**Association of Selenium and Risk of Esophageal Cancer: A Review**

**ABSTRACT**

Esophageal cancer (EC) is one of the most common types of cancer, especially in Asia. Esophageal squamous cell cancer (ESCC) is the most important histological subtype of EC, which accounts for 90% of all EC cases worldwide. ESCC is highly prevalent in Turkey, Iran, Kazakhstan and northern and central parts of China. Selenium is an essential micronutrient that is required for cellular functioning and synthesis of several selenoproteins. It also modulates the antioxidant defense system, cell cycle and apoptosis. This article reviews the most important molecular mechanisms of EC and investigates the association between selenium level and incidence of EC in high-risk areas.

**Keywords:** Esophageal cancer, selenium, selenoprotein.
INTRODUCTION

Esophageal cancer (EC) is one of the most common types of cancer, especially in Asia. In 2018, 572,034 new cases of EC and 508,585 EC-related deaths were recorded worldwide (1). The highest mortality rates among men are 14.1 per 100,000 in eastern Asia and 12.8 per 100,000 in southern Africa, while the highest mortality rates for women are 7.3 per 100,000 in eastern Asia and 6.2 per 100,000 in southern Africa (2). The high-risk areas for EC are in the “Asian EC Belt” consisting of countries such as Turkey, Iran, Kazakhstan and China (3). According to recent reports, of 35,000 cancer-related deaths in Iran, 5,800 cases have had EC (4). Esophageal cancer occurs in the tissue lining of the interior surface or epithelium of the esophagus. There are two main histological subtypes of EC: esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC) (5). Based on epidemiological studies, various factors including gender, obesity, alcohol consumption, smoking, gastroesophageal reflux disease, Helicobacter pylori infection, N-nitroso compounds, toxins and micronutrient deficiency may increase the risk of developing EC (6-13). In countries such as the United States, Australia and Western Europe where EAC is the predominant histological subtype (14), obesity, tobacco use, low intake of fruits and vegetables and gastroesophageal reflux disease are the most important risk factors. The annual incidence rate of ESCC is over 100 cases per 100,000 people in countries such as China, Iran and Turkey. In these countries, tobacco and alcohol consumption, low intake of fruits and vegetables, low socioeconomic status and genetic predisposition are known risk factors of ESCC (15). Generally, ESCC is more common in men (69%) than in women (31%), but the incidence rates vary widely in high- and low-risk areas (16). The highest rate of ESCC and gastric cardia adenocarcinoma is reported from Taihung Mountain range of China and northeastern Iran (17). Previous studies have reported a significant inverse correlation between serum selenium levels and the risk of ESCC. In the high-risk areas of China, selenium deficiency was the main risk factor for ESCC (18, 19). However, in high-risk areas of Iran (such as Golestan Province), the association of dietary selenium intake with risk of ESCC was nonlinear and possibly U-shaped (20). The aim of the present review is to examine association of selenium and risk of EC while focusing on the molecular mechanism of this cancer.

1. Molecular mechanism of EC

The incidence and progression of EC are a multistep process accompanied with activation of oncogenes and inactivation of tumor suppressor genes (21, 22). It has been demonstrated that EC progression is strongly linked with cell proliferation, survival, invasion, metastasis and angiogenesis, cell adhesion, the imbalance of oncogene and tumor suppressor gene expression and participation of the immune system. Key pathways associated with EC occurrence and development are PI3K-Akt signaling pathway, MAPK signaling pathway, cell adhesion pathways and p53 signaling pathway. In addition, increased levels of interleukin 8 and C-X-C chemokine receptor type 7 play a main role in the pathogenesis of EC (23). It has been reported that overexpression of phosphorylated ERK1/2 is associated with several clinical and pathologic factors in ESCC (24, 25). Recent studies show that Rh family, C glycoprotein (RHCG) is mostly downregulated in primary ESCC in contrast with their corresponding normal mucosa (26, 27). Moreover, nuclear transcription factor-κB (NF-κB)/p65-mediated increased expression of MMP1 and MMP9 contributes to tumorigenicity and metastasis in ESCC (28, 29). In addition, RHCG can act as a new tumor suppressor gene in the progression of ES2C by decreasing IkB phosphorylation and inhibiting NF-κB/p65 activation (30). Alcohol consumption also increases the risk of developing ESCC (31) mainly through disruption of DNA methylation (32). LINE-1 hypomethylation, a substitute marker of global hypomethylation, has been proposed as an important phenomenon that can contribute to ESCC (33-35). Long non-coding RNAs (lncRNAs) are both oncogenic and cancer suppressive (36). Overexpression of lncRNA X inactivate-specific transcript (XIST) has been detected in EC tissues and cell lines. This lncRNA can play an oncogenic role in the EC progression by sponging miR-494 and controlling CDK6 expression (37). CDC7, a serine/threonine kinase, plays an essential role in the initiation of DNA replication and DNA damage (38, 39). Studies have shown that CDC7 was remarkably upregulated in ESCC.
tissues, and depletion of CDC7 can prevent cell proliferation and induce apoptosis in ESCC cells (40).

