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Trace elements under the spotlight: a powerful nutritional tool in cancer

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ABSTRACT

Cancer is the second leading cause of death worldwide. Research on the relationships between trace elements (TE) and the development of cancer or its prevention is a field that is gaining increasing relevance. This review provides an evaluation of the effects of TE (As, Al, B, Cd, Cr, Cu, F, I, Pb, Li, Mn, Hg, Mo, Ni, Se, Si, Sn, V and Zn) intake and supplementation in cancer risk and prevention, as well as their interactions with oncology treatments. Advancements in the knowledge of TE, their dietary interactions and their main food sources can provide patients with choices that will help them to improve their quality of life and therapy outcomes. This approach could open new opportunities for treatments based on the integration of conventional therapies (chemotherapy, radiotherapy, and immunotherapy) and dietary interventions that provide advanced personalized treatments.

Keywords: Cancer; cancer treatment; nutrition; trace elements.

1. Introduction

Over the years, rapid urbanization, economic growth, and poor nutritional education have brought with changes in dietary patterns, nutritional status, and lifestyles of the world population. In this context, preferences for refined and junk food have prevailed, increasing vulnerability to various diseases [1]. Adequate nutrition, including optimal micronutrient consumption, is essential for the organism's homeostasis. Adults require about 1-100 mg/day of trace elements (TE) and less than 0.001 mg/day of ultra-trace elements. Despite these low levels, they play a vital role in the physiological and metabolic processes, as well as in signaling pathways produced in our tissues [2,3]. Concentrations of TE can be beneficial or toxic [4] and complex mechanisms in our organism regulate the amount of essential TE and maintain them within the normal range. Several factors contribute to TE balance, such as diet, sex, geographical location, health status, age, and genetics. TE interact with each other, so an alteration in the consumption of one or two elements can produce an imbalance and a competition for their absorption [5,6]. Furthermore, depending on the manner of exposure (oral, dermic or by inhalation) and the chemical structure, their effects can differ [4]. The main source of TE is provided from the diet in natural and embedded biofortified foods and beverages. However, an excess or deficit can provoke different diseases, such as cancer [7]. Among many mechanisms involved in cancer, oxidative stress, inflammatory processes, and DNA damage are regulated by TE [8,9]. However, studies in relation to dietary TE and cancer risk and prevention are controversial because of the complexity of the mechanisms involved [10,11]. In this sense, a specific criterion is required to reduce the risk of nutrient imbalance and, consequently, the emergence of disease. Currently, there is a lack of consensus regarding classification of TE therefore the present review focuses on the World Health Organization (WHO) classification. Based on the nutritional relevance for humans, considering their physiological function in our organism, WHO classifies a total of 19 TE as essential elements, probable essential elements, and potentially toxic elements [2,12].

The aim of the present study is to summarize current evidence about how dietary TE are related to cancer prevention, development and treatment, as well as which mechanisms are involved and which TE could be potentially therapeutic targets in this metabolic disease.

2. Dietary trace elements: from foods to our organism

2.1 Requirements and recommended dietary intakes

Estimate of nutritional requirements currently vary from country to country [13] and different concepts are needed to take them all into account. Even when there is agreement about physiological requirements, dietary requirements can vary according to dietary patterns and interindividual conditions [13]. On the one hand, we need to know the human physiological demand of suitable, absorbable nutrients. However, when the absorption and the utilization of an ingested nutrient are compromised (by the type of diet or intestinal and systemic conditions or diseases), dietary requirements should take precedent over physiological ones [13]. An important nutritional aspect is bioavailability, which is the ingested part of the nutrient that is absorbed and available. It is influenced by diet and human-related factors and contribute to regular metabolic pathways [14]. Bioefficacy is described as the efficiency of the absorption of ingested nutrients and transformation to their active form [15]. All of these factors are important in order to determine the adequate requirements for the population.

Today, there are different categories of Dietary Reference Intakes (DRI), but each category refers to people's average daily nutrient intake over time. The Recommended Dietary Intake (RDA) is described as the average daily intake that is sufficient to meet the nutrient requirement of almost all healthy people (97-98%) taking into consideration their gender and stage of life [16]. Adequate Intake (AI) is considered when there is insufficient scientific evidence available for the RDA. The tolerable upper intake level (UL) is defined as the highest level of daily nutrient intake that does not pose any adverse health risk. This term is used for TE with adverse health effects in any case of excessive consumption [16]. The DRI of TE in the human population is summarized in Table 1.

