Reviewer 1

Dear author, maybe for the purity of the experiment you had to compare the data on colorectal cancer in those countries where there is a national colorectal cancer screening program? In Central Asia, screening is available only in Kazakhstan. And compare your data with our data in our article. https://www.e-ce.org/journal/view.php?doi=10.5946/ce.2019.198

We appreciate your helpful review, which helped us improve the manuscript. Based on your comments and suggestions, we have revised the manuscript, which were showed in the revised paper. Our point-by-point responses are given below. We hope that the revisions make the manuscript easier to follow. Thank you again for your generous help!

We have modified the Discussion(Line 421-424) as follows:

For example, in Kazakhstan, a Central Asian country, after the implementation of the CRC screening program, the incidence rate of residents over 70 years old has increased by 16.0 per 100,000, while that of the 65-69 age group has increased by 23.3 per 100,000[30].

Ref.30 Zhylkaidarova A, Kaidarova D, Batyrbekov K, et al. Trends of Colorectal Cancer Prevalence in Kazakhstan Related to Screening. Clin Endosc,2021,54(1):32-37.

Reviewer 2

this is an excellent article. is it easy to estimate the burden of eating processed meat on colorectal cancer in all these countries? How do you exclude other risk factors for the development of colorectal neoplasia, and what is the incidence of other malignancies in the GIT that also increase. Is there a role for national colorectal cancer screening program in this work.

We appreciate your helpful review, which helped us improve the manuscript. Based on your comments and suggestions, we have revised the manuscript, which were showed in the revised paper. Our point-by-point responses are given below. We hope that the revisions make the manuscript easier to follow. Thank you again for your generous help!

1,Minor language polishing

Response:

We had modified the Abstraction(Lin 41-81), Introduction(line83-118) and Discussion(Line 421-424).

2,is it easy to estimate the burden of eating processed meat on colorectal cancer in all these countries?

Response:

The Global Burden of Disease (GBD) provides a tool to quantify health loss from hundreds of diseases, injuries, and risk factors, so that health systems can be improved and disparities can be eliminated. Institute for Health Metrics and Evaluation(IHME) has created a suite of interactive data visualizations that allow people to make sense of the over 1 billion data points generated.The GBD study is collected and analyzed by a consortium of more than 9,000 researchers in 162 countries and territories. The data capture premature death and disability from 370 diseases and injuries in 204 countries and territories, by age and sex, from 1990 to the present. The GBD's flexible design allows it to be used at the global, national, and local levels to understand health trends over time.And multiple authoritative studies have also predicted and analyzed the development trends of related diseases in different regions based on this database, receiving widespread recognition from journals and peers (Ref 17:GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet, 2020, 396(10258):1223-1249;Ref 18:GBD 2019 Diseases and Injuries Collaborators.Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet, 2020, 396(10258):1204-1222).

3,How do you exclude other risk factors for the development of colorectal neoplasia, and what is the incidence of other malignancies in the GIT that also increase.

Response:

As the GBD 2019 Risk Factors Collaborator indicated in Lancet(2020, 396(10258):1223-1249.):

This method for analyzing the contribution of a single factor to the burden of a certain disease has six analytical steps. (1) We included 560 risk–outcome pairs that met criteria for convincing or probable evidence on the basis of research studies. 12 risk–outcome pairs included in GBD 2017 no longer met inclusion criteria and 47 risk–outcome pairs for risks already included in GBD 2017 were added based on new evidence. (2) Relative risks were estimated as a function of exposure based on published systematic reviews, 81 systematic reviews done for GBD 2019, and meta-regression. (3) Levels of exposure in each age-sex-location-year included in the study were estimated based on all available data sources using spatiotemporal Gaussian process regression, DisMod-MR 2.1, a Bayesian meta-regression method, or alternative methods. (4) We determined, from published trials or cohort studies, the level of exposure associated with minimum risk, called the theoretical minimum risk exposure level. (5) Attributable deaths, YLLs, YLDs, and DALYs were computed by multiplying population attributable fractions (PAFs) by the relevant outcome quantity for each age-sex-location-year. (6) PAFs and attributable burden for combinations of risk factors were estimated taking into

account mediation of different risk factors through other risk factors. Across all six analytical steps, 30 652 distinct data sources were used in the analysis. Uncertainty in each step of the analysis was propagated into the final estimates of attributable burden.
Therefore, GBD 2019 study can estimate the PAFs and attributable burden of risk factors, including Smoking,Diet low in whole grains,Diet low in milk,Diet high in red meat,Diet high in processed meat,Diet low in fiber and Diet low in calcium.

