Vitamin intake and risk of liver cancer: potential for prevention?

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Primary liver cancer is the fifth most commonly diagnosed cancer among men and the seventh among women worldwide. The prognosis is poor and it is therefore the second most common cause of cancer-related death in men and the sixth among women (1). Incidence rates show considerable geographic variation, with high rates in developing countries, and half of all cases occur in China (1). However, in Western countries with generally lower rates of liver cancer the incidence has increased over the past years (1).

Chronic liver disease and cirrhosis are established risk factors for liver cancer (2). Further major risk factors for liver cancer include hepatitis B (HBV) and C (HCV) virus infections, alcohol abuse and toxins (e.g., aflatoxin) (2). The distribution of these well-known risk factors might reflect the geographical differences of incidence rates. Due to comparably low rates of hepatitis virus infections or aflatoxin contamination in Western countries, other risk factors related to Western lifestyle have been suggested to be associated with liver cancer risk. These include smoking, alcohol-related cirrhosis and non-alcoholic fatty liver diseases, and are themselves strongly associated with obesity and diabetes mellitus (3-5). Non-alcoholic fatty liver disease is a chronic liver disease - it progresses from fatty liver to nonalcoholic steatohepatitis to cirrhosis (6) - which is associated with hepatocyte injury, inflammation and fibrosis (7).

Studies have indicated that dietary intake might be associated with risk of liver cancer. Most studies focusing on food groups investigated coffee consumption and reported a reduced risk of liver cancer (8). Studies on other food groups than coffee are sparse. Few studies have suggested that consumption of white meat (9-11) and fish rich in n-3 polyunsaturated fatty acids (12), were associated with decreased, and red meat intake with increased liver cancer risk (10,11,13). The associations between fruits and vegetables and liver cancer risk have been reported to be inconsistent and conclusive evidence is lacking (9,14,15). Furthermore, little is known about macro- and micronutrients and the relationship with risk of liver cancer. Some studies have indicated that polyunsaturated fatty acids might reduce the risk of liver cancer (11,12,16), whereas another study did not find an association (10).

Regarding vitamin intake and risk of liver cancer, the evidence of epidemiological studies has been sparse as well. In the latest issue of the *Journal of the National Cancer Institute*, Zhang *et al.* (17) have presented a well-conducted epidemiological cohort study, attempting to fill this gap. Zhang and colleagues have examined the association between vitamin intake and risk of liver cancer among 132,837 participants of the Shangai Women's Health Study (SWHS) and Shangai Men's Health Study (SMHS). During an average follow-up of 10.9 years in the SWHS and 5.5 years in the SMHS, 355 liver cancer cases were diagnosed. Of these, 267 cases occurred after the first two years of follow-up and were included in analyses. Liver cancer cases were coded following the International Classification of Disease, Ninth Revision (ICD-9), codes. Liver cancer was defined as primary malignant neoplasms (ICD-9 155.0), malignant neoplasms of the intrahepatic bile ducts (ICD-9 155.1), and unspecified malignant neoplasms of the liver (ICD-9 155.2). In detail, dietary vitamin intake (vitamin A, B1, B2, C, E, retinol, carotene, niacin, and folic acid) has been assessed at baseline with a semi-quantitative food frequency questionnaire. The questionnaire also inquired about supplement intake (vitamin B, C, E,

multivitamin, and calcium). The authors reported an inverse association between dietary vitamin E intake [multivariable HR and (95% CI): 0.60 (0.40-0.89); comparing extreme quartiles] and intake from supplements [multivariable HR and 95% CI: 0.41 (0.18-0.96); no intake *vs*. intake] and liver cancer risk. Dietary intake of all other vitamins in focus was not related to risk of liver cancer. Surprisingly, the authors' findings indicated exposure to vitamin C and multivitamin supplements was associated with increased liver cancer risk, particularly in men. These associations varied by smoking status and the presence of self-reported liver diseases or family history of liver cancer. In comparison, two hospital-based case-control studies, conducted in Greece (18) and Italy (16), could not find a statistically significant association between vitamin E intake and risk of liver cancer. Another Chinese case-control study (19), based on participants with positive HBV status only, did not find a statistically significant inverse association between vitamin E intake and risk of liver cancer as well. However, the merits of the study by Zhang *et al*. are its prospective, population-based study design and higher number of liver cancer cases. Case-control studies are prone to recall bias, which is a particular difficulty in nutritional epidemiological studies.

The study by Zhang and colleagues added to the current evidence on dietary exposure and liver cancer risk. This study focused on nutrients and knowledge on the relevant food items or groups is of interest for subsequent studies. In general, further studies with prospective design are warranted to elucidate the relevance of dietary behavior in liver cancer prevention. Studies investigating dietary components, like food items or nutrients, as well as dietary patterns are needed, both in geographical high risk and low risk areas.

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