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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13307-review.doc).

Title: Association of cholesterol with risk of pancreatic cancer: a meta-analysis

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) What drugs are commonly used for anti-cholesterol, and how they are impact on pancreatic cancer?

Statins and bile acid sequestrants are commonly prescribed medications that effectively reduce cholesterol levels. We searched studies on the association between bile acid sequestrants, statins and the risk of pancreatic cancer. No relevant study on the association between bile acid sequestrants and the risk of pancreatic cancer was found. Under daily doses for cardiovascular event prevention, there was no association between statins and pancreatic cancer risk. (Cui X, *Cancer causes & control* 2012; **23**: 1099-1111)

(2) For the association between dietary cholesterol and pancreatic cancer, the strength of the association is on the case-control study, how do you exclude the possibility of recall bias?

Yes. Results from case-control studies are susceptible to recall bias, thus prospective cohort

studies that do not suffer from recall bias are believed to provide better evidence. However, only 4 cohort studies were included in this meta-analysis. Therefore, further cohorts studies are warranted to confirm this association. In addition, patients might change their dietary habits after their diagnosis of pancreatic cancer; however, in most case-control studies included in this meta-analysis, the investigators collected the dietary information of participants at least 1 year before the interview. As we all know pancreatic cancer is relatively rare, so the case-control study design is appropriate to identify an adequate number of patients to provide a large sample size within a reasonable time frame. We discussed this comment further in this revision.

(3) As a common cause, high blood glucose is related to high cholesterol, and a risk factor for pancreatic cancer as well. To remove the residual effect of high blood glucose, a sensitivity analysis on studies with the fully adjustments, including diabetes?

Cholesterol intake has been positively associated with diabetes mellitus. (Tajima R, *Clinical nutrition* 2014; pii: S0261-5614(14)00074-0). Diabetes mellitus is associated with an increased risk of pancreatic cancer. (Huxley R, *British journal of cancer* 2005; **92**: 2076-2083). Therefore, diabetes mellitus could be an intermediate rather than a confounding factor, and adjusting for diabetes may distort the observed associations. (Nothlings U, *Journal of the National Cancer Institute* 2005; **97**: 1458-1465).

(4) More clearly underlying mechanism of cholesterol on pancreatic cancer. Descript differences between dietary cholesterol and serum total cholesterol.

We have revised the second paragraph of the discussion section in our manuscript as follow. The exact mechanism whereby high total cholesterol levels could lead to an increased risk of pancreatic cancer is unclear. There are several theories to explain the possible role of cholesterol in pancreatic cancer. Increased level of serum TC is related to increased levels of proinflammatory cytokines. (Feingold KR, *Diabetes* 1990; **39**: 1569-1574; Haddy N, *Atherosclerosis* 2003; **170**: 277-283; Hardardottir I, *Current opinion in lipidology* 1994; **5**: 207-215) Longstanding pre-existing chronic pancreatitis is a strong risk factor for pancreatic cancer. (Raimondi S, *Best practice & research Clinical gastroenterology* 2010; **24**: 349-358)

Moreover, dietary cholesterol may affect bile excretion. This may cause bile reflux into the head of the pancreas via the common duct, where most tumors occur. (Mack TM, *Journal of the National Cancer Institute* 1986; **76**: 49-60; Baghurst PA, *Am J Epidemiol* 1991; **134**: 167-179)

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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