Author’s response to reviews

Title: For patients with breast cancer, geographic and social disparities are independent determinants of access to specialized surgeons. A eleven-year population-based multilevel analysis.

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Author’s response to reviews: see over
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To the BMC Cancer Editorial Board,

Please find below our point by point response to the comments made by the editors and the two reviewers:

**Editor’s comments:**
Comments to be passed to the authors:

While the reviewers acknowledge the importance of the topic addressed in this manuscript they have highlighted a number of major concerns regarding the approach to the analysis which the authors would need to address before the manuscript could be reconsidered. In particular we would like to draw the authors' attention to the following issues as raised by reviewers:

1. Use of overall rather than relative survival as the main outcome.
2. Choice of variables relating to socioeconomic status to be included in the adjusted analysis.
3. The possibility of presenting results on the extent to which any geographical or social disparities in survival is accounted for by access to specialised surgeons (for example by conducting analysis of the effect of geographical and social variables on survival with and without adjustment for access to specialised surgeons).

One further comment as raised by an editor relates to the analysis of survival according to surgeon class as shown in Table 2. Although the adjusted hazard ratio by surgeon class is nominally significant (RR=0.79 .65-.94), it is not clear whether finer adjusted for stage (eg using more than just two categories for tumour size), or additional adjustment for whether or not the cancer was screen-detected (which the authors show to be significantly associated with access to specialist surgeons) would lead to any further attenuation of this result. We would appreciate it if the authors could comment on this.

**Answer to point 1, and further comment:**

In fact survival was not the main objective of this study. The study was exclusively based on prognostic factors of access to care and in particular to a specialized surgeon. The analysis of survival was simply to give the context, to explain why we were interested in access to reference surgeons; this is why the analysis is simple. However, as you are interested in this, we have slightly refined the analysis by adding the comorbidities, the circumstances of the diagnosis, and by dividing the T stage into 3 categories rather than 2. The Methods section has been modified accordingly.

**Answer to point 2:**

The Townsend index has been a reference for several years and makes it possible to compare studies. Nonetheless, we had had many aggregated socio-economic variables, on top of those included in the Townsend index, and we decided to include these. Indeed, they were not
significant in multivariate analysis; they have therefore been removed from the analysis, as requested by both reviewers.

**Answer to point 3.**

The study was exclusively based on predictors of access to care, and in particular access to a specialized surgeon. It was not to study socio-economic factors as prognostic factors for survival. Many other confounding variables would need to be taken into account – this could be the subject of another study.

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**Editorial Requests:**

1) **Copy Editing** - After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

   **The article has been read by a native-English speaker, M. Philip Bastable.**

2) **Ethical Approval** - Research involving human subjects (including human material or human data) 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/en/30publications/10policies/b3/index.html). 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 authorization number provided by the CNIL ((National Commission on Informatics and Liberties), has been included in the METHODS section.**
**Reviewer 1 : Dr Cyrille Delpierre**

**Major compulsory revisions**

Methods: The main point is the threshold chosen by authors. Why 100 breast cancer operations? And during the study period (11 years if I well understood)? Do 10 operations constitute a relevant threshold? In literature, it seems that the threshold is bigger (cf Chen et al. 2008). Why do authors use a binary variable and not a continuous one or a qualitative variable with more than 2 categories?

we used a threshold of 100 operations, as we had done several survival analyses using various categories of reference surgeons: there was no significant difference among surgeons who had operated on more than 100 breast cancers, but there was a significant difference between the above surgeons and those who had done fewer than 100 operations, among whom there was no significant difference either.

In addition, in practice, among the 92 surgeons who had operated on at least one breast cancer between 1998 and 2008, the eight who had performed the most operations, in a regular manner during their years of practice, and were known to be surgeons of the department specialized in breast cancer surgery, were those who had done more than 100 operations each, the ninth and the following surgeons had all done less than 100 operations over the study period.

Finally, the fact of having a binary variable also simplified the survival analysis, which was used to set the context for the principal study, which focused on predictors of access to care and in particular access to a specialized surgeon. The survival analysis was to explain why we were interested in access to specialized surgeons; this is why the analysis is rather simple.

In the article by Chen, survival according to the number of operations performed by surgeons was the main objective, and the population of patients was far greater (13,360 vs. 3,928 in our study). This allowed them to divide into three categories and remain discriminating.

