

Vitamin E in prevention against hepatocellular carcinoma: right type, right dose and right population

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Globally, cancer has surpassed cardiovascular disease as the leading cause of death. In 2008, more than 7.5 million deaths are attributable to malignant diseases worldwide (1). To the general public, cancer prevention has always been a topic of concern, and strategies such as dietary modification or the intake of health supplements have been thoroughly investigated in the past. Amongst all the natural health supplements, vitamin E is probably the most intensively studied cancer preventive agent because of its renowned anti-oxidant property. Vitamin E consists of a group of fat-soluble compounds including the tocopherols and tocotrienols. Because vitamin E cannot be synthesized in the body, human has to rely on dietary sources of vitamin E. Tocopherols are the major source of vitamin E in the diet. Structurally, the tocopherol family consists of four structurally related compounds namely α -, β -, γ -, and δ -tocopherols. α -tocopherol is most well studied subtype because of its preferential secretion by the liver and higher plasma concentration in the body.

The epidemiological link between vitamin E and cancer risk remains a controversial issue. Inconsistent results have been reported by various case-control and cohort studies. For lung cancers, there have been at least three cohort studies and four case-control studies evaluating the association between vitamin E and the risk of lung cancer (reviewed in reference 2). Five of these studies have demonstrated that dietary vitamin E intake or serum tocopherol levels were associated with a reduced risk of lung cancer, especially in light smokers. Out of the eight cohort or case-control studies that have been performed on the risk of colorectal cancer, only four studies have demonstrated

a protective effect of vitamin E (2). For prostate cancer, more than twenty studies have been conducted to date, and ten of them were considered positive trials (2). Similar inconsistencies are observed in studies on the prevention of breast cancer, with less than half of the fifteen case-control studies suggesting that vitamin E could lower the risk of breast cancer (2). In China, hepatocellular carcinoma (HCC) is one of the most alarming medical problems with an annual incidence and mortality of 39,000 and 32,000 cases, respectively (3). The total caseload of HCC in China accounts for half of the global burden of HCC (4). The association between vitamin E and HCC has been poorly understood. There have been only two reported case-control studies which evaluated the effect of protective micronutrients against HCC, but these studies did not show that vitamin E could protect against HCC (5,6).

In the article by Zhang *et al.* in the *Journal of National Cancer Institute* (7), the investigators aimed to study the association between vitamin intake and the risk of HCC. By analyzing data from two cohorts which comprised of 132,837 participants in China, Zhang *et al.* calculated the vitamin intake of participants through a comprehensive food questionnaire. The authors have also identified new cases of HCC by rigorous methods including regular surveys, establishing linkage with independent population-based databases and also cross-checking by oncologists. After a median follow-up of 10.9 years for women and 5.5 years for men, a total of 267 participants developed HCC. The most salient finding of this study is that the oral intake of vitamin E, either from the diet or vitamin supplements, are associated with a reduced risk of HCC development.

In addition, this statistically significant association between vitamin E and a lowered risk of HCC remained after adjusting for the influence from self-reported liver diseases and family history of liver cancer. On the other hand, other micronutrients including vitamin C were found to have no impact on the risk of HCC. The authors concluded that a high intake of vitamin E, either from the diet or as supplements, is related to a lower risk of HCC.

How should we interpret the results of this study? Compared to the two previous case-control studies (5,6), the cohort study by Zhang *et al.* is unique in several aspects. First, the paper is based on cohorts consisting of more than 130,000 participants (7). This large sample size has enabled robust statistical analysis and optimization of the study's power. Second, the study subjects are based on general population rather than selected subjects from institutions or clinics (7). This is reflected by the close similarity of the calculated annual incidence of HCC in Zhang's study (women: 14.9/100,000; men: 44.1/100,000 population) and the incidence figures reported by other cancer surveys in China (women: 14.2/100,000; men: 37.9/100,000 population) (8). Hence, we are confident that the results are applicable to the general population in most urban cities in China. Third, the two previous studies were conducted in predominantly non-Asian subjects, while the current paper is the only study based on Chinese population (7). In China and other parts of Asia, more than 80% of HCC cases are due to chronic hepatitis B virus (HBV) infection (9,10). Nowadays, it has become increasingly clear that the HBV-related HCC is genetically different from the Western counterparts (11,12). Therefore, the results of Zhang's study provide the first relevant data on the role of vitamin E which is specific to an endemic area of HBV-related HCC.