1. Nutritional aspects of selenium
Selenium is an essential trace element that was first discovered by Jöns Jakob Berzelius in 1817. Although initially known as a toxic compound (41), selenium has been recognized as an important micronutrient since the 1950s (42). Selenium is present in various organic and inorganic chemical forms. The organic chemical form is found mostly in food, but inorganic selenium is mainly found in water and air (43). Organic forms of selenium (such as selenocysteine and selenomethionine) and inorganic compounds such as selenate and selenite are absorbed through the intestinal lumen and converted to selenide for selenoproteins (SePs) synthesis or selenosugar for elimination (44). To date, twenty-five SePs genes have been identified in humans (45). Most SePs, including glutathione peroxidase (GPx) and thioredoxin reductase (TrxR) family of proteins are involved in the antioxidant defense system. Other mechanisms related to SePs include control of apoptosis, modulation of immune system, synthesis of thyroid hormones and deoxyribonucleoside triphosphates, reduction of oxidized proteins, selenium transport and storage, protein folding and degradation of misfolded proteins in the endoplasmatic reticulum (46). Various studies suggest that insufficient levels of selenium and SePs are related to cancer (46, 47). Because of the inhibitory effects of selenium on tumor cells, this compound can be used to prevent tumorigenesis (48).

3.1 Selenium and antioxidant defense systems
Oxidative stress occurs when the production of free radicals, such as reactive oxygen species (ROS), reactive nitrogen species (RNS, e.g. nitric oxide, NO) as well as oxidised lipids and proteins overbalances an organism’s antioxidant abilities, which leads to cell/tissue damage (49). Reactive oxygen species-induced DNA damage can trigger carcinogenesis and cancer progression (50-52). Glutathione peroxidase and thioredoxin reductase are responsible for redox homeostasis and neutralization of peroxides and other electrophiles (53, 54). The glutathione peroxidase family consists of eight known glutathione peroxidases (GPx1-8). In humans, GPx1, GPx2, GPx3, GPx4 and GPx6 contain selenocysteine, whereas GPx5, GPx7 and GPx8 have cysteine instead of selenocysteine. This family of proteins protects membrane lipids and macromolecules against the oxidative damage generated by peroxides through conversion of hydrogen peroxide to water by utilization of glutathione (GSH) as an electron donor (H₂O₂ + 2GSH → GS-SG + 2H₂O)(55, 56).

The most abundant member of this family is GPx1, which is generally expressed in cytosol and mitochondria of different tissues (57). Expression of this protein is directly linked to selenium levels (58). This GPx can prevent oxidative DNA damage and prevent tumorigenesis in the initiation phase (59). Since GPx2 is solely expressed in the gastrointestinal tract (60), it might have protective effects against oxidative damage (61). Overexpression of GPx2 has been reported in neoplastic transformation of squamous epithelial cells (62) and Barrett's esophagus (63). Furthermore, GPx2 was remarkably overexpressed in ESCC tumor tissues compared with non-tumor tissues. Thus, GPx2 can be an important prognostic factor in ESCC patients (64). While GPx3, a plasma antioxidant enzyme, its expression is reduced in ESCC tissues and ESCC cell lines, and through the FAK/AKT pathway, it inhibits tumor gene in ESCC (65). It is proposed that low selenium levels might increase GPx2 expression, decrease GPx1 expression, but does not alter GPx4 expression (66). Thioredoxin reductase (TrxR) enzymes consisting of TrxR1, 2 and 3 reduce thioredoxins and play a role in the reduction of selenite, selenodiglutathione and methylseleninate. Hence, the TrxR family plays a vital role in selenium metabolism (67-69). In addition, TrxR expression is necessary for maintenance of redox balance and many tumor suppression pathways. For instance, TrxR1 boost maturation of p53, inactive forms of protein kinase C and phosphatase and tensin homolog (70-72). Selenoprotein W (SEPW1) contains a single selenocysteine residue at its active site and has been reported to have glutathione-dependent antioxidant activity in vivo (73).

