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Reassessing the Risk of Pancreatitis With Alcohol

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The relationship between heavy alcohol consumption, regardless of type, and acute and chronic pancreatitis is well established. A clear association is consistently demonstrated.^{1,2} Whether lower amounts or social drinking influence this susceptibility is less clear. Alcohol consumption even at low or moderate levels (<50 grams a day) is associated with progression from acute to chronic pancreatitis³ and can alter the natural course of chronic pancreatitis.⁴ After the onset of alcohol-related acute pancreatitis, reducing consumption or total abstinence decreases the risk of recurrences.⁵ The development of pancreatitis only in a small fraction of alcoholics is likely related to inherent susceptibility.^{6,7} Alcoholics are more likely to be smokers, so there was initial skepticism of the role of smoking in pancreatitis. Smoking is now accepted as an independent risk factor for susceptibility as well as progression of pancreatitis.⁸ The effect of smoking is dose-dependent and likely greater in the presence of concomitant alcohol exposure. The relationship between alcohol, smoking, and pancreatitis has been elegantly summarized in previous editorials.^{9,10}

In a study published in this issue of *Pancreas*, Setiawan et al¹¹ assessed the relationship between alcohol, smoking, and incident pancreatitis in 145,866 subjects recruited in a multiethnic cohort from 1993–1996. Participants completed a detailed questionnaire at study entry, including questions on their drinking and smoking habits. Information on alcohol exposure was limited to the year before enrollment. Hospitalizations for incident pancreatitis through 2012 (n = 2810) were identified by a variety of record linkages. Pancreatitis events were divided into acute gallstone (37.9%), acute nongallstone (43.5%), and recurrent acute or chronic pancreatitis (18.6%). Subjects were aged between 45 and 75 years at study entry, and the average time from study entry to hospitalization for pancreatitis was 10.1 years.

Setiawan et al¹¹ found that smoking, particularly current and heavy, increased the risk of acute nongallstone and recurrent acute or chronic pancreatitis in both men and women; alcohol, at any level, did not increase the risk of pancreatitis; moderate drinking (defined as <2 drinks/day in men; <1 drink/day in women) decreased the risk of recurrent acute or chronic pancreatitis in men and acute nongallstone and recurrent acute or chronic pancreatitis in women; and all levels of alcohol drinking decreased the risk of acute gallstone pancreatitis in women. No interaction was observed between alcohol and smoking in either sex. The association of alcohol exposure with pancreatitis was stronger among

smokers — it reached statistical significance among current smokers in men at all levels of drinking and in women who drank 2 or more drinks a day.

The study confirms associations between smoking and pancreatitis. The increased risk of pancreatitis with alcohol was modest at best and statistically significant only in current smokers. Based on these findings, one may question the fundamental association between alcohol and pancreatitis, especially in nonsmokers. However, this lack of robust association is not a limitation of the study but is likely related to the characteristics of the study population. A closer look at the cohort and collection of exposure information provides 4 potential reasons for this observation.

First, alcoholic pancreatitis typically affects individuals between 35–55 years of age,¹² who had their peak exposure in the preceding 15 to 20 years. The risk of new-onset alcohol-related pancreatitis decreases after this age. In contrast, the risk of acute pancreatitis, especially gallstone-related (caused by the increasing prevalence of gallstones), increases with age and is the highest among the elderly.¹³ The multiethnic cohort is older, as reflected by the mean age at the time of enrollment (approximately two thirds were 55 years or older)¹⁴ and at the time of pancreatitis diagnosis (mean age, 71.5–73.8 years).¹¹ Being an older cohort, it is likely that subjects were at a lower risk for incident alcohol-related pancreatitis. Second, the assessment of accurate alcohol exposure to associate with chronic diseases is challenging. The study used detailed questionnaires to assess alcohol exposure, but this information was limited to the year preceding study enrollment. Individuals often change their drinking behavior with age.¹⁵ This may have limited the ability of the study to accurately determine the level of and cumulative exposure an individual had in the years preceding the assessment and possibly resulted in misclassification of some study subjects. This is suggested by the greater-than-expected prevalence of nondrinkers in the year before study entry¹⁶ and lower than expected prevalence of heavy drinkers among patients with pancreatitis. Third, because of a narrower spectrum of etiologies and a higher probability of transition from acute to chronic pancreatitis among drinkers, the association of alcohol with chronic pancreatitis is expected to be stronger than acute pancreatitis. The authors' approach to combine patients with recurrent acute pancreatitis and chronic pancreatitis into 1 group may therefore have limited their ability to assess for independent effects of alcohol on chronic pancreatitis. Lastly, sample sizes for many subgroups, as acknowledged by the authors, were small, limiting the power to evaluate associations.

A moderate amount of alcohol consumption can be beneficial for certain cardiovascular outcomes because of its effect on lipid profile, endothelial function, insulin sensitivity, and coagulation profile.¹⁷ The observation of Setiawan et al¹¹ that moderate alcohol exposure may also protect from incident pancreatitis is intriguing. Equally interesting is the mechanistic basis for how alcohol may exert protection in a series of publications by the group, providing a biologic plausibility of this association. In a recent systematic review and meta-analysis, less than 40 grams per day of alcohol consumption was reported to have a protective effect on acute pancreatitis in women but not in men.² Two possible explanations were suggested — a reduction in gallstone formation with moderate alcohol consumption (because women have a higher prevalence of gallstones, the effect on biliary pancreatitis may be more pronounced in them) and contamination of the control (reference) group by

former drinkers. The latter possibility may be relevant for the Setiawan et al¹¹ study. Therefore, their observation should be considered preliminary, hypothesis generating, and should drive us to continue our efforts to better define the relationship between alcohol consumption and pancreatitis. Additional studies should evaluate the reproducibility of their finding and its generalizability to different populations.

What type of studies could provide data to confirm these results? Pancreatitis, especially chronic, is a low-prevalence disease, and social drinking is highly prevalent in the general population. Thus, to evaluate a small protective effect of moderate drinking such as observed in the Setiawan et al¹¹ study would require a very large number of subjects to have enough power. Rather than onetime assessment, longitudinal, preferably prospectively collected data will be needed to assess changes in exposure through time. Randomized studies to answer such a question will not be feasible for ethical and cost considerations. A practical approach would be to use existing data from randomized controlled trials performed or prospective observational cohorts developed for other purposes, where information on alcohol consumption (and smoking) was collected at regular intervals, and where outcome (pancreatitis) can be ascertained by direct (confirmation of cases) or indirect (administrative data) methods.

Another relevant and important question is whether the protective effects, if true, will translate into secondary prophylaxis — ie, whether moderate drinking can prevent disease progression. In alcoholic pancreatitis, continuing alcohol consumption even at lower levels has been empirically shown to result in disease progression.^{3,5} Such data are not available for nonalcoholic pancreatitis. However, it is not unreasonable to assume that exposure to alcohol after pancreatic injury from other etiologies would have the same effect as when the cause was alcohol.

Subjects in the general population who consume alcohol should be advised that consumption at levels greater than daily (3 or less drinks in a day in women and 4 or less drinks in a day in men) or weekly (up to 14 drinks a week in men and up to 7 drinks a week in women) limits increase the risk of alcohol-related disorders.¹⁸ Patients diagnosed with pancreatitis should be cautioned that there are no established safe levels of alcohol consumption, that consumption of alcohol and tobacco after pancreatitis is linked to disease recurrence and progression, and abstinence is the best strategy.

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