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LETTER TO THE EDITOR

Increased risk of pancreatic cancer after acute pancreatitis: A meta-analysis of prospective cohort studies

What is already known on this subject?

Some animal model studies suggest that acute pancreatitis can induce pancreatic cancer. However, results from epidemiological studies are inconsistent or even conflicting.

What are the new findings?

Our meta-analysis demonstrates a strong association between acute pancreatitis and pancreatic cancer. Patients with acute pancreatitis history have an increased risk of pancreatic cancer compared with the general subjects.

How might it impact on clinical practice in the foreseeable future?

Pancreatic cancer prevention and screening should be considered among patients with acute pancreatitis history.

Pancreatic cancer is a major cause of cancer-related death in men and women worldwide [1]. Many patients' condition become incurable at the time of diagnosis because it is difficult to diagnose early [1]. Therefore, prevention and early diagnosis is essential to improve the survival of pancreatic cancer. Some risk factors have been identified including smoking [2], diabetes [3] and chronic pancreatitis [4]. Since developing into chronic pancreatitis is not uncommon among patients with acute pancreatitis, it is plausible that acute pancreatitis may also be a risk factor of pancreatic cancer. In addition, some animal model studies suggest that acute pancreatitis can induce pancreatic cancer [5,6]. However, results from epidemiological studies are inconsistent or even conflicting [7,8]. Therefore, we conducted the meta-analysis of prospective cohort studies to evaluate the association between acute pancreatitis and pancreatic cancer.

Two investigators independently reviewed published studies in PUBMED and EMBASE databases from their inception to May 2018 using the following combined text and MeSH heading search strategy that included the terms for 'acute pancreatitis', 'pancreatic cancer' and 'cohort studies' or 'follow-up studies'. A manual search for additional studies using references of selected retrieved articles was also performed to identify other possible articles. No limitation on language was applied.

Studies were included if they met the following inclusion criteria:

- cohort study;
- the type of pancreatitis was 'acute' pancreatitis and subjects in the control group had no pancreatitis history;
- risk ratio (RR) or equivalents with 95% CI was provided.

We excluded animal studies, clinical trials, cross-sectional studies, case-control studies, reviews, commentaries, and letters.

Data extraction was performed independently by two reviewers, using a predefined data extract form. Disagreement was resolved by discussion among all investigators. Information on study characteristics, participants' characteristics, exposure and outcomes were extracted. The analysis was performed using Review Manager 5.3 software. When the heterogeneity was low among studies ($I^2 < 50\%$), a fixed-effects model was used. Otherwise, a random-effects model was deployed.

Of potentially 195 relevant published studies, 191 were excluded, because of duplication ($n = 38$), article types including two case-control studies [7,9] ($n = 69$) or because the title and abstract did not meet the inclusion criteria ($n = 82$). Subsequently, 2 articles were excluded because there were no control group [8,10]. Finally, four cohort studies [11—14] met all inclusion criteria.

In these studies, male patients with acute pancreatitis accounted for a larger part with mean age of over 50 [11—13]. Overall, the follow-up duration was approximately more than 5 years [11—13]. But only 2 studies reported estimates of association at different follow-up times [11,13].

Four prospective cohort studies with 5412 patients in the acute pancreatitis group and 1,303,408 subjects in the control group were included in the analysis to assess