Regarding the choice of variables, why do authors choose aggregate variables? It is needed to explain why they use ecological variables: is it because of a lack of individual data? Is it to characterise the context?

Indeed, the principal reason for using aggregated data was because we did not have individual data for the variables being studied. But this also allowed us to assess the effect of a context, which is more useful for establishing and implementing health policy at a local level.

Why do they choose several variables which are correlated with index of deprivation that is a more global variable? Why Townsend index, which is an English index known to be not so well adapted with French data because of major difference regarding rural/urban area (a ref is needed to justify the definition of this variable)? I think that explanations and assumptions made by authors need to be clarified.

The Townsend index has been a reference for several years and makes it possible to compare studies. Nonetheless, we had had many aggregated socio-economic variables, on top of those included in the Townsend index, and we decided to include these. Indeed, they were not significant in multivariate analysis as the correlation with the Townsend index, which was significant, was too strong. They have therefore been removed from the analysis as also suggested by the other reviewer. The way the rural or urban nature of the area of residence was determined has been described in the METHODS section.
Regarding statistical analysis, how do authors check proportional hazard assumption of the Cox regression model?

The proportional hazards assumption was first of all assessed by the graphic method of the log-log curves of the survival function, and a test of proportionality of hazards using Schoenfeld residuals showed that the proportionality assumption was satisfied for all covariates. This has now been explained in the Methods section.

Why do they use overall survival and not for example relative survival? It is possible that people are different in the two groups regarding comorbidity. This variable could influence care management and overall survival. And as it seems that high-volume surgeon have patients with a more favourable profile, it is likely that patients with comorbidities are likely not to be operated by high volume surgeons.

In fact survival was not the main objective of this study. The study was exclusively based on prognostic factors of access to care and in particular to a specialized surgeon. The analysis of survival was simply to give the context, to explain why we were interested in access to reference surgeons; this is why the analysis is simple. However, as you are interested in this, we have slightly refined the analysis by adding the comorbidities, the circumstances of the diagnosis, and by dividing the T stage into 3 categories rather than 2. The Methods section has been modified accordingly.

Moreover why do authors not include care centres in their analyse? Maybe survival is explained by centers and not by surgeons? Same remark regarding circumstance of diagnosis.

We also analysed the impact of the reference centre; though they were, of course, significant in univariate analysis, they were no longer so in multivariate analysis – they lost out to the surgeons.

The circumstances of the diagnosis have been included in the analysis.

Regarding multilevel analysis, why do they decide to consider rural/urban area (as distance) as an individual variable?

The variable rural/urban was determined from the home address of the patient; it was thus classified as an individual variable. We reclassified using the Insee classification of rural and urban IRIS, which changed nothing, and this variable was analyzed as an aggregated variable.

Discussion: Limitations of this study have to be discussed. In particular, the fact that some variables of confusion may potentially explain the association found between high volume surgeon and overall survival, as the threshold used for defining high volume surgeon.

We have developed the discussion section and have included variables that could be confounders in the survival analysis.

Minor essential revisions

Introduction: I think that authors should talk first on studies on health disparities before talking about the potential role of surgeons “quality” to explain social disparities. And I would insist more on the French situation regarding studies on
health disparities in cancer management and survival, and on the potential influence of surgeons “quality” on that. Many references studying health disparities in cancer management are actually from other countries than France. It is not sure than the situation is the same in France (authors explain a difference regarding urban/rural distribution for example). Maybe French studies are rare. In this case it is important to say that this study is one of the first to study the influence of surgeons experience on survival and the link between social determinants and access to specialized surgeons.

Indeed, there are hardly any French studies on this subject. We have corrected the introduction as suggested.

Result: I think that the proportion of operations by year in the two groups is useful, as the proportion of high volume surgeons according to care centre.

The proportions of operations per year according to the class of surgeon have been added in the Results section.
The number of surgeons in each centre has also been added. There were in fact four specialized surgeons in each of the two centres: this information has been added in the methods section.

In table 1, missing values for circumstance of diagnosis are missing.

An oversight – they have been added.

In table 3, multivariate logistic regression analysis should be replaced by multilevel logistic regression analysis.

Done.

“level 2 variance” and the variance partition coefficient are needed.

