

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Disease burden of liver cancer in China from 1997 to 2016: an observational study based on the Global Burden of Diseases
AUTHORS	Ding, Cheng; Fu, Xiaofang; Zhou, Yuqing; Liu, Xiaoxiao; Wu, Jie; Huang, Chenyang; Deng, Min; Li, Yiping; Li, Lanjuan; Yang, Shigui

VERSION 1 - REVIEW

REVIEWER	Jiachen Zhou SmartNuclide Biopharma Suzhou, China
REVIEW RETURNED	16-Sep-2018

GENERAL COMMENTS	<p>In this manuscript, the authors conducted a secondary data analysis to investigate the trend of liver cancer in the recent 20 years in China, and reported an increase in the cancer. Overall, the interpretation of findings and discussion need to be strengthened.</p> <p>Abstract: Line 33: In the methods, the authors used “collected data”. It is more accurate to use “extract” since the primary GDE data was not collected by the authors. Line 43. Given the AAPC of the rate of DALYs to be -0.1%, why authors called it increasing? Line 44: The term of “Mortality incidence ratio” better be changed to “mortality-to-incidence ratio”. Line 45: It'd be better to report the elevated relative risk and confidence intervals instead of P-value for different risk factors. And why only reported p-value for age here, while left alone sex and viral factor?</p> <p>Article summary/strengths and limitations In the section, in my opinion, no strengths were actually listed at all. The authors just mentioned the purpose of the study and the statistical method applied which are not the strengths. The authors are encouraged to reconsider what major strengths their study has. Some more details are needed to explain, in the discussion/limitations sections if not here, why using estimated GBD data is a limitation and if it is why the authors still decided to use this data instead of some other sources.</p> <p>Introduction Line 71 the term “risk factors in vitro” may be better stated as “environmental risk factors”.</p>
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	<p>Line 79: “in” to “between” if the authors mean the years from 2003 to 2007.</p> <p>Methods and Results</p> <p>Line 128: The number of liver cancer patients increased from 349 127 (prevalence: 28.22/100 000, AR: 129 38.64/100 000) in 1997 to 814 026 (prevalence: 60.04/100 000, AR: 53.18/100 000) in 2016. While from citation [11], Chen et al reported the number of new cases of liver cancer in China was 446 100 in 2015 (line 81). Why is the authors’ number much higher than Chen’s?</p> <p>Figure 1: The authors did a very nice job having the trend adjusted by age. Regardless of the increasing trends in all four measures, the age-adjusted trends of incidence, mortality, and rate of DALYs were all flat, if not decreasing. Only the prevalence in the recent years was still increasing after age adjustment. The authors did not seem to explain much on this observation later on. Do the authors think the aging population explains most part of the increasing cases of liver cancer in China? And why the following trend analysis was merely based on the crude trends instead of the age-adjusted trends?</p> <p>Table 1. The P value column is unnecessary since 95% CIs were reported already.</p> <p>Why did the authors use different year cutoffs for different measurement? 2009 was used for prevalence, 2010 for incidence, and 2013 for mortality and DALY. It seems that these cutoffs were automatically determined by modeling. Do they have any explanations for different cutoff years?</p> <p>Line 160: The full name of the abbreviation “MI” needs to be listed.</p> <p>Conclusion:</p> <p>Line 192: Based on findings in Table 1, Rate of DALYs remained rather constant from 1997 to 2016 (AAPC: -0.1%, 95% CI: -0.4%-0.3%), which is conflicted with the statement in this line. Could the authors give any rationales about how the rate of DALYs could stay constant while incidence, mortality, and prevalence soared during the same time period?</p> <p>Also going back to Figure 1, rate of DALYs was apparently decreasing over the years after adjusting by age, which is not discussed by the authors. The authors are encouraged to have it discussed thoroughly.</p> <p>Line 202-204 and supplementary Table 5. The authors used the AAPC from 1997 to 2016 to predict the numbers in 2030 and 2050. Unless they can provide a rationale that their increase rate would remain constant for the next 30 years in China, the supplementary Table 5 projection would most like be arbitrary and unjustified.</p> <p>Supplementary table 2 and Figure 4: About Mortality to Incidence ratio, why was the ratio from 1997 to 2004 for female larger than 1?</p> <p>Line 210-215. Literatures all indicate the mortality to incidence ratio of liver cancer stay well above 0.9 globally while this study showed it to be as low as 0.76 in the more recent years in China. Do the authors have an explanation for this large gap? If like they said in the article it is due to the improvement in medical care, I’d like to know what specific kinds of technology/medication enhanced the liver cancer treatment in China so dramatically and please give some citations here.</p> <p>About gender disparities: It is well known male gender is more vulnerable to liver cancer. From figure 2, the male to female ratio of prevalence increased dramatically from 1997 to 2017, which is</p>
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	<p>almost 5 times different in 2017. The authors need to discuss more about this observation.</p> <p>Line 230: What is time period for the increase in age of diagnosis from citation [27]?</p> <p>Limitation: The authors stated that using estimated data is a major limitation in the study, so how is the estimated GBD data supposed to affect the findings in this study? Whether it would cause systematic error or non-systematic error?</p>
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REVIEWER	Wen-Chung Lee National Taiwan University, Taipei, Taiwan
REVIEW RETURNED	08-Oct-2018

