Author's response to reviews

Title: Association Between Frequent Use of Nonsteroidal Anti-Inflammatory Drugs and Breast Cancer

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Author’s response to reviews: see over
Reviewer: Randall E Harris

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Cases with a prior history of breast cancer (or cancers other than basal cell skin cancer) should be excluded from the analysis in this nested case control study.

We have excluded patients with any type of cancer from the current analyses.

2. The reference group used in the analysis should be clarified. Was one reference group used for all comparisons or did the investigators use different reference groups in estimating Odds Ratios for different compounds?

The reference group consists of patients who were not exposed to any of the study drugs during the year prior to the index date. It is the same in all comparisons. We have added this in a footnote of the tables. For technical purposes, to complete the exposure categories, we have created a category that we called other exposure and entered in the model. We are not showing the result of this group because it is a mixed bag of people and is not of interest to the study. However we have added an explanation in the footnote of Table 3.

3. Mean levels of exposure among only cases and controls are not helpful. Table 2 could be omitted without compromising the report.

We have replaced this table by one showing the numbers and percent of patients in each of the exposure groups of interest.

4. The numbers of exposed cases and controls should be presented for each level of exposure as well as the reference category (Tables 3 & 4).

This is now presented in Table 2.

5. Complete data on coxibs, aspirin, other NSAIDs, and acetaminophen should be included in Table 3 (numbers of cases and controls should be given for each strata).

This is now presented in Table 2.

6. Separate data on NSAIDs, Coxibs, and the combined data should be included in Table 4 with the numbers of cases and controls for each strata.

Table 4 has been deleted from the current analysis. The current analysis showed similar but significant results in all categories as shown in Table 4 of the previous version. Therefore, the interpretation of the results would change. Saying that the results did not depend on duration would be misleading because we don’t know how many of those who used 1-30 days of NSAIDs in the preceding year used them in the past and how frequently they used them. The study assumes that those who used NSAIDs frequently >90 days during the preceding year were likely to have used them in the past but does not make any assumption regarding those who used them for less than 90 days did not use them frequently in the past. We thought that this analysis would be misleading and
would not add anything to the study. Therefore, we did not include it in the resubmitted version.

7. The data on aspirin should be divided on regular aspirin (325 mg or more) versus low dose aspirin (100 mg or less) for analysis of effects.

We have divided the data on aspirin as indicated.

Minor Essential Revisions

1. The relative frequencies of exposure to the target compounds should be included in Table 1.

These data are included in Table 2.
Reviewer: Patricia Moorman

Major Compulsory Revisions

Methods, page 5 and 6:
1. The rationale for limiting the study to women who had undergone screening mammography is never clearly explained. Generally, studies of NSAIDs and breast cancer have not been limited to screened women and it is unclear why it would be advantageous to exclude unscreened women.

We repeated the study including women who did not have a mammography in the years 2-3 prior to the index date. We had excluded these women from the previous analysis to limit the possibility of surveillance bias. We have conducted a subgroup analysis in the currently resubmitted study among women who have undergone a mammography 2-3 prior to the index date but the main analysis concerns all women who met the other eligibility criteria.

2. It is also unclear why all women undergoing diagnostic procedures such as fine needle aspirates, core biopsies, etc. in the year prior to the index date were excluded. Some women undergoing these procedures are not found to have cancer, therefore women who were not found to have cancer when undergoing these procedures should not have been excluded.

We agree with the reviewer and have deleted this requirement from the eligibility criteria.

3. Page 7: It is not clear why the investigators only considered use of NSAIDs in the year prior to diagnosis. It appears that information from earlier years probably was available and would have allowed a better categorization of frequent versus intermittent users. In addition, use in the year prior to diagnosis is often considered weaker exposure data in that women may have been more likely to have used analgesics in that time period if they were not feeling well in the time before the cancer was diagnosed.

