Author's response to reviews

Title: Breast cancer stage at diagnosis and area-based socioeconomic status: A multicenter 10-year retrospective clinical epidemiological study in China

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Author's response to reviews: see over
Dear Mr. Danrolf de Jesus and Dr. Julie M. Kapp,

Thank you very much for your email dated January 18 and for the accompanying comments and editorial requests on our paper (2138977867638088). We are submitting a revised manuscript that incorporates the comments and editorial requests. A point-by-point response to the comments is attached as follows. We hope that our paper has been revised satisfactorily and will be accepted for publication in *BMC Cancer*. We have split the original Table 1 into three tables in the revised manuscript. Additionally, we have our manuscript proof read by a native English speaker, Shawna Williams, and have noted her help in the acknowledgments section.

We look forward to your response.

Sincerely,

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Attachment:  Point-by-point response to the comments received on 1/18/2012

**General comments**

This is a hospital-based study to compare the risk of later stage diagnosis of breast cancer among 7 hospitals in China. Using data from 7 Chinese hospitals, the authors found that women with breast cancer living in less developed regions in China were more likely to be diagnosed with later stage disease compared with their counterparts in wealthy regions. These results have important implications: as geographical disparities in wealth and health are increasingly widening in China, efforts to reduce these disparities would have significant impact on population health as Chinese population affected by breast cancer is much greater than any other population in the world. If the risk of being diagnosed with later stage breast cancer in the wealthy regions applies to the whole Chinese population of these with breast cancer, there would be huge reduction in later stage diagnosis of breast cancer. Consequently the outcomes of breast cancer patients would be improved dramatically in China. Thus, this is an important step; the next step following this should be attempts to find the underlying causes for these disparities and then recommend policy makers to take targeted interventions to the high risk groups in the population to reduce, ultimately eliminate, these disparities in China.

However, the way of categorising socioeconomic status (SES) of the whole Chinese population into 3 groups is not appropriate because the building block is too big (7 regions in China). Therefore, a comparison of risk of getting later stage diagnosis in the highest SES region with low or median SES regions was essentially a comparison of Beijing with other regions in China. Thus, it would be more accurate to change the term of SES into regions to reflect the nature of the comparison. In addition, the socioeconomic variation in the risk of getting later stage diagnosis
within region may be larger than that between regions; and regional health authorities have direct responsibility to reduce disparities within their regions.

Response:
This is a sample survey according to the traditional administrative divisions in China, which divides all of China into seven regions: north, northeast, northwest, central, east, south and southwest. This division accords with the pattern of economic growth and regional inequality in China during the reform era. Our government gave eastern and southern China priority in terms of development, while central, southwest, and northwest China were regarded as secondary considerations. Based on this economic development plan, eastern and southern China have become more developed areas, while central, southwest, and northwest China are recognized as less developed areas. It cannot be denied that SES varies within these regions; however, the differences between regions are also significant, as shown in this study. We selected a key province from each region as the representative in order to show policymakers how regional economy, culture, and healthcare influence breast cancer prevention and control. And we found that some regions had similar SES, so we combined these regions by cluster analysis (P6) in order to better reveal the effects of SES on breast cancer stage. We agree that the area-based SES was measured at a large geographic scale in our study and that studying area-based SES differences among smaller geographic areas would be worthwhile to do in a future study. We have mentioned the large areas as a limitation in the Discussion of the revised manuscript. However, almost all the cases included in our study were ethnically Han, and in China, health administrative management is implemented under the unified standards of the central government. Thus, although the area-based SES was measured at a large geographic scale, the studied cases within the same SES levels had similar culture, customs, behaviors, and language, and the selected regions within the same SES used the same general model of health services. So we think the study is still valuable.

Among the study provinces/municipalities, Beijing is a unique city because it is the capital of China and has special economic and political functions; thus, it cannot be viewed as representative of northern China. Therefore, we separated Beijing from other regions. In accordance with the reviewer’s comments, we have substituted the names of regions with names of each province/municipality in our revised manuscript and tables.

