Esophagus cancer and essential trace elements

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Numerous epidemiological and laboratory studies on essential trace elements have reported protective associations in developing various cancer types, including esophagus cancer (EC). However, the results are not always consistent. Some essential trace elements could play a vital role in preventing esophagus cancer. Some showed no association with esophageal cancer risk, while others harmed individuals. This article reviews the association between the intake or supplementation of essential trace elements (especially zinc, copper, iron, and selenium) and the risk of esophageal cancer. Generally, zinc intake may decrease the risk of esophageal cancer (EC), especially in high esophageal squamous cell carcinoma (ESCC) prevalence regions. The association between copper supplementation and EC remains uncertain. Total iron consumption is thought to be associated with lower EC risk, while heme iron intake may be associated with higher EC risk. Selenium intake showed a protective effect against EC, especially for those individuals with a low baseline selenium level. This review also prospects the research direction of the association between EC and essential trace elements.

KEYWORDS
esophagus cancer, essential trace elements, minerals, zinc, copper, iron, selenium

Introduction

Esophageal cancer (EC) is the seventh leading cause of cancer death worldwide (1) and the fourth leading cause of cancer death in China (2). The 5-year survival rate for EC remains one of the lowest in all cancer types, with a 5-year survival of 20% in the United States (1) and 40.1% in China (3). More than 90% of EC patients in China are diagnosed with esophageal squamous cell carcinoma (ESCC) (3, 4), the world’s most common type of EC. In Western nations, alcohol drinking and smoking are the primary risk factors for ESCC (5), whereas, in so-called “esophageal cancer belts” such as South Africa, France, Iran, and China, these behaviors are less prevalent (6). Environmental and dietary factors have also been reported to affect ESCC, and essential trace elements may be dose-dependent on the risk of ESCC. Essential trace elements of the human body account for roughly 0.00001% to 0.01% of the total body weight, including Fe, Zn, Cu, Mo, F, V, Ni, Co, Se, Cr, I, and Mn. They play a significant role in maintaining normal biological function, acting as active centers of enzymes or tracing bioactive substances. Numerous studies have attempted to illustrate the meaning of balancing essential trace elements in EC protection or treatment. Yet, the findings of these studies are not always the same. Here, we focus on the connection of esophagus cancer with essential trace elements, especially zinc, copper, iron, and selenium.
Zinc

Zinc is one of the most abundant trace elements found in almost all organs and tissues of the body. It plays a critical role in stabilizing the structures of many proteins, especially those participating in DNA synthesis and RNA transcription, thus regulating cell growth, development, and differentiation, maintaining an immune response, and mediating oxidative stress and apoptosis (7–9). Among all the biological functions, it should be highlighted that zinc could inhibit chronic or acute oxidative stress, which is one of the mechanisms of cancer development. Zinc deficiency impairs the antioxidant activity and renders the organism more susceptible to injury induced by various oxidative stressors (10). Therefore, an adequate level of zinc is important for individuals. Some laboratory studies have established an association between zinc deficiency and cancer (11–16). Zinc homeostasis could influence T-cell activation as well as the polarization of T helper (Th) cells into their different subpopulations [Th1, Th2, Th17, regulatory T cells (Treg)], thus regulating immune microenvironment (15). Choi et al. found that zinc could inhibit cell proliferation of EC cells through Orai1-mediated intracellular Ca$^{2+}$ oscillations and revealed a possible molecular basis for zinc-induced cancer prevention and the Orai1-SOCE signaling pathway in cancer cells (16). Several studies have already shown the relationship between dietary zinc deficiency and ESCC (17, 18). ESCC in Linxian is a high-incidence area in China. A study from Linxian showed that the zinc concentration in biopsy samples was negatively correlated with the venture of EC development, exhibiting strong proof for the connection of dietary zinc deficiency with the higher risk of EC in humans (17).

