Author's response to reviews

Title: Medical expenses of urban Chinese patients with stomach cancer during 2002-2011: a hospital-based multicenter retrospective study

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Responses to the editor's comments:

Comment #1: The authors submitted a manuscript revised on the basis of previous comments from the editor and reviewers. Although the revision as done in the spirit of the comments if it is either flowered or unclear. Duration cancer treatment was set as 2 Month before and 10 months after the date of diagnosis. This seems unlikely considering variation in stage in cancers. Why were all treatment duration's arbitrarily set this way? Page 8 lines 14-19 should be actually be part on the discussion section. In the Discussion section, the steep increase and subsequently decrease in the use of radiotherapy was unclear. In addition two reviewers also suggested several problems to be revised. Until the authors complete these revisions, we cannot decide whether or not this manuscript is acceptable for publication.

Our response: Thanks for the editor's comments. Our definition is based on existing studies. Please refer to the following articles[1, 2]:

1. Hornbrook MC, Fishman PA, Ritzwoller DP, Elston-Lafata J, O'Keeffe-Rosetti MC, Salloum RG: When does an episode of care for cancer begin? Med Care 2013, 51(4):324-329.

2. Yabroff KR, Warren JL, Schrag D, Mariotto A, Meekins A, Topor M, Brown ML: Comparison of approaches for estimating incidence costs of care for colorectal cancer patients. Med Care 2009, 47(7 Suppl 1):S56-63

Comment #2: Page 8 lines 14-19 should be actually be part on the discussion section.

Our response: Revised accordingly （discussion part, page 10, line 4-10).

Comment #3: In the Discussion section, the steep increase and subsequently decrease in the use of radiotherapy was unclear.

Our response: Thanks for the editor's comments. We have modified the explanations as "we also found that there were steep increase and decrease of radiotherapy expenses from 2003-2007, which was mainly caused by the obviously bigger variations (2004, 95% CI: 7622-60022; 2005, 95% CI: 11809-58398; 2006, 95% CI: 12378-31151) resulted from the smaller sample sizes of cases receiving radiotherapy during 2004-2006" (discussion part, page 9, line 29-30; page 10, line 1-3).

Responses to the reviewer 1's comments:

Comment #4: The abstract should be shortened, it contains some double information.

Our response: Thanks for the reviewer's suggestion. We have shortened related double information. In the results part of the abstract, we deleted "and about twice as high as the per capita disposable income of urban households in 2011"; in the conclusion part of the abstract, we deleted "The expenses per patient increase at a yearly rate of over 7%, equivalent to their GDP growth rates at the same time period".

Comment #5: The average yearly increase of costs, i.e. 7.5%, is not important, because increases are largely dependent on introduction of new agents and changing guidelines. As a consequence, sudden increases of costs may appear after which costs may stay the same for some years. This limitation should be added.

Our response: Thanks for the reviewer's comments. Yes, some of the increases may be due to introduction of new agents and changing guidelines; however, our study showed that medical

expenses of the first course treatments per patient increased steadily by an average annual rate of 7.4%, rather than sudden increases.

Comment #6: line 14: why is the prevalence of gastric cancer lower in the US than in China?

Our response: Thanks for the reviewer's comments. We have added the reason why China has a higher prevalence of gastric cancer in the background part, which is written as "high prevalence of Helicobacter pylori, cigarette smoking and high intake of salt/salty food were regarded as important risk factors of stomach cancer in China" (background part, page 2, line 8-9).

Comment #7: the background section can be shortened by half at least.

Our response: Thanks for the reviewer's suggestion. Our original manuscript indeed had a background part of about a half of the present one; later, based on the previous reviewers' suggestions, we added much information to respond to their questions. Considering different reviewers' views and suggestions, we decide to keep the present contents in the background.

Comment #8: in the discussion session the limitation of data from 2002-2011 should be commented in relation to new treatment developments in recent years; content of actual guidelines for treatment of gastric cancer should be described.

