Vitamin E: potential therapeutical approach for prevention of liver cancer development

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Hepatocellular carcinoma is the third leading cause of cancer deaths worldwide. In developed countries, its incidence has particularly increased in the last twenty years with 500,000 people affected a year (1). However, the majority of the liver cancers occurs in developing countries, with 54% in China (2).

Hepatocellular carcinoma (HCC) is a frequent complication in patients with cirrhosis caused by chronic inflammatory diseases like non alcoholic steatohepatitis (NAFL), hepatitis B or C virus (3). There are also some genetic predispositions. Indeed, child with progressive familial intrahepatic cholestasis type 2 (PFIC type 2) are predisposed to hepatocellular carcinoma (4). This pathology is characterized by a genetic deficiency of the canalicular bile salt export pump BSEP or ABCB11, leading to severe cholestasis with elevated serum and liver bile acid levels, particularly chenodeoxycholic and cholic acids (5).

Liver cancers still have quite bad prognosis with an overall 5-year survival rate under 15% (6). This highlights the need to better understand the mechanisms responsible for its development and progression. Because of the involvement of reactive oxygen species in carcinogenesis, the antioxidant molecules have been suggested to have cancer preventive functions. Thus, it has been a long matter of debate to define whether antioxidants, such as vitamins, are protective against cancers. Even if there are many studies supporting this concept, the numerous epidemiological evidences remain, after all, contradictory and unconclusive (7).

Recently, in their article "*Vitamin intake and liver cancer risk: a report from two cohort studies in China*", Zhang *et al*. evaluated vitamin intake from diet and supplements and the potential association with risk of liver cancer (8). This study was performed on 132,837 women and men from China who were recruited from the Shanghai Women's Health Study or the Shanghai Men's Health Study from 1997 to 2000 from 2002 to 2006, respectively. A follow-up approach consisted of in-person surveys and record linkage was conducted. Among all the participants of these two cohorts, 267 persons (including 118 women and 149 men) developed liver cancer during 10 (Shanghai Women's Health Study) or 5 (Shanghai Men's Health Study) years of follow-up. To ensure the potential association between vitamin intake and liver cancer risk, the authors also studied the correlation between liver cancer development and several parameters such as age, body mass index, clinical and familial history of the patients.

All these statistical analyses allow the authors to show that the use of vitamin C supplements was associated with increased risk among participants with self-reported liver disease or family history of liver cancer. Surprisingly, dietary intake of vitamin C and other vitamins was unrelated to liver cancer risk. These data, showing such discrepancy depending on the source of vitamin C, are in line with many other epidemiological studies which do not manage to make definitive conclusion for the impact of vitamin C on cancer risk.

Next to this, the authors also studied the impact of vitamin E intake on liver cancer development. The major dietary sources of vitamin E are vegetables. It is a fat-soluble

vitamin. There are eight different forms of tocopherols (alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol). If all are antioxidants, each tocopherol has slightly different biological properties (9). In the body, vitamin E is incorporated in chylomicrons and then transported to the liver. Then transferred in very low density lipoproteins (VLDL), vitamin E is secreted in the circulation and transported to peripheral tissues, where it can act.

In their report, Zhang *et al*. made an interesting conclusion on the impact of vitamin E intake regarding liver cancer risk (8). Indeed, they demonstrate that dietary vitamin E intake was inversely associated with liver cancer risk. Similar results were obtained with the use of vitamin E supplements. It has to be noticed that the data did not reach statistical significance when only results obtained from men (Shanghai Men's Health Study) are analyzed. However, this association was consistent among participants with and without self-reported liver disease or a family history of liver cancer.

In the same line of evidence regarding vitamin E as an anti-tumoral molecule, it has been previously demonstrated that the use of tocopherols is efficient to inhibit chemically induced cancer development and growth of xenografted tumors in mice (10). This protective effect was demonstrated by several epidemiological studies regarding risk of lung, colon and prostate cancers. Even if these effects were found in several studies, there are some controversial ones showing no correlation (11). This is the major problem of epidemiological studies. This highlights the difficulty to clearly designed the experimental procedure and define the different patient cohorts that are needed to answer a specific question. Moreover it is really difficult to have homogenous population; even more when the follow up runs for 10 years. Indeed, development of cancers is associated with many different factors like age, nutrition habits, environment, social factors and medical history. This difficulty reinforced the positive effects observed by Zhang and coll. regarding the protective effect of vitamin E intake against liver cancer risk.

Involved mechanisms?