Zinc consumption was significantly associated with a lower risk of EC and gastric cancer in Asia but not in the United States or Europe (19). The results of a meta-analysis also indicated that increasing zinc supplementation by 5 mg/day was associated with a 15% decrease in EC risk (20). It was reported that the mechanisms between zinc deficiency and the development of EC lie in that zinc deficiency could result in the upregulation of multiple genes related to DNA damage, oxidative stress, immune response, cell proliferation, and apoptosis, thus inducing the development of EC (18). Animal studies showed that ESCC cells proliferated more rapidly in mice fed zinc-deficient diets via inducing overexpression of COX-2, P38, PCNA, and NF-κB (18). ESCC can also be promoted by zinc deficiency through inflammatory gene expression (21, 22) and oncogenic microRNA expression, including upregulation of oncogenic miR-31 and other miRNAs (21, 23). Deeper molecular mechanisms induced by nutrient bioavailability or dietary interventions have recently been studied using integrative genomics methods (24). Fong et al. (25) demonstrated that zinc intake reduced COX-2 mRNA by 80%, an enzyme involved in inflammation, thus bringing prevention or therapeutic possibilities of zinc supplementation for EC. A recent study found that zinc supplementation could protect Barrett's epithelia from transforming into esophageal cancer cells (26), further revealing zinc supplementation's protective effects. The role of zinc in EC diseases is not fully answered and needs further investigation. It seems that zinc intake may decrease EC risk, especially in high ESCC prevalence regions.

Copper

Copper is an essential trace element that the body requires and is vital in many biological functions, including maintaining DNA integrity, synthesizing essential metabolites, transporting oxygen to the mitochondrial respiratory chain, and involving redox reactions as an active site metabolic cofactor. Emerging laboratory studies showed that copper could act as a dynamic signaling metal and metalloallosteric regulator, participating in cell growth and proliferation, autophagy, and antioxidant defense, thus regulating cancer development, as tumor growth and metastasis have a high requirement for this metal nutrient (27). Such properties make the dual copper effect beneficial and toxic to the cells. An intake of 900 μg per day is recommended for this essential trace element, while a level of 10 mg per day is the maximum permissible (28). Excess copper may promote radical damage and decrease the activity of proteins or enzymes, thus causing cellular injury via over-activated oxidative stress, lipid peroxidation, inflammation, and DNA damage, finally helping in the angiogenesis of tumors (29). It remains controversial whether copper intake contributes to EC prevention, despite many studies focusing on the relationship between copper intake and the disease. Chen et al. (30) claimed that copper intake was negatively correlated with EC mortality in Shanxi, China, via estimating average copper intake in 21 Chinese communes, where EC mortality rates were much higher than average (30). Similarly, according to Sohrabi et al. (31) the copper levels were obviously lowered in EC tissues compared to non-cancerous tissues (31). Recently, Zhuang et al. (32) even explored the therapeutic effect of copper nanoparticles in EC treatment via their antioxidant activities (32). However, in the Kashmir valley, an area at high risk for EC in India, as reported by Mir et al. (33) plasma levels of copper in patients with EC were significantly higher than in controls, indicating an imbalance in plasma levels of copper may be responsible for the development of the disease (33). Copper supplementation and ESCC risk were evaluated by Hashemian et al. (34) and a nonlinear association was found between copper intake and ESCC risk, but the supplementation trend related to ESCC was not evident (34). In addition, a meta-analysis found that copper supplementation at 1 mg/day did not reduce the risk of EC (20). Altogether, the relationship between copper and EC remains uncertain. Copper supplementation recommendations still require additional research.
Iron

