Author’s response to reviews

Title: Weight change during chemotherapy is a poor prognostic in non metastatic breast cancer

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Version: 2 Date: 5 June 2010

Author’s response to reviews: see over
Dear Sir,

Please find enclosed a revised manuscript MS 9851151553337963 entitled: “Weight change during chemotherapy is a poor prognostic in nonmetastatic stage breast cancer”, that would like to submit for publication in BMC Cancer.

The manuscript is a resubmission following extensive revisions. Corrections have been performed according to the reviewer recommendations. The new version is including the changes made in response to each point raised by the reviewers.

We believe that this manuscript will be of interest to your readership.

The person responsible for editorial correspondence is: Emilie THIVAT

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We thank you very much for considering this manuscript and remain,

Yours sincerely.

Emilie THIVAT.

Clermont-Ferrand, le 04 June 2010
Please read carefully the reviewers comments in particular it seems to be mandatory to:

i) improve the coherence of data presentation (it remains unclear how the authors could consider T4 tumour as early breast cancer)

« early breast cancer » has been changed by « nonmetastatic breast cancer » or « early stage breast cancer and locally advanced breast cancer »

ii) moreover contradictory data have been provided on the percentage of patients receiving anthracycline based chemotherapy);

Chemotherapy treatment «anthracycline based chemotherapy » has been replaced by « mainly treated by anthracycline based chemotherapy » or « mostly treated by anthracycline based chemotherapy »

iii) revise statistical analysis (consider to include more covariates in multivariate analysis)

In multivariate analysis, we included 3 others covariates : initial BMI, menopausal status and treatment by hormonotherapy.

iv) provide much more appropriate definitions of weight change and BMI thresholds is required.

Definitions of weight change and BMI thresholds have been completed in the method section. Concerning Weight change, a number of studies suggest that a 5% change in body weight is clinically meaningful and relative weight variation is a better measure in that it considers the potential confounding by initial body weight. is a better measure [Saquib, 2007].

v) Finally, it seems mandatory to clearly declare in the manuscript the major limitations of the study.

A paragraph presenting the major limitations of this study has been added before the conclusion.

In addition to the concerns of the reviewers and Associate Editor, please also ensure that you document ethical approval in the Methods section of your manuscript. Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental
research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate. 

*The study was approved by ethical committee of Clinical Investigation Centers of Rhone-Alpes-Auvergne inter-region (N°IRB 5044).*
Reviewer's report

Title: Weight change during chemotherapy is a poor prognostic in early stage breast cancer

Version: 1 Date: 15 February 2010
Reviewer: Rebecca Cleveland

Reviewer's report:

MAJOR COMPULSORY REVISIONS

1. One of the major issues with this study is that they state that they are investigating early stage breast cancer, yet over 20% of their population has tumor stage T4 which is not a component of any early stage breast cancer (Stage 0, Stage IA, IB, Stage IIA, IIB, or Stage IIIA).

   *As several patients presented T4 tumour, « early breast cancer » has been replaced by « nonmetastatic breast cancer » or « early breast cancer and locally advanced breast cancer ».*

2. The introduction indicates that this study is being conducted in a group of women who received exclusively anthracycline-based chemotherapy, however they report that 5% of population did not receive this type of treatment.

   *Chemotherapy treatment «anthracycline based chemotherapy » has been replaced by « mainly treated by anthracycline based chemotherapy » or « mostly treated by anthracycline based chemotherapy »*

3. How they took their weight measurements was not detailed enough and their analysis did not indicate an accounting for weight at the beginning of treatment which is a strong prognostic indicator on its own.

   *Weight has been prospectively measured at the hospital by nurse at the beginning of treatment and at each chemotherapy cycle.*

4. The use of the terms “weight variations” is misleading. It is suggested that the terms “weight gain” be used instead to be more precise.