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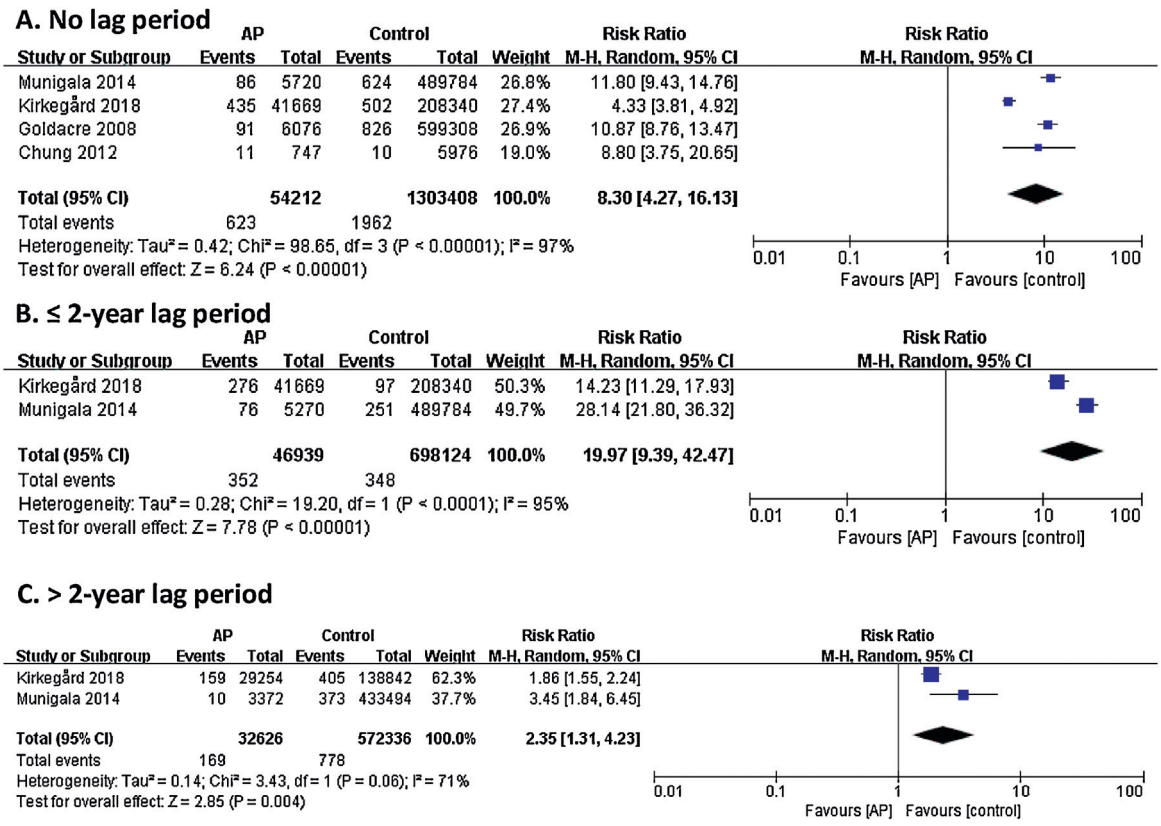

Figure 1 Forest plots of risk of pancreatic cancer with acute pancreatitis vs. control, stratified by follow-up time. A. No lag period. B. ≤ 2-year lag period. C. > 2-year lag period.

the association between acute pancreatitis and pancreatic cancer. The pooled RR was 8.30 (95% CI: 4.27—16.13, $P < 0.00001$) with random-effects model (Fig. 1). Then, two studies were included to explore the time effect in the association between acute pancreatitis and pancreatic cancer. In 2-year lag period, the pooled RR was 19.97 (95% CI: 9.39—42.27, $P < 0.00001$). After 2 years, the pooled RR turned into 2.35 (95% CI: 1.31—4.23, $P = 0.004$).

Our study is the first meta-analysis, conducted to summarize all cohort studies presently available, demonstrates a strong association between acute pancreatitis and pancreatic cancer. The pooled RR shows acute pancreatitis is associated with increased risk of pancreatic cancer and can be regarded as a risk factor for pancreatic cancer. Interestingly, the pooled RR of over 2-year lag period is quite smaller than that of no lag period or under 2-year lag period (2.35 vs. 8.30 or 19.97). Some previous studies investigating the association of acute pancreatitis and pancreatic cancer did not report risk estimates by follow-up time [7,9]. However, it is necessary to do such estimates by time, as pancreatic cancer usually develops and evolves over several years [15]. If the pancreatic cancer is observed shortly after the start of acute pancreatitis follow-up, acute pancreatitis would be less likely to be a causal factor. Our meta-analysis provides estimates of association at different follow-up times. After 2 years, there is still an over twofold (2.35) increased risk of pancreatic cancer among patients with acute pancreatitis, which is consistent with other studies [7,13,14].

Conclusion

Patients with acute pancreatitis history have an increased risk of pancreatic cancer compared with the general subjects. Pancreatic cancer prevention and screening should be considered among this population.

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Disclosure of interest

The authors declare that they have no competing interest.

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