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Review article

Role of vitamin E in prevention of human esophageal squamous cell carcinoma: a review

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Abstract

Vitamin E (Vit E) has enormous potential for cancer growth inhibition and cancer prevention. It has been studied widely for its antioxidant, anti-inflammatory and anti-cancerous activity. The aim of this review is to provide a summary of the research so far in regards to Vit E and its role in the prevention of human esophageal squamous cell cancer (ESCC), which is among the most malignant types of cancers. Its prevalence is high in China and poses a serious threat to the health of the residents. Therefore, finding new strategies to prevent and lessen the risk of ESCC and comprehensive understanding of carcinogenesis is essential. This review will provide the brief guidelines in understanding of Vit E in the prevention of ESCC. The data suggest that the combination of tocopherols like γ-tocopherol-rich mixture of tocopherols (γ-TmT) would be highly effective to use in the future for the prevention of cancers.

Keywords: Antioxidant, cancer prevention, esophageal squamous cell cancer (ESCC), vitamin E

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Introduction

Cancers of the upper aerodigestive tract, including the oral cavity, pharynx, larynx and esophagus, are significantly causing high morbidity and mortality throughout the world. More than 482,000 esophageal cancers had been estimated to occur globally in 2008, with incidence rates substantially higher in men than in women [1].

Vitamin E is a lipid-soluble vitamin and exerts its effect through its antioxidative properties [2]. Dietary antioxidants are food additive that significantly lower the adverse effects of reactive oxygen and nitrogen species (RONS), on normal physiological functioning in humans [3]. These RONS consequences lead to adaptation of the cell or organism by upregulation of immunity, cell damage; involving oxidative damage to carbohydrates, proteins, lipids, and DNA, and cell death in which cell may be recover or may survive with persistent oxidative damage. The damage mainly to DNA may trigger cell death by apoptosis or necrosis [4]. Antioxidants neutralize the harmful effects of DNA oxidation from free radicals especially produced by smoking [5]. These feed antioxidants have commonly emerged as protective and esstenical roles in previous studies reported for ESCC and unspecified esophageal cancers [6]. Nutritional deficiencies have main roles in the development and progress of ESCC especially in developing countries [7], however, facts from survey studies indicate the significant effect of dietary components on esophageal cancer.

Esophageal squamous cell cancer

Prevalence

Esophageal cancer is the 7th most prevalent cancer in the world. It is the 5th most common cause of death from cancer, responsible for 455800 new esophageal cancer cases and nearly 400200 deaths in 2012 [8]. Its prevalence rates vary widely among different countries. Previous studies suggest that esophageal cancer is 100 times more widespread in parts of China than in North America and Europe. However, southern and eastern Africa, south-central Asia, and some countries in South America are on high risk [9]. The esophageal cancer has two categories: squamous cell cancer and adenocarcinoma. The squamous cell cancer has been the most frequent type in the world. Prevalence of the ESCC is higher in less-developed regions [10]. The prevalence of esophageal adenocarcinoma, less than 10% of all esophageal cancer, has increased dramatically in western European countries [11].

Etiology

In all occurring esophageal cancers, the etiology of ESCC has been studied mostly due to its frequent prevalence. There are many risk factors in the development of ESCC like smoking, alcohol drinking, consumption of hot liquids and spicy foods, consumption of red meat, pork and processed meat, poor oral health, nutritional deficiencies, mutation of enzymes responsible for metabolise alcohol, non-epidermolytic palmoplantar keratoderma, achalasia, caustic injury, exposure of radiation on thoracic region

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and lower socioeconomic status were positively associated with esophageal cancer risk. [12-18].

Nutrition and esophageal squamous cell cancer relationship

Previous studies found that particular nutrients has potential roles in the prevention of ESCC. A previous study has found that the low nutrient intakes of calcium, zinc, selenium (Se), and riboflavin is responsible for the ESCC in humans both in spring and autumn seasons in Linxian, P.R.China. Vitamin A, C, E and protein consumption decreased largely with the onset of autumn due to seasonal variations in the availability and consumption of eggs, leafy and root vegetables. Foods are deficient in several minerals and vitamins, including those linked with esophageal cancer in Linxian, P.R.China [19]. Such studies provide evidence as to which specific nutrients have a protective effect against cancer. A light breakfast with salads has protective effect for the ESCC and lower the incidence of ESCC [20].

