Author's response to reviews

Title: Adherence to hormone therapy among women with breast cancer

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Version: 5 Date: 14 April 2014

Author's response to reviews: see over
Reviewer Arier Lee

Major Compulsory Revisions:

1. Table 1, 2 and 3 looked into the distribution of each individual variable compared between adherent and non-adherent patients using Chi square test. A significant p-value from a Chi square test tells us the distribution of the variable tested is not the same between the adherent and non-adherent patients. That p-value does not test to see which is the significantly different group, and certainly does not test if the two means are significantly different. For example, p.7 'The group of adherent women was slightly older than the group of non-adherent women, with mean ages of 58.0 and 56.0 years, respectively (p <0.0001)'. It is misleading to associate the two means with the Chi-square test p-value. Chi-square test doesn't tell us which category has lower or higher likelihood of adherence. It is especially difficult to conclude from Chi-square test the least or highest likelihood group when the 'no information' group was also included. This appears in the interpretation of all Table 1, 2 and 3 results.

The chi-square test was not used to compare the means. To test the means it was employed the t-student, (Gosset, 1906) as indicated in the Method section. In order to clarify to the reader, we indicated in the text that the p-value refers to t-studen: “The group of adherent women was slightly older than the group of non-adherent women, with mean ages of 58.0 and 56.0 years, respectively (student’s t-test, p <0.0001)”.

2. Page 8 '...logistic regression model that identified the independent effects of the explanatory variables...'. It looks like table 4 displays result from a multiple logistic regression model. If this is the case, it should be labeled clearly. Also the explanatory variables from a multiple logistic regression model are not 'independent effects'. The explanatory variables are analysed and adjusted for all other explanatory variables presented in the model.

We modified the text: “Table 4 shows the multiple logistic regression model that identified the effects of the explanatory variables for adherence to hormone therapy.”
We also modified the title of the table: “Table 4 – Multiple logistic regression model for adherence to hormone treatment (N=5,861).”

3. The display of Table 4 and also the interpretation of Table 4 result on page 8 requires revision. Confidence interval of odds ratio should be presented together with OR in the text.

The confidence intervals were included.

It is not clear what were used as reference level for all of the explanatory variables. OR is a type of comparison, although stated in the text regarding the direction of effect, without knowing what reference levels were used it is confusing. It is especially confusing because Table 1,2 and 3 all included 'no information category'. It is not clear if data with 'No information' were still included or excluded from logistic regression analysis displayed in Table 4. It is difficult to see which rows in Table 4 are for the same variable. For example, are 'Completed 2nd grade' and 'Higher education' two categories of a three-categories Education variable? If so, what is the reference level for this 'Education variable'? It is not directly comparable to Table 1 'Education' variable, where there are 4 categories including a 'No information' category. What is 'Alcohol consumption' variable? Is this a continuous variable representing the amount of alcohol consumption? Or a categorical variable indicating 'Consumed any alcohol' as opposed to 'No alcohol consumption'? If so, is 'No alcohol consumption' the reference level? What about the 'No information' category in Table 1? DATS (tests) is another problematic variable. In Table 3 there were 4 categories, if taking out the reference level, there should still be 3 categories in Table 4. I wonder if Table 4 is an analysis with complete cases only. If so, does that mean the 'No information' were excluded from the logistic regression in Table 4? But for variable such as DATS, if none means no tests were done, it may not mean the same as 'No information'.

The references for all categorical variables were included in Table 4.

Yes, observations with missing data were included in the logistic regression.
Minor Essential revisions:

1. On page 5 it was stated that 'If the initial hormone treatment date was # 3 months earlier than the date of diagnosis, the diagnosis and the initiation of hormone treatment were assumed to coincide (i.e., the difference was equal to 0)'. It is not clear that how the dates were corrected. Was the initial hormone Rx date updated to the date of diagnosis or the date of diagnosis updated to the initial hormone Rx date?

   *The date of treatment beginning was considered as the diagnosis date.*

2. The adherence was defined as 'the number of doses dispensed in relation to the dispensing period'. What about the doses dispensed but not consumed by the patients? If MPR accounts for only the doses dispensed by not adjusted for doses dispensed but not consumed by the patients, there could be an overestimate of adherence rate.

   *We agree that we do not know whether the pills were consumed. That's why MPR is a proxy, as indicated in the Discussion.*

   *In the case of the reviewer is referring to the number of pills received in the last dispensing date considered, it is noteworthy that the last quantity dispensed enters in the numerator and in the denominator, avoiding super-estimation.*

3. In 'Results' section. means are often represented with ± a number. It is not clear what the number is. Is it standard deviation? For example, on page 7 '...with a mean age of 57.5 (±13.6) years...' What does the number 13.6 represent?

   *We explicitly wrote SD in the new version.*
This study aimed to identify the factors associated with adherence to hormone therapy for breast cancer. This aim was reached to some extent but further modification is recommended before publication. The flaws mentioned in the first review have been clarified but not completely solved. The non-expert reader could benefit from some more clarification of the definitions used and the limitation that probably many non-adherent patients were lost is still not adequately discussed. A general comment is that retrospective studies of this type can only reveal associations and coincidences. They are able to create and not to prove hypothesis. The authors therefore should be more careful in interpreting their data – examples are provided in the specific comments. Altogether this is an interesting and important study, the limitations are yet not clear enough discussed and explained.