Our response: Please refer to the above response to sudden increase of costs (response to comment #5).

Comment #9: a further limitation is the widespread differences in costs between regions because of accessibility differences to treatment.

Our response: Thanks for the reviewer's suggestion. We have added the limitation, which is written as "fourthly, the widespread differences in medical expenses between regions may be

related to accessibility differences to treatment, which should be further explored in the future" (discussion part, page 11, line 10-11).

Comment #10: (p. 2 l. 6) Although gastric cancer is one of the rare cancers in western countries, it is common in eastern Asian countries. In Japan, Hori et al. (2015) reported that in 2012 was 36.3. Perhaps, this commonality could be added to the rationale of this study.

Our response: Revised accordingly (background part, page 2, line 3-5).

Comment #11: (p.3 l.26) Please elucidate the relationship between CanSPUC and study population in this research. Does the study population in this study comprise patients with cancer detected by the cancer screening programme? If this is the case and if gastric cancer is often diagnosed incidentally or further examined after symptomatic outpatient visits, the study population loses some fractions of detected cancers.

Our response: Thanks for the reviewer's comment. The Cancer Screening Program in Urban China (CanSPUC) started in August of 2012. To facilitate the health economic evaluation in this project, the baseline expense data of patients of gastric cancer in selected project sites were necessary. In this study, we collected expense data of patients whose last discharge was between January 1, 2002 and December 31, 2011. So, the study population in this study was not comprised of patients with cancer detected by the cancer screening programme.

Comment #12: (p.4 l.10) How were admissions for non-cancer conditions excluded from the analysis? Please define cancer-related conditions.

Our response: The reviewer put forward an important question. Because a patient may have been hospitalized many times in one hospital, we only collected patient-level data from medical records of those diagnosed with stomach cancer or with suspicion of stomach cancer. We have added some supplemental information to explain non-cancer conditions, which is written as "not

diagnosed with stomach cancer or with suspicion of stomach cancer" (methods part, page 4, line 11-12).

Comment #13: (p4. l.12) This study uses CPI of medical care. Please define 'medical care'. In some countries, this definition includes health-related goods as well as healthcare services. It is better to focus on the latter if you can describe it. Is this number country-based or provincial? If you use country-wide data, provincial price changes could not be provided in this analysis. In such case, it is challenging to separate the trend changes from price changes on regional levels.

Our response: Thanks for the reviewer's suggestion. The whole name of the CPI of medical care in China is CPI of healthcare and personal articles (eg. medicine, healthcare appliances and cosmetics) （methods part, page 4, line 14-15）. So this definition includes health-related goods as well as healthcare services. A country-based CPI number was used in this study because we couldn't get all the selected provinces' CPIs of medical care during 2002-2011. So just as the reviewer mentioned, it is challenging to separate the trend changes from price changes on regional levels.

Comment #14: (p.4, l22) It is better to illustrate the data of inclusions and exclusions of the samples according to criteria (1) through (6) in a flow chart.

Our response: Thanks for the reviewer's suggestion. The sample selection process was not done in a step-by-step manner. Our study is a multicenter retrospective study, and the 40 general or cancer hospitals in 22 cities collected and submitted eligible data of targeted sample sizes to the research group respectively, based on the six criteria together. So, we were not able to use a flowchart to illustrate this course.

Comment #15: (p. 5, l. 16) It is true that along with Poisson and Gamma distribution, GLM is a famous method to estimate health expenditure at microlevel. Please refer some related literature.(e.g., Manning et al., 2005).

Our response: Thanks for the reviewer's suggestion. We have added related literature （methods part, page 5, line 19）.

Comment #16: (p. 5, l. 18) The definition of 'number of episodes of care' is unclear. Please clarify.