Specific comments
Major revisions
1. It is not correct in my opinion to claim that this is a representative study of breast cancer in China (on page 10) and I don’t believe that you can generalise your results to the whole Chinese population. The reasons for this include (but not limited to)
   ● This is a hospital-based study and all hospitals selected were leading public hospitals in China and also the selection method was convenient sampling;
   ● I don’t think the claim is true that each hospital selected covers the entire region (on page 4); it is logic to believe the majority of patients probably would seek care locally (I mean here in their own province especially for the provinces along the east coast in China). For example, it is hard to image that many breast cancer patients in Shandong province (one province in the East China region) would travel so far to Hangzhou, where the selected hospital for East China region located, to seek medical services;
Shanghai is widely considered to have some of the best medical facilities in China, thus the geographic disparities would be even bigger if Shanghai was included in this comparison.

Response:
Although each hospital selected may not cover the entire region, these hospitals were tertiary cancer hospitals named the best cancer hospitals in each province, and all had comprehensive cancer therapy facilities. As patients in China often prefer to go to the highest-ranked specialty hospital, especially when first diagnosed with cancer, we surmised that the patients from the selected hospitals might come from various regions within the provinces. In addition, the pathologic characteristics of breast cancer cases in each study province/municipality were in accord with the region’s own socioeconomic status. And the selected provinces/municipalities represented the different SES levels, low, medium and high. So, we think our results from this kind of sampling survey do represent the general situation in China with some validity. However, we cannot analyze the geographic disparities between Shanghai and other regions because Shanghai was not included in this study. Since Shanghai is one of the most developed areas in China, it cannot be viewed as representative of eastern China. So we selected Zhejiang to represent general economic development in the region. What’s more, Shanghai has a similar economic development level and health care services to Beijing, so the comparison between Beijing and other regions provides a clue to the differences between Shanghai and other regions. More details about the study design can be found in a previously published paper (A Nationwide Multicenter 10-year (1999-2008) Retrospective Clinical Epidemiological Study of Breast Cancer in China, BMC Cancer 2011).

2. It is not clear to me how these hospital records were reviewed, whether pathology reports were reviewed as well, how the stage determined for these patients without surgery, who did the reviews (researchers in each local hospital or all reviews were done centrally at Beijing)

Response:
The data of qualified patients were collected with standard case report forms (CRF) to extract the primary medical reports, including general information, risk factors, diagnostic imaging tests, therapy models, and pathologic characteristics. Cancer stage at diagnosis was categorized into six groups using the American Joint Committee on Cancer (AJCC) TNM System (0, I, II, III, IV, and unknown stage or not applicable). The cases admitted between 1999 and 2002 were staged using the fifth edition (revised in 1997) [27], and the cases from 2003-2008 were staged with the sixth edition (revised in 2002) [28]. The cancer stage of those patients who did not undergo surgery (717, 17.1%) was categorized as “unavailable” (Table 3). The hospital records were reviewed in each local hospital by local researchers who had been trained centrally in Beijing. We have added some details to the revised manuscript (P4).

Minor revisions
Almost all the literature on this topic cited in this paper was US studies. How about studies from other developed countries in the world? Such as similar kind of studies from Europe, Canada or Australia. In a more recent study, I also found that women with breast cancer from socioeconomic disadvantaged areas in the United State had higher risk of being diagnosed with later stage.
Response:
We have added references to one global report, one new study from China, four new studies from other developed countries, and to the recommended papers (references 16, 17, 18, 38, and 41).

Comments from Reviewer: Mansoo Yu

This study focuses on examining how individual demographic variables (e.g., education and occupation) are associated with breast cancer stage, and how these differ between lower and higher SES areas in a sample of 4211 breast cancer patients in China.

I. Major points:

1) In Table 3, the researchers used ordinal logistic regression models to examine how individual demographics predict breast cancer stages (early, middle, and late stages). For logit models with ordered categories (see Allison, 1997), it would be appropriate to report models such as Model 1 (early vs. middle), Model 2 (middle vs. late), and Model 3 (early vs. late). Then, in each model, they could examine how SES areas (high vs. low) moderate the effects of the different levels of individual demographic variables, particularly education, on breast cancer stages. Interaction plots would be useful as well.

Response:
First, we should mention that we tried to fit multilevel models to examine how SES areas (high vs. low) moderate the effects of individual demographic variables. However, this failed because we did not have enough regions sampled in level two. Additionally, we thought it would not be appropriate to put area-based SES, a variable in the group level, and individual demographic variables into a regression model. Thus, we implemented stratified analysis by area-based SES to further explore the association between individual demographic characteristics and breast cancer stage at diagnosis (Table 5).