We have added an explanation to the discussion it reads
‘Pharmaceutical data of the study patients were available since 1998. We have used only one year of these data to assess frequent use of the study drugs for the following reason. In Quebec, patients are covered by the provincial drug plan starting at their 65th birthday. Therefore, women had to be 66 years of age or older at the index date to have one full year of pharmaceutical data available prior to that date. Women would have had to be older at the index date if we had chosen to use more years of data for the assessment of frequent use.’

4. Some information should be provided about the number of days supply of the medication that is allowed with each prescription, to give a better indication if obtaining a 90-day supply is truly indicative of frequent use. If an individual is allowed to get a 90 or 100 day supply of medication with an NSAID prescription and only filled one prescription for the drug, it is not clear that woman is a
frequent user (i.e., she could have had the prescription filled but not have taken it for more than a few days because of side effects). On the other hand, if prescriptions are typically for a 30-day supply, an individual who has filled 3 or more prescriptions to reach a 90-day supply would be more credibly be characterized as a “frequent user”.

We have calculated the mean number of prescriptions in each exposure category and have included the one for our main exposure NSAIDs/coxibs which was 8 ± 4 and the median was 7 prescriptions. The mean number of prescriptions for aspirin and acetaminophen among frequent users were a little higher (9 and 10 respectively). We have included this information in the reviewed manuscript in the section ‘Exposure to the drugs of interest’

Statistical Analysis, Page 8:

5. The authors describe doing a secondary analysis in which individuals with a history of cancer in the three years prior to diagnosis were excluded. It is standard practice in etiologic studies of cancer to include only incident cases of cancer (not recurrences), therefore the primary analysis should have excluded those with a past history of cancer.

We have excluded patients with prior cancer from the reviewed study.

Results,

Page 10:
6. The language used in the paragraph describing patient characteristics associated with breast cancer is not appropriate for a case-control study. For example, it is more correct to state, breast cancer cases were more likely than controls to have uses estrogen therapy in the year prior to the index date, rather than saying patients who used estrogen therapy did not have more breast cancer (which is language more consistent with a prospective cohort study).

We have modified the text according to comment.

Minor Essential Revisions
Introduction:
1. Page 4, 1st paragraph, 2nd sentence: “older women” needs to be defined to support the cited

Older women was replaced by women 50 years of age or older.

2. Page 4, 1st paragraph, 4th sentence: “Non-selective” needs to be defined as related to NSAIDs.

We have used nsNSAIDs to refer to nonselective NSAIDs
3. Page 5, 1st full sentence: A reference should be cited for the “alternative treatment option” of intermittent NSAID use. This reviewer has never heard of this treatment option being used or recommended.

We have deleted this sentence.

4. Page 5, 2nd paragraph: Although this statement indicates that the study will evaluate regular or intermittent use of NSAIDs, the type of data used in the study really cannot address this type of use. It would be better to phrase it in terms of the data used for analyses, i.e., whether frequent use in the past year was more common among breast cancer cases than controls.

We have modified the text according to comment.


We have now included a more comprehensive literature review and have added these references.

6. Page 12, 2nd paragraph: It would be useful to know if dose and quantity of aspirin was available in the database allowing the investigators to distinguish between use that was likely for cardioprotection versus use for pain and inflammation.

We have included a description of aspirin use and looked at aspirin at doses ≤100 mg/day and aspirin at doses >100 mg day separately.

7. Page 13: The paragraph on HRT is tangential to the primary focus of this paper and could be eliminated.

We have deleted this paragraph from the discussion.

8. Table 1: The percentages of patients exposed to NSAIDs, aspirin and acetaminophen should be included in the tables, not just the numbers.

These percentages are now included in Table 2.

9. Table 2: It should be indicated if the days of use is calculated among users only.
This Table was deleted as per Reviewer 1 suggestion.

10. Table 3: The title of the table does not accurately reflect the content of the table, i.e., odds ratios are presented for risk factors other than analgesics.

We have modified the title of Table 3.

Discretionary Revisions (which the author can choose to ignore)
1. Page 4, 2nd paragraph, 3rd sentence: Use of the word “trimester” is awkward when it's not used in the context of either pregnancy or school terms.

We have deleted trimester from the sentence