3.2 Selenium and cell cycle regulation
Cyclins, cyclin dependent kinases (CDKs) and CDK inhibitors are cell cycle regulators (74). Selenocysteine reduces the expression of cyclin A, thus inducing S phase cell cycle arrest via ROS-mediated DNA damage and controlling the MAPKs and AKT signaling.
pathways (75). Selenoprotein W is the only selenoprotein whose mRNA was increased by sub-micromolar concentrations of selenium in cultured human cells (76). It may control cell cycle via several mechanisms. Selenoprotein W promotes cell cycle progression by regulating the dissociation of 14-3-3 from CDC25B (77). Moreover, SEPW1 silencing increases p53 level by reducing proteasomal degradation of p53, induces p21 expression and prevents G1/S transition (78). SELENOH is a selenium-sensitive SePs with a disturbed expression under suboptimal selenium concentrations. Unlike GPx2, TXNRD1 and SELENOF, knockdown of SELENOH improves cell proliferation in vitro and promotes tumor growth in vivo, indicating that SELENOH may suppress tumor progression (79-82). SELENOH affect cell cycle through inhibition of G1/S transition by modulating p21 and CCNE1 expression (83, 84). The 15-kDa selenoprotein (Sep15) can also contribute to cancer progression (85-89). A study reported that Sep15-deficient Chang liver cells are arrested at the G1 phase by upregulation of p21 and p27 (82). Both p21 and p27 inhibit cell cycle progression by interacting with cyclins and CDKs (90).

3.3 Selenium and apoptosis
At low concentrations, selenium exerts antioxidant effects by suppressing apoptosis and inhibiting oxidative stress (91). In high concentrations, selenium acts as a prooxidant and hence could contribute to the fight against cancer cells (92-96). Pharmacological doses of selenium compounds stimulate apoptosis in cancer cells through p53-dependent pathways (97-100). Sodium selenite induces apoptosis via ROS-mediated inhibition of NF-κB signaling, increases Bax expression and reduces expression of anti-apoptotic proteins, such as Bcl-2 (101). Selenomethionine can lead to apoptosis and prevent the growth of cancer cells by significantly reducing level of β-catenin and c-Myc expression. In addition, selenomethionine can suppress growth of cancer cells through mechanisms related to Wnt/β-catenin pathway (102). Methylseleninic acid strongly inhibits the growth of ESCC cell lines by promoting β-catenin degradation through ubiquitin–proteasome pathway (103).

4. Association of EC and selenium
Several studies have investigated the correlation between selenium and EC. In a high-risk area for EC in Iran (Golestan Province), there was a significant positive association between selenium levels in the soil and EC incidence rates (104). Another study in the Golestan Province showed that total selenium content in soil, grain, loess and sediments is higher in high-risk areas for EC. However, this study indicated that selenium deficiency does not play a main role in the etiology of EC in the Golestan Province (17, 105). A significant positive correlation was found between selenium level in rice seeds and EC rates in the Golestan Province. These results propose that selenium levels in soil and rice might be involved in the pathogenesis of EC (106). Another study in a high-risk area of Iran revealed a U-shaped association between selenium intake and incidence of ESCC (20). Cohort studies in the Netherlands revealed an inverse association between selenium level in the toenail and risk of ESCC (107). However, a case-control study in the Golestan Province did not find such correlation (108). In a Chinese population, low dietary selenium intake was found as a major risk factor for ESCC (109), especially in smokers and heavy drinkers with p53 Pro/Pro and GSTP1 Ile/Ile genotypes (110). In southeastern Iran, serum selenium level was significantly lower in cancer patients than in healthy individuals (111). Furthermore, there was a significant positive correlation between serum selenium level and occurrence of esophageal squamous dysplasia in East Africa, a high-risk area for incidence of ESCC (112).

CONCLUSION
Findings suggest that GPx3, TrxR1 and SELENOH can prevent cancer progression, while GPx2, SEPW1 and Sep15 promote cancer progression. Several studies in high-risk areas for EC demonstrated that both selenium deficiency and increased selenium level could alter the risk of developing ECs. Further research is needed to understand the molecular mechanisms related to the association of selenium with EC.

ACKNOWLEDGMENTS
The authors would like to thank the Golestan University of Medical Sciences, Iran.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.
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