Vitamin E corresponds to several tocopherols. Even if the intake concentrations of the different tocopherols seem to be inversely correlated with the liver cancer risk; it remains to discriminate the active form of tocopherol in these protective effects. This will be of major importance to define the involved mechanisms. Indeed, for other cancers, it has been previously determined that γ and δ-tocopherol can inhibit tumors growth and that α-tocopherol could not (12). Thus the identification of the tocopherol involved must be of particular interest as the relative concentration of specific tocopherol can impact on the concentration of others. It was thus suggested that high α-tocopherol level can lead to a decrease of γ-tocopherol, which could lead to undesired effects on pathologies such as cancer.

These differences in the effects of the different kinds of tocopherols, on cancer risk, are quite surprising as all tocopherols present anti-oxidant properties, suggesting a potential cross-talk with other signaling pathways. This could be of interest as some interactions between vitamin E and PPARγ as well as ERα have been recently suggested (13-15).

In prostate tumor cells, it was also reported that tocotrienols lower cholesterol levels, what could be of major importance regarding liver cancer incidence as steatosis is a risk factor for this tumor type (16). It seems to be link with a decreased activity of the transcription factor Sterol Binding Protein 2 (SREBP2) which is known to control the expression of key enzymes involved in cholesterol synthesis such as the HMG-CoA (17).

As recently reviewed (18), bile acids may be implicated in liver carcinogenesis, through the binding to the two specific receptors: the nuclear receptor Farnesol-X-receptor (FXRα, NR1H4) and G protein-coupled receptor TGR5 (GPBAR1, G protein-coupled bile acid receptor). Regarding vitamin E, it could be of interest to analyze if there could be a cross-talk with bile acid pathways. Indeed FXRα has been shown to play a role in the induction of genes encoding for proteins involved in anti-oxidant defense system (19). At the molecular level, by promoting CCAAT/enhancer binding protein β and LKB1 functions, FXRα limits reactive oxygen species induced injuries in hepatocytes and protects liver against fibrosis development and evolution to hepatocellular carcinoma (20,21). This potential cross-talk is highlighted by the fact that subcutaneous vitamin E injection provided significant protection against hepatic injury induced by the bile acid: glycochenodeoxycholic acid (22).

Is there a sexual dimorphism for vitamin E protective effect?

Vitamin E intake is inversely associated with liver cancer risk in the overall study population including both men and women. However, even if there is a trend for vitamin E, the association was not statistically significant when data from only men were analyzed. This point has to be considered to

determine if it is due to the small number of liver cancers developed in these two cohorts or whether there could be some sexual dimorphism. Thus other epidemiological studies will be necessary to conclude. Indeed, it is already known that HCC is sexually dimorphic in rodents and humans, with significantly higher incidence in males, an effect that is dependent on sex hormones (23). Male mice treated with estrogen develop fewer liver tumors than control males. Moreover, ovariectomized females develop more liver tumors than normal females during chemically induced carcinogenesis (24-27). In the same line of evidence, female mice deficient for the estrogen receptor alpha are more sensitive to HCC. At last, the male mice lacking the androgen receptor show a lower incidence of HCC (28). All these data suggest protective effects of estrogens and deleterious effects of androgens which might contribute to the sexual dimorphism in HCC incidence. However, the molecular mechanisms involved remain poorly understood. A recent report suggested that estrogens could prevent HCC through inhibition of IL-6 expression in the liver which then altered hepatocyte proliferation (24). Moreover, Li *et al*. recently discovered that sexually dimorphic HCC is reversed in Foxa1- and Foxa2-deficient mice after diethylnitrosamine-induced hepatocarcinogenesis (29). They also characterized single nucleotide polymorphisms at FOXA2 binding sites which reduced binding of both FOXA2 and ERα to their targets in human liver and correlate with HCC development in women. Thus, Foxa factors and their targets must play a central role in the sexual dimorphism of HCC.

Thus it will be of interest to deeply analyze if a long term treatment with vitamin E could affect sexual hormone synthesis and/or their signaling pathways.

Perspectives

The study by Zhang *et al*. shows protective effect of vitamin E intake to counteract the development of liver cancer. However, there is still a long road to go before using it as therapeutical molecule. If the work by Zhang *et al*. is in line with many epidemiological studies suggesting that low vitamin E nutritional status is associated with increased cancer risk; some recent human trials with high doses of α-tocopherol have produced disappointing results. It points out the question of using either pure tocopherols or mixtures. This also highlights that we have to better define the biological activities of the different forms of tocopherols. Then we will have to measure the beneficial and deleterious effects of each tocopherol and mixtures in long term period of treatment, depending on the pre-determined clinical parameters of the patients.

One of the main questions that came from this study is that it deals with protective effect of a treatment, thus we cannot plan to give it to everyone, so we have to better characterize the population at risk for liver cancer (men, women, obese, ect…). We will also need to clearly define the people who will be more sensitive to such a treatment (men, women, ect…). It appears clearly that we must have to define personalized therapeutic strategy taking into consideration history of the patients (genetic, environment, food habits…).

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