Liver cancer in severe alpha-1 antitrypsin deficiency: who is at risk?

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To the Editor:

We would like to congratulate Hiller *et al.* [1] on their systematic analysis of cancer occurrence in a large prospective cohort of individuals with severe alpha-1 antitrypsin deficiency (AATD; Pi*ZZ genotype). The data on development of hepatic cancer are of particular relevance for two reasons: 1) the current evidence is low and controversial [2]; and 2) the early detection of liver cancer is associated with markedly improved prognosis and, because of that, surveillance programmes are recommended in high risk individuals [3, 4].

While the type of hepatic cancer was not specified in the study, it is likely predominantly due to hepatocellular carcinoma (HCC) since it constitutes the leading type of liver cancer and is markedly enriched in Pi*ZZ subjects [5]. While the 23 times increased hazard ratio appears high, it is in line with a previous report from a large community database and corresponds to only 1.6 cases per 1000 person years [6]. To put things into perspective, regular HCC surveillance is officially recommended at an HCC incidence of ⩾1.5% per year [3], *i.e.* 10 times higher than reported by Hiller *et al.* [1]. This is not surprising, since ∼90% of HCC cases develop in individuals with liver cirrhosis, while the risk for non-cirrhotic individuals is markedly lower [7]. In line with that, both American and European liver disease associations recommend surveillance programmes for cirrhotic patients, while HCC surveillance in non-cirrhotic individuals is less well backed up by the data and dependent on liver disease aetiology [3, 4]. This being said, the key question that remains to be answered is how frequently HCC arises in Pi*ZZ individuals with different fibrosis stages. Earlier data suggested that cirrhotic individuals with AATD had a yearly cumulative HCC rate of 0.9%, which was lower than in other liver disease aetiologies, such as hepatitis C virus cirrhosis (2.7%), nonalcoholic steatohepatitis (1.5%), and alcohol-induced liver disease (0.9%) [8]. However, this might be due to a parallel consideration of different AATD genotypes since subjects with heterozygous Pi*Z mutation (Pi*MZ genotype) seem to only infrequently develop HCCs, while the occurrence in Pi*ZZ cirrhotics remains unknown [6, 9]. Therefore, regular HCC surveillance in cirrhotic Pi*ZZ individuals seems to be justified, while more data are needed for non-cirrhotic subjects. The latter is particularly important, since liver cirrhosis seems to develop only in approximately 10% of Pi*ZZ subjects [10].

In conclusion, the findings from Hiller *et al.* [1] are of great importance, since they raise awareness about the risk of liver cancer development in Pi*ZZ individuals. While more research is needed, given the current lack of data, we advocate for regular HCC surveillance in Pi*ZZ individuals with advanced liver fibrosis (*i.e.* fibrosis stage 3 or 4). The fact that the median survival time after the detection of hepatic cancer was only 0.4 years strongly suggests that the tumours were mostly detected at advanced stages. In contrast a median survival of HCC at intermediate and early stage exceeds 2.5 and 5 years, respectively [3], once again highlighting the importance of surveillance programmes for early detection.

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The stage of liver fibrosis needs to be considered when evaluating the individual liver cancer risk
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