   *The terms « Weight variations » was used instead of the association of « weight gain » and « weight lost ». In effect, we chose to combine these 2 groups in regard to literature on prognostic value of weight variation. Most studies showed that a weight gain is a poor prognostic but also one study reported some evidence that women who had a weight loss had a higher risk of recurrence and death compared to women with no weight variation. Moreover, weight change reflected a metabolic disorder comparing to patient who maintained their weight.*

5. How was WV calculated? It is indicated that measurements were taken at various time points during treatment. Was the WV calculated with the last measurement subtracted from baseline, or some combination of all the weight measurements taken during treatment?

   *Weight variations (WV) were calculated as the relative percent weight change between weight measurement from baseline to post-chemotherapy treatment ((baseline weight – weight after chemotherapy)/baseline weight X 100).*
6. Did you adjust for any covariates such as BMI or treatment? Both of these factors could affect survival and recurrence.

*In multivariate analysis, we included 3 others covariates: initial BMI, menopausal status and treatment by hormonotherapy. In a multivariate Cox model (Table 2) that included WV, tumor stage, and nodal involvement, initial BMI, menopausal status and treatment by hormonotherapy, only WV and nodal involvement were significant on overall survival and recurrence.*

7. Also, there was no accounting for weight gain after treatment had ended. Since the follow-up time in this study was quite long (median 20.4 years), there is a long period of time unaccounted for after treatment where women could have gained quite a substantial amount of weight which could also affect prognostic outcomes. *This argument has been inserted into the paragraph of study limitations.*

8. Although there was a section in the Methods describing treatment, was no mention of adjustment for this, or other factors, in the analysis. *In the result section we added data concerning treatments that have been administered after chemotherapy (hormonotherapy, radiotherapy) and could influence survival and recurrence of these patients. As mostly patients received radiotherapy (96%), this factor has not been included in multivariate analysis. The analysis adjustment for hormonotherapy has been added in table 2.*

9. There needs to be section in the Discussion on how/why chemotherapy can cause weight gain.

**MINOR ESSENTIAL REVISIONS**

1. What is “early breast cancer”? Do you mean early-STAGE breast cancer or breast cancer at a young age?

   “early breast cancer” means « early stage breast cancer », *As several patients presented T4 tumour, “early breast cancer” has been replaced by “nonmetastatic breast cancer” or “early stage breast cancer and locally advanced breast cancer”.*

2. Were the different treatment modalities accounted for in the analyses?

   After chemotherapy treatment, 96% had radiation and 40% have received hormonal therapy (90% with tamoxifene).

3. What is an “H” statistic? This needs to be explained better and using common terms. In general the Analysis section could use more specific details.

   The « H test » has been replaced by « Kruskal-Wallis H test», that is a non-parametric method for testing equality of population medians among groups, variance analysis.

4. Page 7, sentence 2: Is this the reported median age at diagnosis, or at follow-up?

   *Page 7, sentence 2, median age at diagnosis was reported.*

5. What is meant by hormonal status? Exogenous hormone use? Hormone receptor status? Menopausal status? This is the first time it is mentioned in the manuscript.

   « Hormonal status » has been replaced by « hormone receptor status »

6. Were the different treatment modalities accounted for in the analyses?

**DISCRETIONARY REVISIONS**

1. The abstract needs to be reworked. The language is a little awkward, and since this is the first part of the manuscript people will see, it needs to be well-written.
2. Add a little more information about your study population (e.g., age at diagnosis). 
Corretion done.
3. Page 5, sentence 1: this sentence should begin “Deaths and recurrence” instead of “Results”. 
Correction done.
4. In the “BMI and weight variation” section I believe the first sentence should read “The initial MEDIAN BMI was…..” Correction done.
5. Page 8, sentence 3: Did you mean the OS was “dependent ON” or “INDEPENDENT of”? «Dependant of » has been changed by «dependent on».
6. Page 10, sentence 1 and 2: These sentences do nothing to prove your point. If 68% of your population maintained their weight, then the median weight gain will reflect that, showing no weight gain in your study. In our series, however a median WV equal to zero during chemotherapy treatment of breast cancer patients, 32% of our population presented a significant weight variation (>5%) whereas 68% had maintained their weight.
7. Page 10, sentence 3: Suggested change: “Our findings of significant weight gain are in contrast….”. «Our findings are in contrast with » has been changed by «Our findings of no significant median WV are in contrast with »