Iron is an important component of heme, iron-sulfur proteins, and enzymes and participates in many biological processes, including oxygen transport, ferroptosis, immune response, cellular energy metabolism, and many other enzymatic reactions. Physiological processes have evolved for iron acquisition to meet metabolic needs while avoiding the toxicity of free radicals generated from iron. Iron excess and iron deficiency are related to pathological states (35). Recent studies have focused on ferroptosis, a newly discovered iron-dependent mode of cell death that plays an important role in the biological behavior of cancer cells. Zhu et al. (36) and Qiao et al. (37) found that ferroptosis-related noncoding RNAs correlate with the prognosis, tumor microenvironment, and therapeutic sensitivity of ESCC, indicating new therapeutic approaches for noncoding RNAs targeting ferroptosis in ESCC (36, 37). The role of iron in EC development has been under investigation. However, the results are still conflicting regarding the association of iron levels with the risk of EC. Sohrabi et al. (31) evaluated the iron concentrations between cancerous and non-cancerous tissues in EC. The results showed that the iron level in cancerous tissues was higher. However, no significant differences were revealed in EC (31). Several basic research indicated that the excess levels of iron enhanced EC (38–40), and the mechanisms possibly were related to the over-expression of iron import proteins, DNA damage, ferroptosis, and oxidative stress (41, 42).

Furthermore, it was found that total iron intake and heme iron intake were different from the risk of EC. Total iron supplementation was significantly inversely correlated with the risk of EC, especially among the Asian population and ESCC subgroup. A dose-response analysis indicated that each 5 mg/day increase in total iron supplementation was related to a 15% reduction in EC risk. However, heme iron intake was positively related to the risk of EC, especially in the United States. Each 1 mg/day increase in heme iron supplementation increased the risk of EC by 21% (20).

Similarly, a large European cohort study found that higher intakes of processed meat and heme iron may be related to an increased risk of developing EC, especially esophageal adenocarcinoma (43). Cross et al. (42) also found that heme iron supplementation may be associated with a risk for esophageal adenocarcinoma (EAC). They observed a positive association between red meat intake and ESCC but no association with adenocarcinoma (42). Overall, total iron intake may be related to reduced EC risk, while heme iron intake may be related to increased EC risk. More evidence is required to clarify the relationship between imbalanced iron levels (iron deficiency or overload) and the risk of EC.

Selenium

Selenium is a naturally occurring element to which humans are mostly exposed through food intake, air, drinking water, and dietary supplements. A moderate amount of selenium is vital for maintaining biological functions, but a slightly higher amount of selenium may have potential toxicity. Basic research showed an anti-tumor effect of selenium, including inhibiting cancer cell proliferation (44), preventing tumor formation in cell populations already exposed to carcinogens (45), reducing carcinogen-induced DNA mutations, and antioxidant and anti-inflammatory effects (46).

Numerous studies have shown selenium to be related to the risk of EC. It was reported that selenium could slow down the development of ESCC by decreasing the expression of Ki-67, inducing apoptosis, and lowering inflammation and oxidative DNA damage, thus exerting an important chemopreventive effect on ESCC by reducing high-grade dysplasia to low-grade dysplasia (47, 48). Zhang et al. (49) found that β-catenin/TCF pathway played a vital role in selenium induced-growth inhibition and apoptosis in ESCC cells (49). Liu et al. (50) also revealed that methylseleninic acid acted as a chemopreventive agent via the regulation of KLF4/miR-200a/Keap1/Nrf2 axis in ESCC cells (50). Several studies measured serum selenium levels between patients with EC and controls. Steevens et al. detected selenium levels in toenails. They found that selenium concentrations were inversely related to the risk of ESCC, while an inverse association was only found in esophageal squamous dysplasia, which was reported as the precursor lesion of ESCC (51). Mark et al. (52) found a significant inverse relationship between serum selenium concentrations and the incidence of EC (52).

Further, they also observed significant inverse associations between the baseline concentration of serum selenium and death from ESCC (53), indicating that selenium intake may help reduce the incidence of EC and death from EC. A randomized controlled trial showed evidence that selenium played a preventive role in subjects with preexisting esophageal squamous dysplasia, which was reported as the precursor lesion of ESCC (54). In a follow-up of the Linxian General Population Nutrition Intervention Trial, selenium intake with vitamin E and β-carotene helped reduce the risk of EC, and the beneficial effects on mortality from EC were still evident up to 10 years after the cessation of supplementation and were consistently greater in younger patients (55). However, some meta-analyses showed different results regarding the relationship between selenium exposure and the risk of EC. Cai et al. (56) showed that high selenium exposure might decrease the risk of EC (56), while Hong et al. (57) observed that a higher selenium concentration was not significantly related to a decreased risk of EC (57). The Golestan Cohort Study also mentioned that the association between dietary selenium supplementation and the risk of ESCC was nonlinear but probably U-shaped, which suggests that the
FIGURE 1
An overview of how integrated omics technologies could be applied to study the relationship between essential trace elements and EC.

