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Response to the letter by Lai et al. regarding our manuscript "Statin use and pancreatic cancer risk in two prospective cohort studies"

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We appreciate the comments by Dr. Lai and colleagues on our article [1]. Despite plausible anti-tumor effects of statins, epidemiological studies suggest that statins may only elicit modest suppressive effect on pancreatic carcinogenesis. As noted by Lai et al., preventive effects of statins on pancreatic carcinogenesis could theoretically be confined to individuals at higher risk of pancreatic cancer, such as those with established risk factors (e.g., diabetes, smoking, adiposity). However, our data did not support effect modifications for the association of statin use with pancreatic cancer risk by those factors. Given anti-inflammatory properties of statins, patients with long-term inflammation in the pancreas

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may be more likely to benefit from these medications. Unfortunately, we could not assess this possibility, as data on chronic pancreatitis were not available in the cohorts utilized in our analysis.

Molecular pathological epidemiology has emerged as an integrative research field that considers intertumor variations in molecular and pathological signatures, thereby refining effect estimates of exposures for specific tumor subtypes [2]. This analytical framework has been recently applied for epidemiological research on pancreatic cancer incidence. For example, Oyama H, et al. examined distinct carcinoma types arising among patients with intraductal papillary mucinous neoplasm (IPMN) and demonstrated different risk factor profiles between IPMN-derived and non-IPMN-related carcinomas [3]. Statins potentially suppress downstream proteins of the mevalonate pathway including RAS and the Rho protein family. In colorectal cancer, the association of statin use with the incidence might differ by *KRAS* mutation status [4]. Importantly, *KRAS* mutation is the most common driver for the initiation of intraepithelial neoplastic changes in the pancreas. Although this mutation occurs in the vast majority of pancreatic ductal adenocarcinomas, tumor characteristics may differ by specific patterns of *KRAS* mutations [5]. Therefore, considering *KRAS* mutation status in pancreatic cancer may not only provide population-based evidence on molecular mechanism of tumor-suppressive effects of statins, but also open opportunities for chemoprevention against pancreatic cancer. In summary, despite the null findings in our study, further investigation is warranted considering variations in risk profiles of baseline populations as well as molecular and pathological features of pancreatic carcinomas.

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Abbreviations:

IPMN	intraductal papillary mucinous neoplasm

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