2.2 Intrinsic and extrinsic influences on TE requirements

Global intrinsic and extrinsic differences affect the dietary requirements of TE (Figure 1). Among them, we find soil composition in different geographical locations, food availability and composition, preparation and cooking, sociological habits (geophagia), contamination, body composition, and genetic polymorphisms [6]. In relation to food composition, several studies have shown the inhibitory effects of phytic acid (mainly present in dry fruits, grains, maize, and legumes) on mineral bioavailability and their interactions [17,18,19]. For example, foods rich in phytates

reduce the intestinal absorption of Zn because they bind to Zn through its link to oxygen. Food treatments such as malting, microbial fermentation, and soaking have been reported to reduce the phytate content of foods through the activation of the phytase enzyme that catalyzes the transformation of phytates into inorganic phosphorus, which in turn improves Zn bioavailability [6]. Food contamination is a critical problem worldwide and technological advancement is needed to achieve accurate and reliable data on TE concentrations. Toxic TE such as Pb, Cd, and Hg can be present in relatively high concentrations in seafood and the maximum allowable limit in the European Union is controlled by the European Commission regulation 1881⁄2006 [20]. Other foods such as dried mushrooms can accumulate toxic TE including Hg, Cd, As and Pb, although cooking can reduce their levels [21]. Furthermore, in recent years, the application of artificial nanoparticles is increasing in some fields such as agriculture and textile, cosmetic, pharmaceutical and biotechnology industries. On the one hand, exposure to these particles can increase environmental toxicity and cause damage to the ecosystem at different levels [22]. On the other hand, the correct application of nanoparticles can decrease food toxicity by reducing the absorption of TE. Nanoparticles have been reported to reduce TE translocation from roots to shoots by promoting structural alterations, modifying gene expression, and improving antioxidant defense systems. However, this concept is novel, and studies are required to explore the mechanisms of nanoparticles-mediated TE immobilization in soil and uptake by plants [23].

Intrinsic factors such as body composition and genetics are related to TE status, too. Some studies have described that essential TE deficiency is linked to an increase in fat deposition [24]. It has been reported that overweight and obese Hispanic children have low serum concentrations of Zn and that weight loss can contribute to an increase in plasmatic Zn concentrations in overweight and obese women [25]. It has also been reported that TE are related to body composition variables (fat and muscle mass, skinfold values and body weight) in endurance runners, who need to control their dietary intake of essential TE such as Cu, Se, V and Li to avoid cases of deficit and to establish supplementation regimens [26].

In relation to genetic polymorphisms, some studies have identified and localized chromosomal regions, employing a genome-wide association study (GWAS) that may be able to detect genes that affect TE concentrations in blood[27]. One of the examples in which polymorphisms are linked to TE is the interleukine-6 polymorphism gene, which modulate the intracellular Zn homeostasis [28].

Nutrient status is affected by the stage of life, so the requirements are different. For example, there is fast growth of a baby during pregnancy and a child during adolescence, which

bring with it important biological changes accompanied by an increase in TE demand [6,29]. Moreover, later in life there is an increase in the risk of TE deficiency related to changes in dietary habits and requirements, physiological alterations, drug treatments and chronic diseases, an effective supplementation often being necessary [30]. TE can affect the rate of biological aging due to their influence on the modulation of oxidative damage and DNA repair, immune function, insulin sensitivity and cognitive function. For these reasons, current evidence focuses on the study of the role of TE in the aging process using omics approaches to achieve good biomarkers in these involved processes [31].

2.3 The bioavailability, absorption and excretion of TE

As described above, bioavailability and bioefficacy of the absorption are two important concepts for establishing TE requirements. In the organism, several processes (transport, transformation and utilization) and interactions are involved in adjusting the absorption and excretion of TE depending on the changing intake and aimed at maintaining homeostasis [32]. After ingestion, TE undergo different processes in order to be released from the food matrix and are transported and absorbed by the intestine [33,34]. However, different factors affect nutrient bioavailability.

Concerning diet-related factors, dietary components, chemical structure and TE interactions should be considered [6]. Phytates, oxalate, fiber and polyphenolic compounds influence bioavailability of a TE and therefore its requirement. It has been shown that due to the increased fecal losses vegetarians with a higher fiber consumption have a deficient Zn status. By contrast, food acidulants, such as lime and dry mango powder enhance its bioavailability [35]. In addition, polyphenols have metal-chelating properties through its aromatic hydroxyl groups [36]. Polyphenols also have high reactivity to Cu ions [37].