Other essential trace elements

In a cohort study, calcium (Ca) was reported to be related to a decreased risk of ESCC in men in the United States (58). Similarly, Hashemian et al. (34) observed a significant linear inverse association between calcium supplementation and the risk of ESCC (34). The possible molecular mechanisms may lie in the fact that calcium could inhibit the proliferation and invasion of cancer cells and promote apoptosis (59). The relationship between magnesium (Mg) in drinking water and the risk of EC was also reported. The result showed a significant trend toward decreasing EC risk with increasing magnesium concentration in drinking water (60). It was also reported that compared with healthy tissues, the levels of chromium (Cr), manganese (Mn), aluminum (Al), tin (Sn), and lead (Pb) were higher in cancerous tissues. However, no significant differences were revealed in EC (31). There are only limited studies focused on the relationship between the aforementioned essential trace elements and the risk of EC. Cr was reported to increase the risk of various cancer infections under environmental and occupational exposures (61) via ROS production, DNA damage, angiogenesis, and other molecular process (62, 63); however, its association with EC remains unclear. Mn has been widely studied in neurodegenerative diseases, and it mainly participates in biological roles in the form of manganese superoxide dismutase (MnSOD) by neutralizing the radical superoxide. A few studies have reported that MnSOD may play a role in EC protection (64, 65). In a mouse model, high levels of MnSOD expression promoted ESCC cell growth, whereas moderate MnSOD expression suppressed tumor cell growth (64), indicating the dual effects of MnSOD on ESCC cell proliferation. No evidence showed a clear relationship between Al, Sn, Pb, and EC. Further study may reveal the underlying association.

Discussion

It was found that EC had a close relationship with environmental and dietary factors, in which essential trace elements played significant roles. Studies on the association between essential trace elements and EC were critical and have provided potential direction for the prevention of EC. In this review, we analyzed the studies of some main essential trace elements in EC. Zinc, iron, and selenium supplementation seem to be related to a reduced risk of EC, while copper showed an equivocal effect on the prevention of EC. Despite ample evidence and general consistency in the relationship between essential trace elements and EC, the public or health professionals often view the effect of essential trace elements with skepticism. One explanation could be that the physiologic systems affected by essential trace elements are so complicated that the effects of supplementing with only one or two elements are not effective enough or even sometimes harmful. Essential trace elements belong to the whole diet pattern. Many studies focused on only one essential trace element, which could not reflect the reality that diet as a whole is more important than the sum of its parts (66). In-depth studies on essential trace elements are required. Genome, epigenome, transcriptome, metabolome, proteome, and microbiome have long been used in cancer studies, which significantly improve our understanding of the mechanisms of cancer development or new therapy application of cancers. With the development of such technologies, a molecular biological approach that integrates data of “omics,” including metagenomics, transcriptomics, proteomics, metabolomics,
genetics, and other molecular technology, is expected to help us enhance our understanding of the association between essential trace elements and risk of EC incidence or development (66) (Figure 1). Moreover, a clearer connection between essential trace elements and the molecular alteration and variation of patients is gradually becoming identifiable and quantifiable, thereby renewing the old general view associating specific phenotypical changes with the differential intake of essential trace elements (67). Further research is needed and is expected to clarify how essential trace elements act in the development of EC and whether essential trace element supplementation could protect against EC.

Author contributions

XY carried out the primary literature search, drafted, and revised the manuscript. JL and ZT contributed to drafting and revising of the manuscript. JJ and JL helped modify the manuscript. ZT and JJ carried out the literature analysis and revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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06