Should we proceed to an interventional trial to test the hypothesis of vitamin supplementation for the prevention of HCC? This question is not straight-forward if we consider the lesions learnt from previously reported phase III trials in other cancers. Over the past decades, several international cancer-prevention trials on oral vitamin E have reported disappointing results in prostate, lung and breast cancers (review in reference 2). For example, the 'SELECT' study which recruited 35,533 healthy men from more than 420 study sites from 2001 to 2004, addressed the question of whether vitamin E and/or selenium might protect against prostate cancer (13,14). In this study, participants were randomized into four groups, namely vitamin E supplement and matched placebo, selenium supplement and matched

placebo, both vitamin E and selenium supplements, or placebo only. After more than 7 years of follow-up, vitamin E supplementation was unexpectedly found to increase the risks of prostate cancer (13,14). One of the possible explanations of this result was the differential efficacy of the different subtypes of tocopherols in cancer prevention. In most of the interventional studies including the SELECT study, α -tocopherols are the main components of oral vitamin E supplements. Recently, there are growing preclinical evidence showing that γ - and δ -tocopherols are the more important vitamin E subtypes than α -tocopherols in the prevention of cancer (15,16). In fact, a number of recent preclinical studies suggested that α -tocopherols did not have cancer-preventing properties (17,18). It is possible that the wrong choice of vitamin E subtypes had been evaluated in some of the negative trials. Further studies are necessary to delineate the role of different subtypes of vitamin E in prevention of HCC before further large-scale studies on vitamin E should be conducted.

The dose of vitamin E used in cancer prevention studies may also be an important consideration when interpreting the results of these studies. For adults, the recommended daily dietary allowance of vitamin E is about 15 mg/day (19). On average, the amount of vitamin E in an ordinary daily diet is in the range of few mini-grams (e.g., one kiwifruit, one medium-sized tomato, and 100 g of broccoli consists of 1.1 mg, 0.7 mg and 1.3 mg of α -tocopherols, respectively). On the contrary, commercially available vitamin E tablets are usually composed of high 'supra-nutritional' levels of α -tocopherol, typically at a range of few hundred mini-grams. For instance, in the 'SELECT' study (13,14), the daily dosage of vitamin E was 400 IU of all *rac*- α -tocopherol acetate (approximately equivalent to 280 mg), which was much higher than the daily amount as derived from an ordinary diet. Further analysis of the 'SELECT' trial found that participants taking the vitamin E supplements had very high plasma level of α -tocopherol, which was associated with a reduction in the plasma level of γ -tocopherols (14). This finding suggests that the supra-nutritional dosage of α -tocopherol supplements could paradoxically deplete the level of other more 'protective' tocopherols, thereby increasing the risk of prostate cancer in the study. If we review the daily dosage of vitamin E in Zhang's study, the lowest quartile is 9.977 mg/day while the highest quartile is 16.176 mg/day (7). It is reasonable to deduce that the sources of vitamin E in most participants are mainly derived from natural food types rather than commercially available vitamin supplements. Although Zhang's study tells us that

dietary vitamin E intake is beneficial in lowering HCC risk, it is not clear whether additional supplements of vitamin E could protect against HCC. Therefore, it is too early to recommend to the general public to take extra vitamin E supplements based on the result of this study.

Finally, a large proportion of HCCs in China are etiologically linked to HBV infection. In patients with chronic HBV infection, hepatocarcinogenesis is accompanied by chronic process of necroinflammation in the liver (20). Large-scale cohort studies by different groups, including ours, have demonstrated that HBV viral load is a strong risk factor for HCC, and the use of anti-viral therapy against HBV infection, such as the nucleot(s)ide analogues, could significantly reduce the risk of HCC (21,22). Zhang *et al.* have elegantly shown in a subgroup analysis that the benefits of vitamin E remain valid in both populations with and without viral hepatitis (7). However, the study cohorts in Zhang's study were collected from 1997 to 2006, a period when potent antiviral nucleot(s)ide analogues were not yet widely available in the most parts of China. Nowadays, patients with chronic HBV infection in China will have more access to various antiviral treatments, and their viral loads should be lower compared with HBV-infected patients in Zhang's cohort. Since viral load is a powerful risk factor for HCC, it is unclear whether vitamin E may still offer added protection in populations where vaccination against HCC and anti-viral therapies are readily accessible. Before one can extrapolate the results of this study in HBV-endemic regions, further studies are crucial to determine the role of vitamin E in the prevention of HCC amongst selected populations of HBV-infected individuals with different levels of viral load.

In summary, the study by Zhang *et al.* provides solid epidemiological data on the protective role of dietary source of vitamin E on the risk of developing HCC. This study should re-ignite interests in the chemo-prevention of HCC using vitamin E. Future studies should be directed at the identification of the optimal subtype and dosage of vitamin E, as well as the target population which will most benefit from such intervention. Without the advancement of knowledge in these areas, it seems premature to head towards a randomized interventional trial, or recommending the routine use of vitamin E to prevent HCC at this point in time.

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