We have substituted ordinal logistic regression with binary logistic regression as the statistical method in the revision for the following reasons. In our original manuscript, we used ordinal logistic regression in a proportional odds model. In this kind of model, two adjacent Y-response categories are pooled together, or Y is changed by moving a cut-off point, the regression parameters $\beta_k$ in the model remain unchanged. Before fitting the proportional odds model, we should have checked the assumption of proportionality by computing the individual cut-off point-specific cumulative odds ratios. However, in the process of revising the manuscript, we found that our data did not comply with the assumption of proportionality, because the $\beta_k$ for two logistic regression models (Model 1: early vs. medium and late, Model 2: early and medium vs. late) were very different (In high SES areas: $\beta$ for Model 1=-2.45, $\beta$ for Model 2=-0.29; in low SES areas: $\beta$ for Model 1=-1.65, $\beta$ for Model 2=1.55), and so we have to apply a method better-suited to our data. So in the final revision, according to common international practice, we reclassified breast cancer stage into two categories, “early stage” (stages 0 & I) and “non-early stage” (stages II & III & IV). We then used binary logistic regression to test the effects of
individual demographic characteristics on breast cancer stage in different SES levels (P6).

2) In Table 3, the findings are counterintuitive. Results show that the effect of education on cancer stage is more evident among those living in high SES areas than among those living in low SES areas. This finding is not consistent with a reference cited in Discussion (Singh et al., 2003) indicating that breast cancer patients from lower income areas had lower survival rates than those from higher-income areas (p.10).

Response:
We have changed the statistical method, using binary logistic regression rather than ordinal logistic regression in the revision, and the new results (Table 5, P6-7 in revised manuscript) are consistent with those of Singh et al.

3) In testing the ordinal logistic regression models, it would be more interesting to test omitted variables from the study variables in Table 2 such as BMI and receptor status in predicting breast cancer stage. In addition to the variables that the authors noted in study limitations (p.10), other variables such as access to breast cancer screening services, alcohol use, and family history of breast cancer would be useful to test their effects on breast cancer stage in the future unless the variables are available to be tested in the current study.

Response:
We used binary logistic regression in the revision with BMI and ER/PR status included in the models (Table 5). Although other variables, such as access to breast cancer screening services, alcohol use, and family history of breast cancer couldn’t be analyzed in the current study due to the high proportion of missing data, they may affect breast cancer stage by influencing women’s attitudes and behaviors to breast cancer prevention and screening. We have stated this limitation in the revised manuscript (P11).

4) Based on the study findings, education is critical to reduce breast cancer patients because the other variables were not significant in predicting breast cancer stage. In other words, the study suggests that promoting education is an important way to prevent for breast cancer. Could education be a proxy variable representing risk factors for breast cancer such as alcohol use, lack of exercise, access to health care services, health insurance coverage, etc.?

Response:
We agree that education may have been a proxy variable representing risk factors for breast cancer such as alcohol use, access to health care services, health insurance coverage, etc. We have found evidence to support this, and have stated in the revision that “Education may be a proxy variable representing individual knowledge and behaviors toward prevention and screening of breast cancer. Women with lower education levels may also have higher risk of alcohol-related death and diseases [1]. Low education itself may also create barriers to receiving recommended screening, since low health literacy, low general literacy, and language barriers impact an individual’s ability to navigate the medical service system, understand screening options and recommendations, and
communicate with healthcare professionals [37].” (P10) However, we have not found evidence of a relationship between education and lack of exercise.

II. Minor points:
5) Sampling: purposive sampling would be more appropriate than convenience sampling because of three inclusion criteria for the hospital selection (page 4).

Response: We agree, and have used “purposive sampling” in the revision (P4).

6) On page 5, the researchers noted that there are seven areas of economic and education status. However, there are only four described in the text.

Response: Yes, there are seven areas of economic and education status studied in our study. However, area-based SES was calculated by k-means clustering by setting k=3, and the seven regions were thus classified into three categories based on four SEIs (P6).

7) In Table 1, range of the study variables would be useful. One way ANOVA analyses are needed for post hoc tests to indicate significance among multiple groups.

Response: We added the range of the study variables to the revised Table 1. The variables were compared using one-way ANOVA followed by the Student-Newman-Keuls (SNK) test, a kind of post hoc test for significance among multiple groups (P6).