Our response: Thanks for the reviewer's comment. According to the definition by Mark C. Hornbrook et al., "an episode of care may be defined by limiting it to the services of a single provider or selected multiple providers or to a single hospital stay or multiple hospitalizations within a specified time period"[3]. In this study, following this definition, we defined a single outpatient visit or hospital stay as an episode of care. And we have added related explanations to the paper (methods part, page 5, line 21).

Comment #17: (p. 7, l. 1) Please provide the estimation results of GLM with Gamma distribution.

Our response: Thanks for the reviewer's comment. I have added the estimation results of GLM with Gamma distribution in the additional files (see additional file 3, table A2).

Comment #18: (p. 9, l. 1) Is GDP here a real term? Real per capita GDP is better for comparing the growth rate of expenses per patient.

Our response: Thanks for the reviewer's suggestion. We have substituted per capita GDP for GDP when comparing the growth rate of expenses per patient (discussion part, page 8, line 27).

Comment #19: (p. 9, l.19) The estimation of the annual cost of initial treatment of gastric cancer is unclear. Did you mean that 'It is safe to use 6851 USD both for urban and rural patients as the yearly expense of the first course of treatments? In this case, it can be estimated that it costs China around $3 billion'? If so, it is better to insert the first sentence.

Our response: Revised accordingly (discussion part, page 9, line 15-16).

Comment #20: (p. 9, l. 20) Are factors enumerated here confirmed as a risk factor for gastric cancer? If not, it may be misleading to rationalise that you do not expect a rapid decline in cancer cases.

Our response: Thanks for the reviewer's comment. Some kinds of pollution (e.g., heavy metal pollution[4]), has been confirmed as a risk factor of gastric cancer. As for sedentary behavior, high-fat diets and obesity, they are all closely related to high body fatness, which has been confirmed as a risk factor of gastric cancer with "convincing" evidence[5]. Tobacco smoking and alcohol intake have also been confirmed as risk factors of gastric cancer with "convincing" or "limited" evidence[5]. We have added related citations in our paper (discussion part, page 9, line 20-21).

Comment #21: (p.10, l. 4) You mentioned that cancer care is an enormous financial burden on Chinese patients. However, the description is rather anecdotal. Could you refer some studies (could be Chinese as well)?

Our response: Thanks for the reviewer's suggestion. We have referred related studies, which is written as "a recent abstract in the lancet showed that out-of-pocket expenditure of newly diagnosed cancer (2 months before and 10 months after diagnosis) per cancer patient in urban China was $4947 (4875–5020), accounting for 57.5% of annual household income, presenting 77.6% of families with an unmanageable financial burden" (discussion part, page 10, line 12-15).

Comment #22: (Table 4) Please explain some measures of the goodness-of-fit (e.g. R-squared and the root mean squared prediction error).

Our response: Thanks for the reviewer's comment. Yes, it's important to report the results of the test for goodness of fit. However, as we use a GLM model, we use deviance and pearson X2

values to reflect the goodness of fit of the model, rather than R-squared and the root mean squared prediction error (see table 4, page 23).

Reference

1. Hornbrook MC, Fishman PA, Ritzwoller DP, Elston-Lafata J, O'Keeffe-Rosetti MC, Salloum RG: When does an episode of care for cancer begin? Med Care 2013, 51(4):324-329.

2. Yabroff KR, Warren JL, Schrag D, Mariotto A, Meekins A, Topor M, Brown ML: Comparison of approaches for estimating incidence costs of care for colorectal cancer patients. Med Care 2009, 47(7 Suppl 1):S56-63.

3. Hornbrook MC, Hurtado AV, Johnson RE: Health care episodes: definition, measurement and use. Medical care review 1985, 42(2):163-218.

4. Yuan WZ, Yang N, Li XK: Advances in Understanding How Heavy Metal Pollution Triggers Gastric Cancer. Biomed Res Int 2016.

5. Stomach cancer risk factors [http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/risk-factors#collapseZero]

The authors' response letter has been included as a supplementary file.