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
vi) I declare that I have no competing interests
Reviewer's report
Title: Weight change during chemotherapy is a poor prognostic in early stage breast cancer
Version: 1 Date: 23 February 2010
Reviewer: Patricia Thompson

Review of manuscript "Weight change during chemotherapy is a poor prognostic in early stage breast cancer" offered by Thivat et al.
The objective of the study was to assess the effect of weight change defined as >5% variation among 132 women treated with anthracycline-based chemotherapy for stage I-III breast cancer between 1976 and 1989 and followed for ~20 years. The authors report women who experience > 5% variation (gain or loss) in their weight with treatment have a near doubling of risk for recurrence and mortality.
The manuscript is generally well written with minor need for English editing. The study replicates findings from other studies showing that BMI at baseline is associated with later stage of diagnosis and is thus associated with higher risk of recur and mortality. This aspect of the study does not add appreciably to the existing literature except to extend the observations to a population with a lower mean BMI than the U.S. counterparts.

The rationale for combining women who gained weight (15%) with those who lost weight (17%) as a weight changing group (32%) is not provided nor is a mechanism for how weight change regardless of direction would influence outcomes. This should be addressed.

In regard to literature on prognostic value of weight variation reported some evidence that women who had a weight gain or loss have a higher risk of recurrence and death compared to women with no weight variation, we chose to group women who gained weight with those who lost weight as a weight changing group. Moreover, weight change reflected a metabolic disorder by comparison to women who maintained their weight with an energy balance in equilibrium.

The description of the present status of the cohort of patients is confusing and suggests that the majority, if not all of the women, who did not experience a recurrence (breast cancer event) are dead from other causes and were therefore censored in the data. In contrast, they appear to be contributing as a large group to deaths in the cohort.

In the result section, additional data has been inserted. Among the 74 women died, 64 developed breast cancer recurrence (86%), also only few patients died from other causes.

It leads one to wonder what role age plays in the relationship between BMI and poor outcomes in this study as older women have higher BMIs. Age nor menopausal status are included in the multivariate model.

There is a need to better describe the population and to consider other factors in the multivariate model of known significance for recurrence and survival (i.e., age, smoking status, menopausal status).

In multivariate analysis, we included 3 others covariates: initial BMI, menopausal status and treatment by hormonotherapy.
In general, the relevance of the manuscript is unclear given the combining of weight loss with weight gain during chemotherapy. This seems somewhat counterintuitive given the mechanisms proposed for effects of weight gain on poor outcomes and lack of discussion of effects of weight loss.

The question asked in this study is not supported by an underlying unifying hypothesis about weight change. If there is one, it should be provided.

Several mechanisms have been proposed to explain the adverse effect of weight gain on risk of recurrence and mortality. One mechanism rests on a greater aromatase activity in the excess adipose tissue [34] and an inhibition of synthesis of sex hormone-binding globuline associated with an increased in free estradiol level which stimulates neoplastic cells [35]. Another mechanism relates to insulin and insulin-like growth factor and the interaction of these hormones with adiposity. It is hypothesized that visceral obesity increases both insulin-like growth factors (IGF-I, IGF-II) which stimulate the synthesis of sex steroid hormones [29] that are involved in the regulation of normal and malignant growth of epithelial breast cells.