8) A number of grammatical errors and inappropriate words are evident in the manuscript. For example, standard variances should be changed to standard deviation (p. 5).

Response: We have corrected the error in the revision (P5). Our manuscript has been proofread by a native English speaker, Shawna Williams.

Comments from Reviewer: Sandi Pruitt

This manuscript examines the role of area SES on breast cancer in China and represents, to my knowledge, the first attempt to explore this topic in a developing country. Overall, the data and analysis are strong and the hypothesis is worthwhile. Overall, the writing is very good. A few rather minor edits for clarity and standard English could benefit the readability, however.

Major Compulsory Revisions:
1. My primary concern with this paper is related to the construct of “area-based socioeconomic status” here. The authors measured indicators of SES across 7 very large geographic regions and do not control for other differences between these areas. For example, the differences across these areas could be a result of other regional differences in culture, behaviors, language, health care access, health care quality, ethnicity, age-distribution, or norms. In the U.S. research has shown
that area SES is most reliably and validly measured when measured at a very small geographic scale, not at a large geographic scale as these authors measure it. It would strengthen the paper to discuss the validity of this approach and the conceptual meaning of area SES in China. It may be useful to control for other area-level covariates in the analysis. The authors may also want to consider discussing in the limitations the fact that instead of measuring area SES, they may be simply identifying geographic variation.

Response:
We agree that the large areas are a limitation of the study, and have mentioned in the Discussion of the revised manuscript that we think studying area-based SES differences among smaller geographic areas would be worthwhile to do in a future study. However, almost all the cases included in our study were ethnically Han, and in China, health administrative management is implemented under the unified standards of the central government. Although area-based SES was measured at a large geographic scale in our study, the studied cases within the same SES levels had similar culture, customs, behaviors, and language, and the selected regions within the same SES used the same general model of health services. So we think the study is still valuable.

Because there is a lack of accepted SES measures in China, we referred to the socioeconomic measures of “percent of the population living below poverty” and “percent of the population ≥25 years of age without a high school diploma” in the United States to devise our own socioeconomic indicators (SEIs) reflecting the economic and education status of the seven areas. The area-based SES was then calculated by k-means clustering by setting k=3 based on four SEIs. As we have noted in the Discussion (P11), although this method may not have assessed actual socioeconomic conditions with complete accuracy, the area-based SES in our study accords with the pattern of economic growth and regional inequality in China during the reform era. Thus, we think this indicator has some degree of validity. However, we still suggest that a valid area-based SES measurement be developed that takes into consideration factors such as concentration of poverty, health insurance coverage, proportion of the population with blue collar jobs, unemployment rate, median household income, and median value of owner-occupied houses.

2. Methods-Please provide more detail what you mean by “cluster analysis.” Do you mean principal components analysis? More information should be provided by what this means and how it was conducted in the methods section.

Response:
Cluster analysis does not mean principal components analysis. The term cluster analysis (first used by Tryon, 1939) encompasses a number of different algorithms and methods for grouping similar objects categories. In other words, cluster analysis is an exploratory data analysis tool which aims at sorting different objects into groups such that the degree of association between two objects is maximal if they belong to the same group and minimal otherwise. In our study, the area-based SES was created by k-means clustering by setting k=3, and the seven regions were classified into three levels based on four SEIs. We have provided more information about this analysis in the Methods section (P6).

3. Methods-Please provide more information on how the categories of SEIs and SES were
categorized and measured as “highest, high, and low.” What are the mean scores and range for these categories? How were these created?

Response:
The single SEI values among the seven areas were compared using one-way ANOVA followed by the Student-Newman-Keuls (SNK) test, a post hoc test of significance among multiple groups. The areas were thus reclassified into ordinal categorical levels of SEI status. We have provided more information on how the categories of SEIs and SES were categorized in the revised Methods (P5-6). The mean scores for these categories have been listed in Table 4.

4. Methods-The rationale for stratifying the analysis by area SES is not clear. Please provide a rationale for why you stratified by this variable. Results-Table 3: Why do you only present stratified analyses here? Why don’t you present the total analysis as well? It is common practice to test whether area SES is associated with an outcome after controlling for individual SES? Please explain why the analysis wasn’t done this way.