GENERAL COMMENTS	<p>This paper studies disease burdens of liver cancer in China. This study involves huge number of cases. However, the analysis is too simple. The study lacks in-depth analysis regarding age effects, birth-cohort effects, geographical variations, and so on. The description of the methodologies in the paper is also too concise.</p>
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REVIEWER	Patricia Valery QIMR Berghofer Medical Research Institute Australia
REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	<p>This paper describes trends in prevalence, incidence, mortality and DALYs of liver cancer in China. The authors also describe the change in risk factors for liver cancer over time. This is a comprehensive analysis of data on liver cancer in China.</p> <p>The paper is interesting and, in general, well written. Methods are appropriate to answer the research question. Publicly available and de-identified data were used (no ethical approval required). Only minor suggestions are warranted:</p> <ul style="list-style-type: none"> - Using unnecessary and uncommon acronyms makes it difficult for readers to follow the text. My suggestion is to use MI and GBD in full. YLLs, YLDs, GHDx, and GAVI are only shown once, so there is no need to use acronyms for these. - Do not use colon after 95%CI (e.g. line 136) - Line 107 – add the reference for GHDx - Lines 193-195 – There is no need to repeat the results in the Discussion. “AAPCs of prevalence, incidence, mortality, and rate of DALYs were 4.0% (95% CI: 3.9%-4.2%),” - Lines 198-204 – new information should not be presented in the Discussion. They belong to Results. Also, do not refer to the tables/figures in the Discussion (line 241)
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Jiachen Zhou

Institution and Country: SmartNuclide Biopharma Suzhou, China

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

(1)In this manuscript, the authors conducted a secondary data analysis to investigate the trend of liver cancer in the recent 20 years in China, and reported an increase in the cancer. Overall, the interpretation of findings and discussion need to be strengthened.

Response: Thank you very much for your comments. In order to improve the quality of this manuscript, we have carefully revised the manuscript and. Please refer to the discussion section (line 214-217, 224-232, 240-245, 298-307).

Abstract:

(2)Line 33: In the methods, the authors used “collected data”. It is more accurate to use “extract” since the primary GDE data was not collected by the authors.

Response: Thank you very much for your suggestion. We have revised the related expression.

(3)Line 43. Given the AAPC of the rate of DALYs to be -0.1%, why authors called it increasing?

Response: Thank you for your comment. Although the DALYs and the rate of DALYs presented an increasing trend, with DALYs of liver cancer in China increased from 10 311 308 to 11 539 102 and the rate of DALYs from 833.52/100 000 to 851.16/100 000. Actually, the trend for the rate of DALYs evaluated by the Joinpoint regression was stable, with the AAPC of -0.1% (95% CI -0.4%-0.3%). In order to avoid causing ambiguity, we have revised the associated parts of the abstract as follows:

From 1997 to 2016, the prevalence, incidence, mortality and DALYs of liver cancer in China were from 28.22/100 000 to 60.04/100 000, from 27.33/100 000 to 41.40/100 000, from 27.40/100 000 to 31.49/100 000 and from 10 311 308 to 11 539 102, respectively. The prevalence, incidence, and mortality were increasing, with the average annual percent changes of 4.0% [95% confidence interval (CI) 3.9%-4.2%], 2.1% (95% CI 2.0%-2.2%), and 0.5% (95% CI 0.2%-0.9%), respectively. Meanwhile, the rate of DALYs was stable with the average annual percent changes of -0.1% (95% CI -0.4%-0.3%).