The chemical form of the nutrient determines the absorption and utilization of TE. For example, organic forms of Zn (from oysters) and Se (from most plant tissues and selenized yeast) are better and more efficiently absorbed than inorganic forms administered as supplements [6,13]. Food and dietary supplements present multi-minerals that interact and compete among themselves due to their common physical and chemical characteristics (Figure 2). These interactions are produced when two or more TE aim to capture the same binding site in biomolecules and therefore block access to other elements [38]. For instance, some studies have observed that an overabundance of Zn can generate an antagonistic effect on Cu levels in adults [39,40]. At the same time, it is known that Cd inhibits Zn absorption, and exposure to Cd is related to serum low Zn levels [41,42]. Also, interactions between Se and I via conversion of thyroxine (T4)

into 3,3',5 triiodothyronine (T3) by the removal of an I atom have been shown to be important for maintaining thyroid hormone stability [43,44].

3. A crosstalk between dietary trace elements and cancer. Cancer risk and cancer prevention

Nowadays, the incidence of cancers and concomitant death is growing exponentially [45]. In recent years, TE have been considered essential components in cancer development, progression, or inhibition [46,47]. Indeed, studies have observed associations between TE levels and cancer (Figure 3) [48,49]. However, understanding their specific role in cancer etiology and pathogenesis needs clarity due to the conflicting results reported in the literature. Moreover, there has been little investigation regarding dietary consumption of TE and cancer risk or cancer prevention. Indeed, there is a need to conduct well-designed randomized controlled trials to establish evidence-based guidelines on dietary recommendations for TE in cancer patients. Alterations in TE concentrations may trigger DNA damage and an imbalance in oxidative burden, and can influence innate and adaptive immunity resulting in a malignant transformation (Figure 4) [48-51].

Intracellular redox potential is measured in order to maintain cellular homeostasis and regulate metabolic cell functions [52]. Reactive oxygen species (ROS) regulate numerous cellular pathways involved in cell differentiation, signaling, and apoptosis under normal conditions. However, when there is an excess of ROS in the organism, the antioxidant system composed of enzymatic and non-enzymatic proteins is essential to prevent the emergence of cancer [53-55]. In this context, among essential TE, Zn elicits antioxidant properties against free-radical injury and then inhibits tumor growth. This TE is a co-factor in superoxide dismutase (SOD) that catalyzes the disproportionation of superoxide radicals to hydrogen peroxide [56]. A decrease in SOD activity produces oxidative stress and results in carcinogenesis and tumor progression. Zn also possesses an anti-carcinogenic function because of its role in DNA, RNA, and ribosome structural stabilization and in many transcription factors and proteins [57,58]. Furthermore, Zn concentrations have been shown to be affected by the cells that constitute a tumoral microenvironment (TME), such as pro-inflammatory mast cells, which are associated with a worse patient prognosis [59]. These cells liberate Zn into neighboring tissues and affect the cellular response [60]. In addition, a great number of cytokines and growth factors (IL-6, hepatocyte, and epidermal growth factors, and TNF α) generated in the TME affect the expression of Zn transporters [61]. Reduced Zn levels are

associated with a reduction in monocyte adhesion, granulocyte chemotaxis, macrophage phagocytosis and the cytotoxicity of natural killer cells. Besides that, the depletion of Zn diminishes the activity of cytokines triggered by macrophages and T cells and T-cell differentiation [62]. Some epidemiological studies have described low serum concentrations of Zn in patients with different types of cancer (bladder, renal, endometrial, ovarian, cervical, and testicular cancer) compared to healthy controls [63-68]. Also, low dietary intake of Zn, measured by a food frequency questionnaire, has been associated with laryngeal and esophageal cancer [69]. Zn consumption from food sources, apart from red meat, has been shown to be able to protect against lung cancer. For these reasons, it is crucial to assess the Zn status in cancer patients and correct any deficiency [70]. Other studies have observed that depending on its concentration, Zn is able to protect against or provoke cell apoptosis because intracellular levels of Zn orchestrate the effect of exogenous Zn on the life and death of cells [71,72]. However, there are no decisive conclusions about the relationship between Zn exposure and skin cancer risk because results are contradictory [73].

Cu is another essential TE implicated in cancer. Many studies have observed that the deregulation of its homeostasis might be the cause and consequence of carcinogenesis due to its role in proliferation and angiogenesis [74]. Cu participate in different proangiogenic pathways and influences enzymes that are responsible for cell proliferation and the formation of secondary tumors. This may be the reason its concentration is higher in areas of tumor and is present inside the nuclear region of breast cancer cells [75-77].

