Paternal alcohol problems, death from liver disease, signal offspring risk for cirrhosis

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While the risk of alcohol-related liver cirrhosis is known to increase with heavy drinking, a number of people who drink large quantities of alcohol seem to escape developing the disease. This variation in susceptibility may be due to several factors beyond quantity such as genetics, gender, and obesity. A preliminary clinical analysis of hundreds of drinkers with and without alcoholic cirrhosis has found that affected individuals often report a father with alcohol problems who had died from liver disease, which underscores the heritability of this disease.

Results will be published in the May 2015 online-only issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Approximately 15 to 20 percent of chronic, excessive drinkers will develop cirrhosis, although rates of up to 50 percent have been reported," said Devanshi Seth, principal scientist at the Royal Prince Alfred Hospital and the Centenary Institute as well as lead author of the study. "Part of the difficulty in obtaining accurate data is the inability to follow large numbers of alcoholics over decades, as well as the difficulty in diagnosing cirrhosis. However, there is widespread acceptance among liver specialists that not all patients who drink excessive alcohol will develop cirrhosis."

"Alcohol-related cirrhosis is a major cause of morbidity and mortality in all-worldwide communities," added Geoff McCaughan, director of the Australian Liver Transplant Unit in the Royal Prince Alfred Hospital at the University of Sydney. "It is under recognized in communities that have a high prevalence of hepatitis infection, such as Asia - Pacific and Africa, but is the major cause of liver-related illness in many western communities."

"This is the first and largest prospective genome wide association study in alcoholic cirrhosis," said Seth. "The unique feature of our study is its ability to evaluate genome-wide for effects of gene variants in thousands of drinkers in order to identify genetic factors that increase the risk for developing cirrhosis."

Seth and her colleagues are in the process of recruiting 5,000 drinkers in Australia, France, Germany, Switzerland, the UK, and the US - having already recruited more than 2,200 participants. Of the first 859 recruited participants: 580 were classified as "cases" (442 men, 138 women), who had alcoholic cirrhosis; 279 were "controls" (205 men, 74 women), who drank comparable amounts over similar time, but were free of significant liver disease. Extensive phenotypic data, including the alcohol history of participants and their parents, were obtained using semi-structured interviews and patient records, and blood samples were collected.

"The important findings in the study population recruited across the countries are, one, alcohol consumption was at least as high in drinkers who did not have liver disease as those who had cirrhosis, emphasizing the existence of individual vulnerability factors, and two, affected individuals were more likely to report that a father with alcohol problems had died from liver disease, underscoring the heritability of this disease," said Seth.

"What this paper outlines is a preliminary look at demographic data in patients who have alcoholic cirrhosis compared to alcoholics who do not have liver disease," noted McCaughan, "which is important as this comparison has not previously been attempted. This will provide the basis of a planned worldwide study to then examine the genes that could be modifying these different outcomes."

Both Seth and McCaughan were surprised by the prominence in the findings of a father who had died from alcohol-related cirrhosis.

"We had suspected a link between parent alcohol/liver disease," said Seth, "but this is the first

report of an association of risk for alcoholic cirrhosis with a father who also had alcoholic cirrhosis."

"There is some evidence that liver fibrosis genes may be modified in such a way in experimental models of liver disease," added McCaughan, "so I wonder whether this could be a human equivalent of such a finding. This would imply epigenetic factors that effect liver-related injury being passed on from the male - versus a female - parent and would be intriguing."

"We don't yet know which genetic factors are the most important risks for the development of alcoholic cirrhosis," said Seth. "The findings in this paper are based on clinical/phenotype data only, and we will perform genetic testing in these samples once our collection is complete. We expect that the genetic information that will be generated in this study will provide the first 'genetic architecture' of alcoholic liver cirrhosis and identify risk factors. This will be a significant advancement in the field of alcohol and liver research, as this level of information is not yet known for this disease. Furthermore, our findings of increased risk of cirrhosis among men whose fathers had cirrhosis will enable clinicians to counsel/caution selected patients about an increased risk of cirrhosis and provide treatment options to those who continue to drink."

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