Some epidemiological survey concluded that people who are vegetarian as well as intake fruits, have a moderately low chances of upper gastrointestinal tract cancer [21]. In another study, they found that the people have a lower risk of 40– 50% of esophageal cancer with relatively high intakes of fruit and vegetables than people with low intakes of fruit and vegetables [22]. It is also suggested that fruits and vegetables are inversely related with the risk for squamous cell carcinoma, but not with the risk for adenocarcinoma [23, 24]. Similalry, in Linxian, China, fruits and vegetables consumption had a protective effect in numerous control cases and cohort studies. Consumption of beans, vegetables and vinegar all had a beneficial effects [25]. A study in New Delhi, India, suggested that fresh fruits, green leafy vegetables, other vegetables spices, and bidi usage provided protection against esophageal cancer [26].

Li et al., reported that the yogurt consumption may have a protective effect on ESCC but no associations with the consumption of milk, butter, cheese and other dairy products [27]. Berries powder have protected against chemically induced cancer in the rodent esophagus and act to reduce cell proliferation, inflammation, angiogenesis, stimulate apoptosis, differentiation, influence the expression levels of multiple genes and signaling pathways associated with these cellular functions [28]. Lyophilized black raspberries have been found to decrease the onset and development stages of ESCC in rats [29]. It is reported that the patients with a high intake of β-carotene, vitamin C and alpha-tocopherol (α-T) showed a 40-50% decreased risk of ESCC as compared with low intake patients [30]. The consumption of raw and cooked vegetables, citrus fruits and other non citrus fruits and olive oil decreased the danger of ESCC [31, 32]. In rats, supplementation of vit E inhibited ESCC carcinogenesis, particularly with a moderate Se-supplemention [2].

Vitamin E

Chemical structure and availability

Vit E are classified into tocopherols and tocotrienols present in forms such as α-, β-, γ- and δ-tocopherols (α-, β-, γ - and δ-T) and α-, β-, γ- and δ-tocotrienols (α-, β-, γ- and δ-TT). Both tocopherols and tocotrienols have methyl groups on the chromanol ring (for α-, β-, γ- and δ-form); however, tocotrienols contain unsaturated 16-carbon side chain with double bonds at the positions of 3′,7′, and 11′ (Fig 1) [33].

Humans and animals do not synthesize Vit E, therefore we obtain it from dietary sources. Vit E most abundantly found in leafy green (spinach, broccoli) vegetables, seed oils (sunflower, soybean, safflower oils, wheat germs, breakfast cereals and yeast beer) while, in animal foods such as egg yolk [34, 35]. α-T and γ-T are the main tocopherols found in the human diet. D-α-tocopherol; a naturally occurring form of α-T, has the highest biological activity [36]; however, γ-T has more consumtion than α-T [37]. As α-T generally recognized as "Vit E" therefore the majority of studies have focused on α-T due to its high blood levels and its role in fetal assimilation [38].

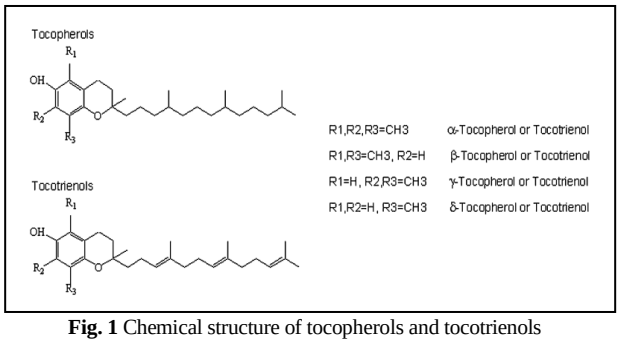

Fig. 1 Chemical structure of tocopherols and tocotrienols

Vitamin E as an antioxidant

Vit E is the powerful biological antioxidant which protects the cell membrane integrity and function by decreasing RONS production and provide shield from residues of unsaturated fatty acids in cell membranes [39]. Vit E also inhibits the production of RONS in the vascular wall and up-regulates endothelial nitric oxide synthase activity which ultimately leads to an increase in production of NO [40]. These RONS lead to

inflammation and cause oxidative damage to proteins, membrane lipids, and DNA. It is well know that the both oxidative stress and irregular arachidonic acid metabolism have contribution in ESCC (Fig 2) [41].

Vit E is a potent antioxidant as well as has anti-inflammatory properties. Several studies showed that α-tocopherol has positive effect on cardiovascular diseases [42, 43]. *In vitro* studies also found that the α-T as an antioxidant has superiority over other tocopherols. However, few other studies found that the γ-T is more effective anti-inflammatory and anti-nitrative than α-T in the prevention of cancer, neurodegenerative and cardiovascular diseases [44-46]. The mixtures of tocopherols are better to a single tocopherol for inhibiting inflammation. A previous study reported that the dietary supplementation of γ-T and α- T combination was more effective than the γ-T or α-T alone in lowering the tumor necrosis factor-α, C-reactive protein, and nitrotyrosine levels [47].