In addition, fasting serum insulin concentration has been directly associated with an increase in both distant recurrence and death in women previously treated for breast cancer [36]. Insulin resistance has been also shown in variety of cancer patients with body-weight loss [37]. Further research is needed to understand the biological mechanisms underlying the relationship between weight variation and breast cancer growth with exploration of insulin resistance in association with body composition, measurement of energy expenditures, calory intake and inflammatory reaction that might be involved in the development of insulin resistance [37].

In general, the sample size is too small to conduct a well powered study of the independent effect of weight gain, weight loss or weight stability on breast cancer recurrence and overall survival. Limitations of the study should be noted.

A paragraph presenting the major limitations of this study has been added before the conclusion.

It is further difficult to reconcile the relevance of the study in light of the observation that treatment with tamoxifen is effective independent of BMI status at diagnosis and that in more recent studies there is less support for adverse effects of BMI on outcomes with change in treatment practices. There is little generalizability of these findings to the current breast cancer patient population, thus the contribution of the study is very modest. The author's should speak to these results in light of change in practice.

In this study, we observed significant independent effect of weight change during chemotherapy (before a possible treatment by tamoxifene) on outcomes of women with non metastatic breast cancer and also when we added hormonotherapy treatment as covariates in multivariate analysis. However, BMI status at diagnosis was not significant prognostic factor in multivariate analysis due to its association between tumor stage, menopausal status, and hormone receptor status.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: 'I declare that I have no competing interests'
**Reviewer's report**

**Title:** Weight change during chemotherapy is a poor prognostic in early stage breast cancer  
**Version:** 1  **Date:** 19 February 2010  
**Reviewer:** Crystal Tyler

**Reviewer's report:**

Is the question posed by the authors well defined?  
The purpose of the manuscript was to investigate the prognostic value of weight variation during chemotherapy treatment. This question was well defined and explained in the introduction.

Are the methods appropriate and well described?  
Kaplan Meier and Cox proportional hazards models, which were appropriate for the data and study questions, were used for analyses. The authors did not indicate whether the proportionality assumption was checked additionally did not state the type of p-values used. Authors also failed to test for effect modification or if effect modification was examined, the authors did not so mention in the text (specifically with respect to menopausal status).  
*The proportionality assumption was verified by log-translation and was not significant. The sentence« P value < 0.05 was considered statistically significant. » has been added. Menopausal status was included in multivariate analysis.*

Are the data sound?  
Data appear to be sound but information on the quality of data was not included in the text.  
*In this database, there is few missing. A quality criteria to study OS and DFS is the absence of patient lost of follow-up. Among the 132 patients, 74 died and 86% after breast cancer recurrence.*

Are the discussion and conclusions well balanced and adequately supported by the data?  
The discussion and conclusions are supported by the data but there is no mention of potential limitations of the study.  
Are limitations of the work clearly stated?  
Limitations of the study are not stated at all  
*A paragraph presenting the major limitations of this study has been added before the conclusion.*

Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?  
Authors conducted a thorough review of European, Asian and North American literature and included studies which agreed and disagreed with their findings. Authors also included possible reasons for differing results between studies.

Do the title and abstract accurately convey what has been found?  
The title used "Weight change during chemotherapy is a poor prognostic in early stage breast cancer" is a bit confusing because it may lead one to think that weight change is not a prognostic factor when examining breast cancer survival, when in fact, the authors found that weight change is predictive of decreased survival. The authors should consider modifying the title to indicate this.
The title has been modified as « Weight change during chemotherapy is a poor prognostic in non metastatic breast cancer »

Is the writing acceptable?
The manuscript could use some minor editing, especially in the discussion section.

The following are Minor Essential Revisions for the authors consideration:

Methods:
Please include the number of individuals excluded from analyses in the population section. Among the 709 women treated by chemotherapy treatment for breast cancer during this period, 132 women were included in the analysis.

Indicate whether weight was measured by the hospital at each chemotherapy session or self-reported by the breast cancer patient? Weight has been prospectively measured at the hospital by nurse at the beginning of treatment and at each chemotherapy cycle.