(4)Line 44: The term of “Mortality incidence ratio” better be changed to “mortality-to-incidence ratio”.

Response: Thank you for your instructive suggestion. We have changed the term in the abstract and also in main text.

(5)Line 45: It'd be better to report the elevated relative risk and confidence intervals instead of P-value for different risk factors. And why only reported p-value for age here, while left alone sex and viral factor?

Response: Thank you for your suggestion. The reported p-value for age and sex in former manuscript may be ambiguous in expression, so we have revised the associated parts in the abstract as follows: Males (OR: 2.98, 95% CI 2.68-3.30 for prevalence, OR: 2.45, 95% CI 2.21-2.71 for incidence) and the

elderly individuals (OR: 1.57, 95% CI 1.55-1.59 for prevalence, OR: 1.58, 95% CI 1.56-1.60 for incidence) had a higher risk. Hepatitis B accounted for the highest proportion of liver cancer cases (55.11%) and deaths (54.13%). Please refer to line 45-49.

Article summary/strengths and limitations

(6) In the section, in my opinion, no strengths were actually listed at all. The authors just mentioned the purpose of the study and the statistical method applied which are not the strengths. The authors are encouraged to reconsider what major strengths their study has.

Some more details are needed to explain, in the discussion/limitations sections if not here, why using estimated GBD data is a limitation and if it is why the authors still decided to use this data instead of some other sources.

Response: Thank you for your comment. We have revised the strengths and limitations section as follows:

- 1) A long-term period (20 years) on the trend of liver cancer burden in China was evaluated in this study.
- 2) Disease burden trends and the associated risk factors of liver cancer were quantified to reveal the extent of the epidemic and suggest potential strategies against liver cancer.
- 3) The findings might be limited by the fact that the data used in this study were secondary estimated data rather than the original epidemic or surveillance data.

In addition, though the GBD study may deviate from the real-world (data collection, model fitting and selection), as far as we know, the GBD study provides the most comprehensive and consistent data for assessments of global descriptive epidemiology (Ref: Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med* 2013;369(5):448-57).

We also have explained this in the discussion section. Please refer to line 298-307.

Introduction

(7) Line 71 the term "risk factors in vitro" may be better stated as "environmental risk factors".

Response: Thank you for your instructive suggestion. We have revised the related expression accordingly.

(8) Line 79: "in" to "between" if the authors mean the years from 2003 to 2007.

Response: Thank you for your suggestion. We were sorry that we had made a mistake. We actually want to express the years from 2003 to 2007 and so we have revised it.

Methods and Results

(9) Line 128: The number of liver cancer patients increased from 349 127 (prevalence: 28.22/100 000, AR: 129 38.64/100 000) in 1997 to 814 026 (prevalence: 60.04/100 000, AR: 53.18/100 000) in 2016. While from citation [11], Chen et al reported the number of new cases of liver cancer in China was 446 100 in 2015 (line 81). Why is the authors' number much higher than Chen's?

Response: Thank you for your comments. Chen et al. reported the incidence of liver cancer, which was calculated with new cases (446 100 in 2015). In our study, we reported the prevalence of liver cancer, which was calculated with aggregated cases (including new cases and previously diagnosed cases, 814 026 in 2016). In our study, the number of new cases was 536 178 in 2015 and 561 249 in

2016, which were both close to the number of new cases (446 100 new cases in 2015) reported by Chen et al.

Additionally, the number from Chen et al. was an estimated value based on the reported data, which was from 72 local, population-based cancer registries in China, representing 6.5% of the population. Our results were estimated from the GDB study. Though difference occurred between the numbers from Chen et al. and our results, we think the small deviation is reasonable..

(10)Figure 1: The authors did a very nice job having the trend adjusted by age. Regardless of the increasing trends in all four measures, the age-adjusted trends of incidence, mortality, and rate of DALYs were all flat, if not decreasing. Only the prevalence in the recent years was still increasing after age adjustment. The authors did not seem to explain much on this observation later on. Do the authors think the aging population explains most part of the increasing cases of liver cancer in China? And why the following trend analysis was merely based on the crude trends instead of the age-adjusted trends?