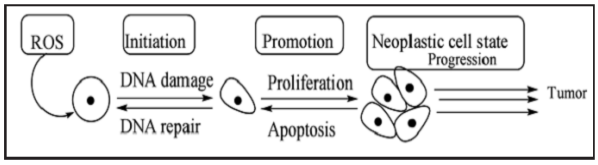

Fig. 2 Effects of ROS on DNA damage leading to carcinogenesis [72].

Vitamin E and Esophageal squamous cell cancer

The relationship between Vit E and cancer and its role in cancer growth inhibition and prevention has been studied widely. These are a few most commonly recognized cancer preventive mechanism of Vit E; down-regulation of NADPH oxidase [48]; quenching of RONS; induction of apoptosis or cell cycle inhibition; control of tumor growth through the initiation of demarcation; and removal of tumor cells by improved efficacy of antitumor actions by the immune system [49-51]. The diets supplementated with Vit E, Se and β-carotene significantly lower the incidence of esophageal, gastric and cardiac cancers [52-54]. In one cohort study association of α-T with decrease in risk of ESCC has been found [55]. The quenching of RONS by γ-T and δ-T and their inhibitory activities against cyclo-oxygenase 2 (COX-2), make γ-T and δ-T more stronger anti-inflammatory and anticarcinogenic agents than α-T [38]. In rats, vit E and Se supplementation inhibited NMBzA-induced esophageal carcinogenesis in low Vit E/Se diets. Furthermore, the supplementation during the early stage had more advantageous than during the later stages of cancer [56].

As a key enzyme in arachdonic acid metabolism, COX-2 overexpression is related to cell proliferation in esophageal dysplasia and ESCC [57, 58]. Similarly, 5-lipoxygenase (5-LOX) overexpression also enhanced carcinognenesis and 5-lipoxygenase (5-LOX) pathway inhibitors showed a chemopreventive property in esophageal cancer in animal models [59]. *In vitro*, prostaglandin E2 (PGE2) stimulates cell proliferation in a different types of carcinomal cell and enhances angiogenesis in humans [60]. The COX-2 inhibitors have been found to restrain and spress cell proliferation by blocking production of PGE2. PGE2 may be has role in tumor growth through inducing angiogenesis which play important role in supplying nutrients and oxygen to cancer cells. Dietary supplementation of Vit E and Se lower cell proliferation, angiogenesis, biosynthesis of PGE2, 8-hydroxy-2′-deoxyguanosine, leukotriene B4, expressions of COX-2 and 5-LOX in the esophagus. Vit E supplementation has been increased the plasma antioxidant enzymes capacity such as glutathione peroxidase, superoxide dismutase and total antiantioxidant capacity while it decreased the isoprostane 8-epi Prostaglandin $F_{2\alpha}$ levels which is a product of oxidative stress [56].

A recent study suggests that the γ-tocopherol-rich mixture of tocopherols (γ-TmT) is perhaps the most promising agent to use; containing α-tocopherol (13%), β-tocopherol (1.5%), γ-tocopherol (57%) and δ-tocopherol (24%) and inhibited carcinogenesis in different animal models [61-64]. Dietary supplementation of γ-TmT suppressess the formation and growth of LNCaP xenograft cancer in severe combined immunodeficiency mice in a dose dependent manner [65]. In another study, it has been reported that the γ-T or the γ- and δ-T combination, were more effective than α-T alone for inhibiting the growth of different types of cancerous cells [66-70]. In addition, the combination of δ- and γ-T were more active than α-T alone for inhibiting pulmonary carcinogenesis [71].

Conclusions

γ –TmT, is a by-product, produced during the refining of soybean oil. It contains γ-T, β-T and δ-T in similar ratios like dietary vegetable oils. It is a cheap and readily available source of γ-TmT. In this review, we propose that mixture of tocopherols; γ-TmT is more effective antioxidant and anticancer agent, however, there are also some controversial effects of Vit E on cancer. Further detailed molecular studies are required to know the exact mechanism of γ-TmT againt ESCC in different animal models and human trials. It is also recommended that extensive studies of individual foods and their roles and mechanism of

actions in carcinogenesis at the cellular level should be conducted.

Abbreviations

ESCC, esophageal squamous cell carcinoma; Vit E, vitamin E; RONS, reactive oxygen and nitrogen species; γ-TmT, γ-tocopherol-rich mixture of tocopherols; NO, nitric oxide; α-, β-, γ - and δ-T, α-, β-, γ- and δ-tocopherols; COX-2, cyclo-oxygenase 2; 5-LOX, 5-lipoxygenase; PGE2, Prostaglandin E2.

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