Is there information available on the patient’s usual adult weight (i.e., before breast cancer diagnosis) No, the patient’s usual adult weight has not been collected prospectively and did not appear in reviewing patients’ medical records.

A clearer explanation should be given on why negative weight change and positive weight change was grouped together. It seems to me that these would represent different circumstances and reactions to chemotherapy. We chose to combine these 2 groups in regard to literature on prognostic value of weight variation. Most of the studies showed that a weight gain is a poor prognostic but also one study reported some evidence that women who had a weight loss had a higher risk of recurrence and death compared to women with no weight variation. Moreover, weight change reflected a metabolic disorder comparing to patient who maintained their weight.

Were other BMI categories or continuous BMI measurements considered for analyses? In the analysis BMI categories were considered :BMI below 24 kg/m2 and beyond 24 kg/m2. The cut-off has been chosen according the median BMI.

Please indicate which variables were statistically significant and included in the multivariate models The multivariate Cox model (Table 2) included WV, tumor stage, and nodal involvement, initial BMI, menopausal status and treatment by hormonotherapy, statistical significance was noticed by « * » in table 2 and was detailed in result section.

Did you have information on smoking status? No, the smoking status has not been collected prospectively and did not appear in reviewing patients’ medical records. This argument has been inserted into the paragraph of study limitations.

Results:
Are the estimates presented in table 2 HRs or RRs? In table 2 the RRs are presented.
It would be clearer if the number of patients in each category along with the point estimates were included in table 2.

The numbers of patients in each category were included in table 2.

Discussion:

Is there evidence that indicates that anthracycline-based therapy has a differential influence on weight gain than non-anthracycline-based therapy? If so, please cite.

Retrospective and prospective reports, have yet demonstrated no increased weight gain with anthracycline-containing regimens compared with other regimens (Makari-Judson 2007). Fisher et al. (1990) noted that 14.4% of patients receiving the AC regimen gained $\geq 5\%$ over pretreatment weight compared with 42.2% of patient receiving CMF. This result were comparable to our result (15% gained weight) indeed the fact that patient accrual took place prior the widespread used of 5-HT3 receptor antagonists in the two studies (cancer-related treatment currently used to reduce the impact of nausea and emesis associated with anthracycline use).


**Level of interest:** An article of importance in its field  
**Quality of written English:** Needs some language corrections before being published  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Reviewer's report

Title: Weight change during chemotherapy is a poor prognostic in early stage breast cancer
Version: 1 Date: 14 February 2010
Reviewer: Xiaoli Chen

Reviewer's report:

General comments

This study examined weight change during chemotherapy treatment and its association with cancer prognosis among 132 women diagnosed with early breast cancer. Although this study has a long follow-up (median: 20 years) and measured weight and height, it has also several limitations including a relatively small sample size, study design (retrospective chart review), and limited covariates considered in the statistical analyses. These limitations were not discussed in this study.

A paragraph presenting the major limitations of this study has been added before the conclusion.

Specific comments

Methods:

Page 4, population: readers may be wondering whether it makes sense to include women who were treated between 1976 and 1989 (across 13 years) in order to have at least 20 years of follow-up for the study. The use of chemotherapy and other cancer-related treatments may have changed over time between 1976 and 1989.

During the studied period, no major change in the use of chemotherapy occurred in France.

Page 5, weight measurements: how did the authors define overweight and obesity in this study?

It seems that WHO obesity criteria was used (BMI: 25, 30 as cut-points for overweight and obesity) as shown in the results. It would be better to describe these cut-points in the Methods section.

The sentence « The different subclasses of patients were categorized as followed: underweight (< 18.5), normal (18.5 - 25), overweight (25 – 29.9) or obese (≥ 30). » has been added in the Method section.

Also, how were weight loss and weight gain defined?