Response: Thank you for your suggestion. In this study, we adjusted the rates by using the population of 2010 in China. We have discussed in detail about the differences between crude rates and adjusted rates. We found that the age-adjusted trends of incidence, mortality, and rate of DALYs did not showed increasing, only the prevalence in the recent years was still increasing after age adjustment. Actually, the crude rates of prevalence, incidence, and mortality presented increasing trends. As the rates were adjusted by the population of 2010, the trends could be influenced due to the significant change of age structure from 1997 to 2016. We think the ageing of the population in China could contribute to the increasing disease burden of liver cancer, as those aged over 60 and over 65 were increasing in recent years. Please refer to line 240-251.

In addition, in order to describe the trends of the actual rates by each year, we presented the crude rates rather than adjusted rates because the proportion of age in the population is changing every year in real world.

(11)Table 1. The P value column is unnecessary since 95% Cis were reported already.

Response: Thank you for your suggestion. We have removed the P values column as you suggested, and rearranged Table 1. And Table 2 was also revised accordingly.

(12)Why did the authors use different year cutoffs for different measurement? 2009 was used for prevalence, 2010 for incidence, and 2013 for mortality and DALY. It seems that these cutoffs were automatically determined by modeling. Do they have any explanations for different cutoff years?

Response: Thank you for your suggestion. In this study, these cutoffs were automatically determined from the models by Joinpoint regressions as you mentioned. Though the turning points occurred at different years, the trends in prevalence, incidence, mortality and rate of DALYs were similar, with higher APCs in the later years. Due to the four measurements calculated by different methods, the turning points varied in years. Prevalence was calculated using aggregated cases (including new cases and previously diagnosed cases), incidence using new cases, mortality using dead cases and DALYs were summed by the years of life lost and the years of life lived with disability.

(13)Line 160: The full name of the abbreviation "MI" needs to be listed.

Response: Thank you for your suggestion. Because the full name of the abbreviation 'MI' was listed in previous text (Please refer to line 117), we think the abbreviation 'MI' will be more appropriate for concise expression in line 167.

Conclusion:

(14)Line 192: Based on findings in Table 1, Rate of DALYs remained rather constant from 1997 to 2016 (AAPC: -0.1%, 95% CI: -0.4%-0.3%), which is conflicted with the statement in this line. Could the authors give any rationales about how the rate of DALYs could stay constant while incidence, mortality, and prevalence soared during the same time period?

Response: Thank you for your suggestion. These expressions would cause misunderstanding in the previous manuscript and we have revised these in the discussion section accordingly. Actually, among the four measurements, only the rate of DALYs was not increasing during the last twenty years (Recently, presenting increasing with APC of 2.3% from 2013 to 2016). From 1997 to 2016, the prevalence, incidence, mortality and DALYs of liver cancer in China were from 28.22/100 000 to 60.04/100 000, from 27.33/100 000 to 41.40/100 000, from 27.40/100 000 to 31.49/100 000 and from 10 311 308 to 11 539 102, respectively. The prevalence, incidence, and mortality were increasing, with the average annual percent changes of 4.0% (95% CI 3.9%-4.2%), 2.1% (95% CI 2.0%-2.2%), and 0.5% (95% CI 0.2%-0.9%), respectively. Meanwhile, the rate of DALYs was stable with the average annual percent changes of -0.1% (95% CI -0.4%-0.3%).

In addition, we considered that rate of DALYs was influenced by the number of the years of life lost (early dead cases) and years lost due to disability, the population size (number of population was increasing in China during the observational period), success rate of treatment (survival rate increasing) and so on.

(15)Also going back to Figure 1, rate of DALYs was apparently decreasing over the years after adjusting by age, which is not discussed by the authors. The authors are encouraged to have it discussed thoroughly.

Response: Thank you for your suggestion. We have discussed the adjusted rate of DALYs together with incidence and mortality on line 240-245. Currently, all these differences between crude rates and adjusted rates for different metrics were attributed to the age structure. We found that the age-adjusted trends of incidence, mortality, and rate of DALYs did not show increasing, only the prevalence in the recent years was still increasing after age adjustment. The ageing of the population in China could contribute to the increasing disease burden of liver cancer, as those aged over 60 and over 65 were increasing in recent years.

(16)Line 202-204 and supplementary Table 5. The authors used the AAPC from 1997 to 2016 to predict the numbers in 2030 and 2050. Unless they can provide a rationale that their increase rate would remain constant for the next 30 years in China, the supplementary Table 5 projection would most likely be arbitrary and unjustified.

Response: Thank you for your instructive suggestion. We agree with these that many factors could influence the prediction numbers (the population, treatment, prevention strategies, and so on). As you suggested that the prediction covers a long period, the results may be unjustified. Our main purpose of this study was to evaluate the disease burden trend of liver cancer in China for the last two decades. This prediction results had little impact on the purpose of this article, so we decided to remove this part.

(17)Supplementary table 2 and Figure 4: About Mortality to Incidence ratio, why was the ratio from 1997 to 2004 for female larger than 1?

Response: Thank you for your comments. The mortality cases were calculated from the dead cases of new and prevalence cases by the year. Due to the added number of dead from the presence of existing patients (prevalence cases) and high mortality rate of liver cancer, the number of mortality cases could be larger than that of incidence cases, which result in the ratio of Mortality-to-Incidence larger than 1.

(18)Line 210-215. Literatures all indicate the mortality to incidence ratio of liver cancer stay well above 0.9 globally while this study showed it to be as low as 0.76 in the more recent years in China. Do the authors have an explanation for this large gap? If like they said in the article it is due to the improvement in medical care, I'd like to know what specific kinds of technology/medication enhanced the liver cancer treatment in China so dramatically and please give some citations here.

Response: Thank you for your instructive suggestion. As we mentioned in the text that the MI ratios were still high even in 2016 (0.76). We have supposed a possible reason (improvement in medical care) for the decline in MI in this manuscript. We have added some more information to support our hypothesis in the discussion section (the increasing number of liver transplant cases and the high 5-year survival rate) (Ref: ZHENG Shusen, YU Jun, ZHANG Wu. Current development of liver transplantation in China. *J Clin Hepatol* 2014;30(1):2-4). Please refer to line 215-217.

(19)About gender disparities: It is well known male gender is more vulnerable to liver cancer. From figure 2, the male to female ratio of prevalence increased dramatically from 1997 to 2017, which is almost 5 times different in 2017. The authors need to discuss more about this observation.

Response: Thank you for your comments. We have discussed the difference between males and females on the factors associated with liver cancer, such as hepatitis B infection, alcohol drinking (higher rates in males than females). And we have included some references to discuss more about these: higher positive rates of hepatitis B surface antigen (HBsAg) were found in males than in females from multiple serological surveys across China, and the male-to-female ratios of HBsAg positive rate showed increasing (10.30% vs. 7.29% in 1979 and 8.6% vs. 5.7% in 2006) . Males also had higher rates of drinking and alcohol consumption than females. The male-to-female ratios of drinking (61.3% vs. 11.6% in 1993 and 38.3% vs. 8.1% in 2006) and alcohol intake (28.0 g/d vs. 12.9 g/d in 1997 and 33.1 g/d vs. 13.1 g/d in 2006) both showed increasing in adults. The above evidences could strengthen the explanations on the increasing male-to-female ratios among all metrics in this study. Please refer to line 224-232.

(20)Line 230: What is time period for the increase in age of diagnosis from citation [27]?

Response: Thank you for your suggestion. We have added the time period ('from 1989 to 2008') in the text.

Limitation:

(21)The authors stated that using estimated data is a major limitation in the study, so how is the estimated GBD data supposed to affect the findings in this study? Whether it would cause systematic error or non-systematic error?

Response: Thank you for your suggestion. In this study, the findings might be limited by the fact that the data used in this study were secondary estimated data and not the original data based on epidemiological or surveillance study. However, the estimated data from the Global Burden of Diseases was used in the study, as the GBD 2016 provides the most comprehensive and consistent data for assessments of global descriptive epidemiology (Ref: Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med* 2013;369(5):448-57). Actually, we believe that the using of multiple sources minimises the possibility of erroneous trends.