4,Is there a role for national colorectal cancer screening program in this work.

Response:

The national CRC screening program indeed plays an important role in estimating the burden of CRC. As a member of the GBD collaborative group （ ***Li Xiaopan*** ， **Contact ID**:***0034o00001nuq4ZAAQ***), the corresponding author is one of the leaders of the cCRC screening program in Shanghai, China. Previously published articles comprehensively analyzed the impact of CRC programs on the CRC incidence, mortality, and survival rate(Ref. 1-3), and GBD research was based on these articles and data for estimation, Therefore, the impact of CRC is included in the study. For example, Kazakhstan in Central Asia carried out cCRCr screening in 2011. The incidence rate increased significantly before and after the screening, the late rate decreased significantly, and the disease burden changed significantly. In this paper, the mortality, early death rate, and DALYs in Kazakhstan decreased significantly from 2010 to 2019, in line with the local actual situation(Ref.4).

And we had indicated in the Introcution(Line96-99) that this work is conducted to better promote population screening:It is crucial to clarify the contribution of risk factors to the burden of CRC in developing countries with rapid aging rates to enhance regional cooperation, strengthen control of risk factors, and develop effective intervention measures for cancer screenings.

Ref.1 Li X#, Zhou Y#, Luo Z#, Gu Y, Chen Y, Yang C, Wang J, Xiao S, Sun Q, Qian M, Zhao G*. The impact of screening on the survival of colorectal cancer in Shanghai, China: a population based study[J]. BMC Public Health 2019, 19(1):1016.

Ref.2 Li X#, Qian M#, Zhao G, Yang C, Bao P, Chen Y, Zhou X, Yan B, Wang Y, Zhang J, Sun Q. The performance of a community-based colorectal cancer screening program: Evidence from Shanghai Pudong New Area, China[J]. Prev Med 2019, 118:243-250.

Ref.3 Li XP#, Chen HM#, Lei XH, Dou GS, Chen YC, Chen LP, Zhang Y, Zhao GM, Zhong W: Cost-effectiveness analysis of a community-based colorectal cancer screening program in Shanghai, China[J]. J Dig Dis 2021, 22(8):452-462.

Ref.4 Zhylkaidarova A, Kaidarova D, Batyrbekov K, et al. Trends of Colorectal Cancer Prevalence in Kazakhstan Related to Screening. Clin Endosc,2021,54(1):32-37.

This is a study focussing on meat consumption and a decrease in colon cancer. There has been an increase in colon cancer screening in some of the countries. In the conclusion, please comment on thebenefit of colon cancer screening in reducing the incidence of colon cancer.

We added the comment on "the benefit of colon cancer screening in reducing the incidence of colon cancer" in the fifth paragraph of the Discussion (Page 14,Line 12-19) as follows: The Decrease in CRC incidence of some developed countries has been attribute to screening, which can detect polyps that can be removed before they become cancerous. Therefore, future attention should be focused on the many regions with a growing and aging population and an increasingly westernized lifestyle[2]. For example, a CRC screening program using the fecal immunochemical test was recently piloted in Thailand and China Shanghai, proved that CRC screening is also effective in controlling the rising CRC incidence rate in the “B and R” countries[50,51]. Ref. 50 Khuhaprema T, Sangrajrang S, Lalitwongsa S, Chokvanitphong V, Raunroadroong T, Ratanachu-Ek T, Muwonge R, Lucas E, Wild C, Sankaranarayanan R. Organised colorectal cancer screening in Lampang Province, Thailand: preliminary results from a pilot implementation programme. BMJ Open 2014;4(1):e003671 [PMID: 24435889 DOI: 10.1136/bmjopen-2013-003671] 51 Li X, Qian M, Zhao G, Yang C, Bao P, Chen Y, Zhou X, Yan B, Wang Y, Zhang J, Sun Q. The performance of a community-based colorectal cancer screening program: Evidence from Shanghai Pudong New Area, China. Prev Med 2019;118:243-250 [PMID: 30412744 DOI: 10.1016/j.ypmed.2018.11.002]