Specific comments:

“The last included dispensing date was 10/29/2010”
Yes.

“The study inclusion criteria for women with breast cancer tumors who were enrolled between 2002 and 2008”
Yes.

How was the overlap dealt with – last observation carried forward?

*For all women the follow-up is, in the maximum, five years. As it is said the Methods “We considered the recommendation of a daily hormone therapy (HT) pill for five years.” This means that some women had their adherence evaluated in a period lower that five years, but always greater than a period with two dispensations (60 days or 120 days or 180 days, depending on a monthly, bimonthly or quarterly dispensation. In the Discussion this limitation is described as follows: “Only women who received drugs at least twice were included in the study, once the MPR formula requires two dispensing*
dates. This procedure could have contributed to over or underestimations of the adherence rates, since who received the medication only one time could have been adherent or not to treatment in another place.”

Cut at the last dispensing date for all patients?

No, the cut on the last dispensing date was for women with less than five years in the cohort.

The problem of the used definition is still that a lot of information is lost (even if many well accepted publications did use this “official way” of measuring, I do believe it is rather not the optimal way to define a non-adherence population to investigate the given questions)

Less than 0.002 of women were excluded for having less than two dispensations. This does not represent a quantity able to change results.

“For patients with multiple recorded tumors, we used the more complete observation, the observation with the highest stage if the diagnosis dates were the same or the earliest observation if the diagnosis dates were different. “ This leads to inclusion of patients that received more than one antihormonal treatment? Did this sub-group do better than the others?

The explanation refers to the procedure used in the data editing of the RHC dataset for women with more than one register (or one tumour), and was oriented by the data related to the tumours, in order to obtain the most complete, linked to the dataset of hormone treatment dispensations.

“Due to the applied criteria, only women that received drugs at least twice were included in the study. This procedure could have contributed to underestimations in the adherence rates. “Overestimations! This excludes probably many non-adherent patients!
Again: Why excluding those not returning for second dispensing? – if they can be
followed they would provide important information on non-adherence.

The paragraph was modified: “Only women who received drugs at least twice were
included in the study, once the MPR formula requires two dispensing dates. This
procedure could have contributed to over or underestimations of the adherence rates,
since who received the medication only one time could have been adherent or not to
treatment in another place.”

“Thus, it is reasonable to believe that the included participants did not differ greatly
from the general population. “To better clarify generalizability comparison to general
population based on baseline and demographics could be discussed

We excluded the sentence “Thus, it is reasonable to believe that the included
participants did not differ greatly from the general population.” Although it is likely
and reasonable that the statement is true based on other studied conducted in Rio de
Janeiro state, we did not make a comparison with the general population in this study.

“It is believed that the observed lower adherence rate among young patients in the
present study is related to the adverse effects of hormone therapy on the women's
sexuality, which include fertility issues and menopausal symptoms [13]. Moreover, the
association between greater compliance and having a partner, which was also found in
other studies [22, 26], might be linked to receiving support. This result is consistent
with the idea that social support is highly predictive of adherence [1]. “This is not based
on the data provided and should be marked as “speculated”

Thank you, we changed the paragraph to: “It can be speculated that the observed lower
adherence rate among younger patients is related to the adverse effects of hormone
therapy on the women's sexuality, which include fertility issues and menopausal
symptoms [13].”
“The importance of investments in early diagnosis is also supported by the present study; it not only has a direct effect on patient survival [4,8] but also an indirect effect by facilitating treatment compliance.”

This sounds plausible but is also speculative as no causality is proven by the study, there might be numerous underlying bias that could be discussed here.

We changed the paragraph to: “The lower adherence rates among women with a non-curável stage at diagnosis emphasize the importance of investments in early diagnosis since it has a direct effect on patient survival [4,8] and also an indirect effect by facilitating treatment compliance.”

“The current study also revealed that patient monitoring by mastologists and oncologists had a positive effect on hormone therapy adherence [19]”

This is the same problem: there is an association of mastologist and adherence – this says that patients that do see their mastologist are adherent – not necessarily that seeing the mastologist is helpful to improve adherence – it is a coincidence and not necessarily a causality

It’s not a causality but is an association indicated by the parameter of regression model. We changed the paragraph to: “The current study also revealed that patient monitoring by mastologists and oncologists had a positive association effect on hormone therapy adherence [19].”

“However, a more intensive use of health care resources such as chemotherapy, tests and hospitalizations appeared to associate with lower adherence; this result was not directly observed in other studies but may be indirectly related to the association between lower adherence and comorbidities [15,20] because lower adherence occurs when patients are more severely ill.” And again, there might a number of explanations why severity of disease or progression might lead to non-adherence or non-persistence – e.g. doctor stops medication due to progression.

We changed the paragraph to: “However, a more intensive use of health care resources such as chemotherapy, tests and hospitalizations appeared to associate with lower
adherence; this result was not directly observed in other studies but may be indirectly related to the association between lower adherence and comorbidities, observed in other studies [15,20].”

The authors should consider to avoid the words “effect” and rather use ”association” and other more hypothetic terms.

We tried to relativize some statements and to qualify the effect as association effect.