As WV were categorized accordingly into weight change (WV > 5%) that combined weight loss and weight gain, weight loss was defined by a relative weight loss > 5% between weight measurement from baseline and to post-chemotherapy treatment and weight gain was defined by a relative weight gain > 5%.

Page 5, covariates: What’s the full name for SBR? « SBR » has been replaced by « Scarff-Bloom-Richardson (SBR) grade ». Were information on other cancer-related treatments such as radiotherapy and tamoxifen use obtained for this study? In the result section, we added data concerning treatments that have been administered after chemotherapy (hormonotherapy, radiotherapy). Lifestyle factors including physical activity have been increasingly reported to be associated with breast cancer prognosis. Was it considered in this study? Did the authors consider other sociodemographics such as education and income?
These factors (physical activity and other sociodemographics) have not been considered in this study because they have not been collected prospectively and did not appear in reviewing patients’ medical records. However these factors has been discussed into the paragraph of study limitations.

Page 6, statistical analyses: ‘…all variables used in this study… presented as means±SD’, however, there were no such means shown in tables or Results section. 
Correction done. The results were presented as median [range] and were not presented as means±SD.

Regarding the statement ‘Initial BMI and tumor stage being strongly associated, tumor stage rather than BMI has been chosen for the multivariate analyses’, readers may want to know the main exposure variables considered for this study. In page 4, the authors stated that ‘We also verified the association of weight at breast cancer diagnosis with survival’. Does it mean that BMI, as well as weight change, is another important exposure variable and should be included in the multivariate models? Further stratified analyses may be needed to test whether the association of weight change/BMI with breast cancer survival varies by tumor stage or other covariate. It would be better to check if the associations of obesity, weight gain, and weight loss with overall and disease-free survival are different or same.

In multivariate analysis, we included 3 others covariates: initial BMI, menopausal status and treatment by hormonotherapy.

Page 7, characteristics of the population: readers may want to know the distribution of TNM stage. How many women were categorized as both ER and PR positive?
Sixty-one percent of patients had a positive hormone receptor status with 25% were ER+/PR+. Fifteen percent of the women were diagnosed with stage I breast cancer while 48% and 37% had stage II and stage III, respectively.

Page 7, BMI and weight variation: if based on the WHO overweight and obesity criteria, the cut-points for overweight should be with a BMI of 25-29.9, but not 30, and for obesity, BMI>=30, not >30.
The cut-points for overweight and obesity have been changed and did not modified our distribution.

The authors used the median of BMI as cut-point, and it seems unnecessary to report the percentage of patients with BMI below or beyond the cut-point as ‘Forth-six percent of patients had a BMI below 24, while 54% had a BMI beyond 24’. The sentence «Forth-six percent of patients had a BMI below 24, while 54% had a BMI beyond 24 » has been deleted.

It would be better to provide the definition of weight gain and weight loss in the Methods section first, then show the percentage of women who had lost weight or gained weight in the Results section. 
Correction done.

Discussion: In general, the interpretation of the findings about overweight is weaker and should be improved. More statistical analysis about overweight and obesity with survival are needed to compare with previous studies as shown in the 2nd para in the Discussion section.
Table 1. better to show TNM stage, give a note about ‘BMI, SBR’. Better to show these study characteristics by BMI (normal, overweight/obesity) and/or weight change (stable, weight loss, weight gain)

*Correction done.*

Table 2. How many variables were included or adjusted for in these models? Need a note. Were the tumor stage and nodal involvement highly correlated in the models? Were the types of other treatments such as radiotherapy or tamoxifen use adjusted for?

*In multivariate analysis, we included 3 others covariates: initial BMI, menopausal status and treatment by hormonotherapy.*

*Tumor stage and nodal involvement were highly correlated (variance analysis, \(p=0.000083\)).*

Figures, give a note what the OS and DFS mean, the definition of ‘stable weight’ and ‘changing weight’.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests