Dear Dr. Yang

Thank you for your correspondence regarding our manuscript entitled “Impact of County-level Gastroenterologist and Colorectal Surgeon Density On Colorectal Cancer Mortality in the United States.” We appreciate the opportunity to make revisions and respond to the reviewers’ comment in bold typeface.

Reviewer 1:

Major revision

This is an interesting paper reporting a negative association between numbers of gastroenterologists and colorectal cancer (CRC) mortality at geographic level (counties in the US). The major comment which arises is the potential for confounding in ecological studies such as this. In particular, a major driver of mortality from the disease is incidence. Do the authors have access to county-level data on incidence of CRC? What happens to the results if incidence is taken account of? If they do not have access to incidence data, this should at least be discussed.

We agree to this, however we don’t have access to data on county-level incidence of CRC and most importantly stage specific incidence rate. We acknowledge in the last paragraph of the comments section the need to account for these in further studies.

2. The method of statistical analysis was linear regression. If the authors have access to numbers of cases and population at risk, a more appropriate analysis is poisson regression. If they do not have such access, at least a sensitivity analysis using log-transformed mortality rates would add further confidence in the results.

Our choice of linear regression was because we didn’t have access to cases and population at risk. This ruled out poisson or negative binomial. The SEER provided us with county level age adjusted mortality rates and fortunately this was found to be normally distributed in the population making linear regression ideal. This therefore makes log transformation unnecessary.

3. In Table 2, the second column is not CRC mortality but the regression coefficient for effect on CRC mortality. This should be corrected.

We have duly amended to table to reflect that.

4. Also in Table two, both univariate unadjusted and multivariate adjusted regression results should be reported.

We have duly amended the table to reflect this.
We acknowledge this in our discussion as the concept of ecological fallacy. We state “The results of this study should be interpreted bearing in mind all limitations inherent in ecological studies. It is noteworthy that no causal inferences can be made and that generalizing results to individual patients risks committing an ecological fallacy”

Reviewer 2:
Major revision

There is a vast amount of published work suggesting that higher cancer resection case load results in better outcomes (i.e., surgeons and institutions that operate more get better results), therefore you may expect that counties with higher surgeon density (and therefore fewer cases per surgeon) will give poorer results (although this paper covers screening gastroenterologists also). This relationship is not linear and this is not surprising, however this paper makes no reference to if the cancer incidence is equal throughout the counties something which would have a large impact on this observation.

We acknowledge our limitation for not accounting for incidence data and call for further studies to specifically look at stage specific incidence rates.

Overall, this paper seems like retrospective data analysis of a large database trying and pick out some associations with no valid rationale.

The reference group is counties with no gastroenterologists/surgeons giving a mortality of 0 per 100,000 which would never be the case- based on this it is unclear whether they have worked out odds ratios (therefore the reference should be 1) or relative risk?

The main outcome is age-adjusted mortality rate and we look for associations between this and the densities for gastroenterologist/surgeons. We use linear regression not logistic because our outcome is a continuous variable which precludes us from reporting odds ratios. The results are interpreted as a unit increase/decrease in mortality rate as stated in the results section. For the specialist densities we

The denominator population should be of colorectal cancer cases rather than general population.

We acknowledge our limitation of not capturing colorectal cancer cases as the denominator as such data is currently not available. However we believe this is an important step to formulate hypotheses, engender discussions and offer opportunities for further studies to investigate geographic disparities in the distribution of gastroenterologists and general surgeons and colorectal cancer mortality in the United States.

There are numerous factors that have not been controlled for e.g., tumour stage, background incidence, medical comorbidities etc. and this needs to be addressed.
We acknowledge these are important and recommend further studies to investigate them. As of now we do not have access to county-specific data on these variable which could confound the associations observed.

The risk reductions based on high school and insurance status are very small and do not lend themselves to concluding statements.

We agree to this.

Please ensure that terminology remains consistent throughout the paper.

We recognize this and have made the necessary changes.

Reviewer 3:

Minor revision

Gastroenterologists and general surgeons are potential care providers for colorectal cancer screening and treatment. This study has investigated the association between county-level density of these two clinical specialist groups and colorectal cancer mortality rates in 2608 out of 3220 counties in the United States. The study has suggested an association between the county-level densities of gastroenterologists and general surgeons, and the colorectal cancer mortality rates. The authors have clearly stated that no causal inferences can be made. Many issues in the study that may affect drawing firm conclusions have been discussed by the authors in the Comments section. However, providing more details on the analyses and the results, as outlined in the following may be of help to support the conclusions.

The population age structure of different counties may vary considerably. The recommended age for colorectal cancer screening is ages between 50 and 75. In addition, most colorectal cancers occur in adults over the age of 50. It would be more relevant for the evaluation of the influence of accessing to colorectal cancer screening and treatment if the calculations of the county-level densities of gastroenterologists and general surgeons were based on the adult population aged 50 and over rather than the whole population of all ages.

This is a very interesting observation. In our analysis we used the Area Resource file with county specific population estimates and considered the population 50 and above as possible denominator for the density of specialist since this would better represent the at-risk population. The ARF reported age stratified population estimates for 1990 and 2000 and the categories used would have made it impossible to isolate the population between 50-75 years. Due to difficulties in isolating this age group from the ARF and outdated nature of such data we made an assumption that the population age structure across counties were similar, which may not necessarily be true. This enabled us to use 2006 and 2008 population estimates which are relatively current.

In the Results section, it was stated that "an increase of 1 gastroenterologist per 100,000 people was associated with a 13.9% (95%CI 5.50-22.4) reduction in CRC mortality". In another occasion, the same result was described as 13.9% (95%CI 5.50%-22.4%). I am not clear whether 13.9 was the coefficient. If it was not, then how 13.9% was calculated from the coefficient?
The 13.9% was the coefficient when the density of gastroenterologist variable was treated as continuous. We commented in the methods section, that we treated Physician density variable separately as continuous and categorical.

The gastroenterologist density was a continuous variable which was divided into four categories, 0, 0.1-1.5, 1.51-3.0 and >3.0. The baseline category is counties without a gastroenterologist. It would be useful to know how the variable was divided up and how many counties were in each of these density categories. In one occasion, the density category “1.51-3.0” per 100,000 people was described as “1.6-3.0” instead.

We have made the necessary changes

The same comments for gastroenterologist density are applicable for general surgeon density analyses. Furthermore, the categories used in the analyses were different from the categories used in county distribution map in Figure 1. For example, the categories for the general surgeon density per 100,000 in the analyses were 0, 0.1-5.0, 5.1-10.0, 10.1-15.0, and >15.0. While the categories in the mapping in Figure 1 were 0, 0-5.8, 5.9-10.0, and >10.1.

Primary care physicians were also considered as care providers in the clinical pathways of colorectal cancer screening and treatment. In the method section of this study, the density of primary care physician per 100,000 people across counties was also calculated but no report on the analysis findings in the Results section. Although it was mentioned in the Comments section that no association was observed between primary care physicians and colorectal cancer mortality. It was not clear whether this was based on this study or other studies.

Our analysis showed that no association between primary care physician and colorectal cancer mortality. This paper looked at whether any association between county level colorectal cancer mortality and the provider density as well as other county level socio-economic factors. In the methods section we describe variables that were tried in the multivariate model. We used a backward stepwise method and only variables with p<0.1 were included. Primary care physician density were found not to be associated with colorectal cancer mortality.

The title of Table 2 should include a specification of “multivariate linear regression analyses”. It would also be useful to report in the Results section the adjusted R square to give readers an indication on the proportion of variability in colorectal cancer mortality rates across the counties can be explained by the predictors included in Table 2. The adjusted R square results could also indicate whether other researchers should consider other potential predictors that may influence the mortality rate variations.

We have dully added the adjusted R square to Table 2 as suggested.

Under methods, the statement “as well as the number of physicians per specialty working in a county” was duplicated with the same statement in the previous sentence.

Under Background in the Abstract, “it” should be “its”.

We have dully made the necessary changes.
Reviewer 4:

Minor revision

The paper is an interesting ecological study of the association between gastroenterologist and general Surgeon densities and colorectal cancer mortality, carried out in several US counties. The aim of this work is appreciably original, given that a few number of studies assessed issues related to the access to care and the paucity of health professionals, as also stated by the Authors.

Suggestions:

1) The range of density categories is different for surgeons and gastroenterologists. I think the Authors have split these data into categories using quartiles (or something similar), and I also think that this information should be added.

2) No data were available for some county. Is this lack of information entirely random or counties with no data possibly differ from the others for significant features, that could introduce a selection bias? Reading the text I thought that the lack of data is random, but this should be clearly stated in the text.

We assumed that missing data occurred randomly and changes have been made in the methods section to reflect this

3) In the Authors opinion, is there any other factor (e.g. occupational exposures) that could explain difference in mortality among counties? If something similar is present, further studies would address the issue of access to care in high-exposed populations.

We think this is an important point, however our data is unable help us determine these. We agree further studies could be done to evaluate the contribution of environmental exposure to our observation.

4) Is there any difference in regression analysis if countries are divided in to two groups by their high or low CRC mortality? In others words, by dividing counties in two groups based on their CRC mortality to carry out two regression analyses, could be found any difference in those results? Given that this paper suggests to improve the access to care, it could be of interest, for instance, to know if to start from high CRC mortality countries would be an effective and useful approach to intervention.

After dividing counties into two (above and below the median mortality rate (17.4) we observed similar associations between county level mortality and the density of physicians across these two groups. An acceptable definition for low and hign CRC mortality counties would be an interesting starting point to look at interventions.

Details:

Pag. 9, line 9: “Figure 3” needs ()

Table 2: Column 2, Title: 100.000 should be 100,000

We have dully made the necessary corrections.