Response:
We have tried to examine how SES areas (high vs. low) moderate the effects of individual demographic variables. We thought it would not be appropriate to put area-based SES, a variable in the group level, and individual demographic variables into a single model. We instead tried to examine the moderation effects using multilevel models; however, this failed because we did not have enough regions sampled in level two. Thus we implemented stratified analysis by area-based SES to further explore the association between individual demographic characteristics and breast cancer stage at diagnosis (Table 5). We have added more explanation in the Methods (P6).

5. Methods-Provide more information regarding how all the variables were measured and categorized. Were they all taken verbatim from the medical record? Were they re-categorized or changed for this analysis? For example, some of my questions about the variables are: is cancer stage determined by a pathologist? Is employment status as measured in your analysis really captured in the electronic medical record (manual, homemaker, etc)? Is this based on self-report of the patient or from some kind of government record? Is this a reliable measure?

Response:
We have provided more information on data collection and categorization in the revised manuscript (P4-5).

6. Results-If you create and use a SES scale, it would be helpful to describe the scale’s psychometric properties. At the very least, provide the scale’s Cronbach’s alpha. Also describe if the SEI measures were reverse-coded in the creation of the scale, the scale’s scoring range, and it’s mean.

Response:
Because there is a lack of accepted SES measures in China, we referred to the socioeconomic measures of “percent of the population living below poverty” and “percent of the population ≥25
years of age without a high school diploma” in the United States to devise our own socioeconomic indicators (SEIs) reflecting the economic and education status of the seven areas. The area-based SES was calculated by k-means clustering by setting k=3 based on four SEIs. As we have stated as a limitation in Discussion (P11), although this method may not have assessed actual socioeconomic conditions with complete accuracy, the area-based SES in our study accords with the pattern of economic growth and regional inequality in China during the reform era. Thus, we think this indicator has some degree of validity. However, we suggest that a valid area-based SES measurement be developed that takes into consideration factors such as concentration of poverty, health insurance coverage, proportion of the population with blue collar jobs, unemployment rate, median household income, and median value of owner-occupied houses.

Discretionary Revisions
1. In the U.S., urban/rural status is not highly correlated with socioeconomic status and is generally considered a different construct separate from SES. Please provide a brief rationale why you include urban/rural status as a marker of SES. I assume because it is highly correlated with SES in China.

Response: Yes, urban/rural status is highly correlated with SES in China.

2. It would help to clarify which categories of “highest” “high” and “low” variables in Table 2 represent “higher” SES. For example, is the ratio of FPI reverse-coded?

Response: The area-based SES was calculated by k-means clustering by setting k=3 based on four SEIs, and the categories of SEIs and area-based SES are shown in Table 4.

3. Why are there 4 groups (highest, higher, high, low) for the PU/PR ratio instead of 3 as used for the other SEIs?

Response: The single SEI values among the seven areas were compared using one-way ANOVA followed by the Student-Newman-Keuls (SNK) test, and the areas between which there were no statistically significant differences according to the results of the SNK were combined to form subgroups. How many groups there were for each SEI was solely determined by the results of SNK.

Minor Essential Revisions
1. The terminology “composited” and “incorporated” and “composited categorized” used to describe SEIs and SES measures are not standard terminology. It appears you mean “composite” SES “scale.” I also do not know what you mean by “incorporated SEIs.”

Response: “Incorporated SEIs” means “SEI status,” and we have corrected this type of non-standard terminology in the revision.

2. The terminology “adjacent” stage is not standard. It may be clearer to substitute the terminology “later” or “more advanced” stage instead.
Response: We agree. However, we have substituted binary logistic regression for ordinal logistic regression in the revision, so this type of terminology is no longer needed for this manuscript.

3. The term “ANOVA-SNK” (p.5) is unclear. What is SNK? Also, why aren’t the results of the ANNOVA provided?

Response: The Student-Newman-Keuls (SNK) test is a kind of post hoc test of significance among multiple groups. We have added more details about the SNK in the Methods (P6), and the results of the SNK are now shown in Table 1 of the revised manuscript.

4. The final statement in the conclusion is somewhat awkward.

Response: We have adjusted the wording of the final sentence for improved clarity (P12).

5. Is there no data available at all regarding mammography or breast cancer screening? I’m just curious because this would be very helpful to your manuscript to know about history of screening.

Response: Yes, data on breast cancer screening is very helpful to our study. We have used the available data about breast cancer screening and discussed its effects on Page 9.