These have been added in the results section.
Reviewer 2 : Dr Ruth Cunningham

Major Compulsory Revisions
Methods:
1. Please provide some justification for the use of so many area based socioeconomic measures, and consider reducing the number used. As there are no individual measures available, I would have thought that the composite Townsend Index would have been a sufficient proxy for socioeconomic status for the purposes of this analysis. Moreover, by including so many likely correlated variables in the model, the chances of finding an independent relationship between any one of them and the outcome is greatly reduced.

The Townsend index has been a reference for several years and makes it possible to compare studies. Nonetheless, we had had many aggregated socio-economic variables, on top of those included in the Townsend index, and we decided to include these. Indeed, they were not significant in multivariate analysis as the correlation with the Townsend index, which was significant, was too strong. They have therefore been removed from the analysis as also suggested by the other reviewer.

Results:
2. I was very surprised to see that 46.9% of all the cases included in this study fell into the most deprived quartile, and am concerned about what this means for the validity of the Townsend Index in this context. What is the deprivation profile for breast cancer cases in all of France? – is it similar to the Cote D’Or, or more like the distribution in most of the world where breast cancer is more a disease of the less deprived? Please provide more detail on the Cote D’Or region’s socioecoomic make up, if this is the likely explanation for the Townsend distribution, or otherwise comment on this surprising finding.

In Côte d’Or, as in the rest of France, it is said that breast cancer is a disease of higher socio-economic classes. We are currently working on the incidence according to the socio-economic level at the departmental level, and this finding seems to be confirmed. If indeed 46.9% of cases of breast cancer in our population are in the least privileged quintile, almost half of the total population: 131,468 women in 267,554 in the whole department; that is to say 49.1% is in this category. And if 8.2% of cases are in the most privileged quintile, this represents 7.2% of the total population (19,451 women in 267,554), which explains the higher incidence in the privileged classes. In absolute terms though, there are more cases in the least privileged quintile. Of course this raises the question of the relevance of the Townsend index for the population of France, or in any case at least for the population of our department, as by following the criteria, almost half of the population are in the least privileged quintile, the least privileged IRIS are indeed the most densely populated. We used this index, because to date there are no other composite indexes available for socioeconomic levels. The index was also chosen to be able to compare our study with other studies in other countries.

Despite the above, the index does reveal inequalities in access to care. In fact, it was for the above reasons that we decided to use other socio-economic variables than the Townsend, to show that all of the analyses were pointing in the same direction, whether we used the Townsend or independent socio-economic variables.

Minor Essential Revisions
Abstract:
3. Please specify the reference groups for the presentation of results by distance to centre and rurality.

This has been corrected in the abstract.

Background:
4. Please change “surveys” in the first sentence to “studies” as survey refers to a particular study type.

Done.

Methods: Data collection and studied variables
5. Please specify the year used for place of residence variables (presumably the year of diagnosis).

This has been added; the address was indeed at the time of diagnosis.

Discretionary Revisions
6. Year of diagnosis will also be a prognostic factor for survival and could be adjusted for in the analysis.

The year of diagnosis was added as an adjustment variable in the multivariate survival model.

7. Another way of looking at this data which might have more policy relevance would be to examine the proportion of survival differences by geographic and socioeconomic measures which is explained by differences in access to a specialist surgeon. As the authors state, we do not know why those from more deprived areas are less likely to access specialist surgeons, and the discovery that those living closer to specialist services are more likely to be seen by them is unsurprising. But if we knew that the relationship between breast cancer survival and rurality or deprivation was mostly (or hardly at all) determined by access to a high volume breast cancer surgeon then we could use this information to try to reduce socioeconomic or geographic disparities by focusing on improving access to specialist services or by looking elsewhere. I would like to see the authors use their data to perform this additional analysis.

The study was exclusively based on predictors of access to care, and in particular access to a specialized surgeon. It was not to study socio-economic factors as prognostic factors for survival. Many other confounding variables would need to be taken into account – this could be the subject of another study.

8. Further discussion of other studies which have examined the relationship between socioeconomic status and surgeon type would be useful. The two studies mentioned were from France and examined colorectal cancer. While few studies have this as their primary question, other studies have examined the socioeconomic profile of those treated by specialist vs non-specialist surgeon (for example: Kingsmore D. Specialisation and breast cancer survival in the screening era. Br J Cancer 2003; 88: 1708–1712).

The article has been added in the text and in the references.
We trust that the reviewers will find that we have dealt with their comments in a satisfactory manner and that the article is now suitable for publication in BMC cancer. We look forward to hearing from you.

Yours sincerely,

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