Reviewer: 2

Reviewer Name: Wen-Chung Lee

Institution and Country: National Taiwan University, Taipei, Taiwan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

(1)This paper studies disease burdens of liver cancer in China. This study involves huge number of cases. However, the analysis is too simple. The study lacks in-depth analysis regarding age effects, birth-cohort effects, geographical variations, and so on.

Response: Thank you for your comments. Actually, disease burdens of liver cancer were influenced by many factors, including age effects, birth-cohort effects and geographical variations. In this study, we have made some primary analysis on the influencing factors of liver cancer. We found that males (OR: 2.98, 95% CI 2.68-3.30 for prevalence, OR: 2.45, 95% CI 2.21-2.71 for incidence) and the elderly individuals (OR: 1.57, 95% CI 1.55-1.59 for prevalence, OR: 1.58, 95% CI 1.56-1.60 for incidence) had a higher risk. Hepatitis B accounted for the highest proportion of liver cancer cases (55.11%) and deaths (54.13%). We have also addressed the factor of age in the discussion section. The ageing of the population in China could contribute to the increasing disease burden of liver cancer, as those aged over 60 and over 65 were increasing in recent years.

However, this study was an observational designed study, and data included in this study were extracted from the GBD study. The main purpose of this study focused on the disease burden trend of liver cancer in China for the last two decades. As the variables in the database were limited, further analysis on birth-cohort, geographical were not carried out. We have described it in the limitation section.

(2)The description of the methodologies in the paper is also too concise.

Response: Thank you for your comments. In order to understand methodologies more clearly, we have made a detailed description in the methods section, especially, we added the algorithm of Joinpoint regression and the definition of prevalence, incidence, mortality and DALYs. We hope the revised expression would be more adequate. Please refer to these in the method section (line 111-114, 125-128).

Reviewer: 3

Reviewer Name: Patricia Valery

Institution and Country: QIMR Berghofer Medical Research Institute, Australia

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

This paper describes trends in prevalence, incidence, mortality and DALYs of liver cancer in China. The authors also describe the change in risk factors for liver cancer over time. This is a comprehensive analysis of data on liver cancer in China. The paper is interesting and, in general, well written. Methods are appropriate to answer the research question. Publicly available and de-identified data were used (no ethical approval required). Only minor suggestions are warranted:

(1)-Using unnecessary and uncommon acronyms makes it difficult for readers to follow the text. My suggestion is to use MI and GBD in full. YLLs, YLDs, GHDx, and GAVI are only shown once, so there is no need to use acronyms for these.

Response: Thank you for your suggestion. For acronyms such as MI, GBD and DALYs appeared many times in the text, we listed as full names in the first time and the acronyms forms later in the text

to make the article concise. For the acronyms which only appeared once in the text, such as YLLs, YLDs, GHDx and GAVI, we have removed the acronyms from the text as your suggested.

(2)-Do not use colon after 95%CI (e.g. line 136)

Response: Thank you for your suggestion. We have modified the all relevant parts through the manuscript.

(3)-Line 107 – add the reference for GHDx

Response: Thank you for your suggestion. We have added the missing reference.

(4)-Lines 193-195 – There is no need to repeat the results in the Discussion. “AAPCs of prevalence, incidence, mortality, and rate of DALYs were 4.0% (95% CI: 3.9%-4.2%),”

Response: Thank you for your instructive suggestion. According to your suggestion, we have removed the associated content.

(5)-Lines 198-204 – new information should not be presented in the Discussion. They belong to Results. Also, do not refer to the tables/figures in the Discussion (line 241)

Response: Thank you for your instructive suggestion. Many factors could influence the prediction numbers (the population, treatment, prevention strategies, and so on) and the prediction covers a long period, so the results may be unjustified. Our main purpose of this study was to evaluate the disease burden trend of liver cancer in China. This prediction results had little impact on the purpose of this article, so we decided to remove this part (new information).

In addition, we have removed the referred tables/figures in the discussion accordingly.

VERSION 2 – REVIEW

REVIEWER	Jiachen Zhou SmartNuclide Biopharma Suzhou, China
REVIEW RETURNED	08-Dec-2018

GENERAL COMMENTS	The author's response well addressed the questions raised by the editor and the reviewers. I have no more questions and thus recommend it for publication.
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