

30th June 2016

Dear Editor,

**Title:** Role of bile acids in carcinogenesis of pancreatic cancer: an old topic with new perspective

**ESPS Manuscript NO:** 26443

Thanks for revising the manuscript. Improvements have been made based on the suggestions of reviewers.

**Responses to the Reviewer #3576082**

**Comment:** The manuscript is well written an interesting review that describes the main metabolic and cell signaling pathways that bile acids induce when are in contact with pancreatic cells and can produce a pancreatic damage such as pancreatitis and pancreatic cancer. This MS considers the effect of bile acids over some pancreatic cancer risk factor such as alcohol intake, smoking, diet, obesity, diabetes and hypertriglyceridemia among others.

**Response:** Thank you very much for your advice. We reviews role of bile acids in metabolic disorders and cancers, with a conclusion that bile acids have systemic effect and local tissue effects on pancreatic duct adenocarcinoma initiation. The review provide a hint to researchers of many kinds of cancer related to high fat/meat diet or western lifestyle, such as breast cancer, prostate cancer, colon cancer, and so forth. Because these kinds of cancer may closely related to bile acids dysregulation. Animal studies and clinical studies are needed for further validation.

**Responses to the Reviewer #3576087**

**Comment 1:** The authors demonstrated that the composition and concentration of bile acids are critical factors for the biological role of bile acids in cancer. The authors supported this evidence by reviewing some in vitro studies using pancreatic cancer cell lines, however, no clinical data has been shown. Are there any clinical studies that demonstrate the effect of bile acids in human pancreatic cancer?

**Response:** We concluded that the concentration of bile acids is a crucial factor in cancers. It is a very good idea to find out some clinical data to support our conclusion. We tried to found out the profile of bile acids in pancreatic cancer. There should be some studies on bile acid concentration in pancreatic cancer patient with jaundice. Because patients with obstructive jaundice usually need to undergo biliary drainage. It is easy to identify the composition of bile acid in these patients. But unfortunately, we fail to find out some related clinical data. And then we turned to find out the profile of bile acids in chronic pancreatitis, which is closely related to pancreatic cancer initiation. We found some animal models of pancreatitis. In setting up acute pancreatitis animal models, bile acid retrograde infusion is often introduced. High concentration

of bile acids will lead to pancreatic acinar cell injury and acute necrotic pancreatitis, but not chronic pancreatitis. No study revealed the concentration of bile acid in induction of chronic pancreatitis. It is what we should be dedicated to address in future studies. At this point, we think it is reasonable to conclude that concentration of bile acids is important in learning the role of bile acids on cancer carcinogenesis.

**Comment 2:** There are some grammatical errors and typos found in the manuscript. A reviewer requires English proofreading by a native English speaker.

**Response:** We are sorry for the substandard English used and the misspellings made in the manuscript. We have carefully revised the manuscript and have language polished by native English speakers at the same time.

Thank you for your consideration.

Best regards,  
Yangchao Chen