prescriptions to prevent adverse effects as previously mentioned.

**Reply 7:** Thank you for this suggestion. We changed the language to describe potential preclinical mechanisms being described and modified the language to include adverse effects as another reason to reduce opioid use.