Several studies have reported higher serum Cu concentrations in patients with osteosarcoma, gastrointestinal tumors, lung cancer, and oral premalignant and malignant lesions, and also found correlations with the histological grade of cancer [78-81]. Further studies have observed higher levels of salivary Cu in patients with oral lesions and with an oral squamous cell carcinoma, with respect to the control group [82,83]. Even so, few studies have analyzed the relationship between Cu intake and cancer risk. While one report has observed no association between Cu intake and lung cancer, another report has suggested that the combination of dietary Zn and Cu supplementation can reduce lung cancer risk [70,84]. By contrast, other studies have observed that dietary intake of Cu, Se, Zn, and Fe does not protect against liver cancer [85], but have found an increased risk of kidney cancer under Cu supplementation among postmenopausal women [86]. In short, the absence of scientific evidence makes it difficult to make a nutritional recommendation on Cu intake for cancer patients. The opposite roles of Cu and Zn is of utmost importance. The Cu/Zn ratio is related to aging, nutritional status, oxidative stress, inflammation,

and immune alterations. This ratio has been associated with gastrointestinal, bladder, breast, and prostate cancers [79,87-91].

Se has been extensively investigated in relation to some cancers but there is little scientific evidence on the relationship between dietary Se (main source) and cancer risk. This TE acts as a co-factor for antioxidant enzymes and possesses anti-inflammatory and antioxidant properties [92]. It is mainly carried by selenoprotein P and its mutations increase the risk of cancer [93]. The potential anticancer effects of Se are related to glutathione peroxidase (GPX) formation, which protects against oxidative damage [93].

Epidemiological studies have reported that geographical regions with insufficient Se intake present a higher risk of cancer development [94, 95]. By contrast, due to an enhancement of the immune system, optimal supplementation doses can prevent cancer growth, relapse, and death [96, 97]. Conversely, an excess of Se supplementation can be toxic, acting as a pro-oxidant, and can lose the cancer-prevention effect [98]. Indeed, in *in vivo* studies, Se supplementation has been shown to increase the incidence of esophageal cancer and tumor volume [99]. In retrospective and supplementation trials, contradictory results have been reported about dietary and supplemented Se and cancer risk but have indicated that dietary Se could prevent cancer more efficiently than supplements [100]. Other studies have shown that Se supplementation reduces the occurrence of lung and gastric cancer in populations with low serum levels of Se [101].

Other human studies have suggested that intake of Se and Zn rich foods such as fish and seafood, meat, fresh vegetables, and fruits may reduce the risk of esophageal cancer [102-104]. However, other studies have not observed any significant associations between Se intake and the risk of skin cancer or the incidence of breast cancer [73,105]. A few studies have even described a positive association between Se exposure and keratinocyte carcinoma risk [72].

Mn is a required element in the defense system and is a co-factor of the SOD antioxidant enzyme, which is essential in the mitochondria to scavenge ROS [106]. In this context, some studies have suggested that lower serum Mn levels with an alteration in the antioxidant mechanism can render organs vulnerable to carcinogens [68]. Indeed, lower serum Mn concentrations with respect to controls were observed in patients with testicular cancer [68]. Also, significant Mn alterations have been found in malignant tissue of colorectal cancer in comparison to healthy tissue [50].

In relation to the intake of Mn, it has been reported that an increase in the consumption of this metal was negatively associated with liver cancer risk, and that the low consumption of foods rich in Mn, such as green leafy vegetables, whole cereals, nuts, legume seeds, and tea predisposes

to liver cancer [85]. Furthermore, an inverse association has been observed between total Mn intake from food sources and a risk of Non-Hodgkin Lymphoma [107]. However, it has been suggested that the mechanistic implications of these associations could be due to the potential synergies between antioxidants or other anti-carcinogenic compounds in these foods. So, prevention measures should consider targeting foods or food groups rather than individual nutrients.

Some non-essential TE, such as Cd, Cr, and As are considered toxic and carcinogenic, and their exposure comes mainly from soil and water sources that affect food and drinking water, and from pesticides [108,109]. In physiological doses, Cd increases endothelial permeability through the inhibition of endothelial proliferation and induces cell death mediated by DNA damage [110]. Some studies have described the implicated mechanisms in Cd carcinogenicity, such as the modulation of gene expression and signal transduction, the generation of ROS through an alteration of the antioxidant enzymatic system, the inhibition of DNA repair and DNA methylation, disrupted cell adhesion, and apoptosis [111].

In this context, an increase in soil Cd has been associated with a 57% increase in lung cancer risk [68]. Moreover, high serum Cd concentrations have been found in patients with bladder cancer [63] and it is believed that Cd acts as a co-factor in prostate cancer development through the stimulation of prostate epithelial cells and the alteration of steroid hormones. By contrast, Se is considered a protector to prostate cancer risk, and the mechanism may involve Cd inactivation due to the high chemical affinity of Se for Cd [112]. However, Cd can suppress the protective effects of Se against cancer, and for that reason, the measurement of the Se/Cd ratio is important for assessing prostate cancer risk [112]. Dietary Cd intake has been evaluated and positively associated with a risk of hormone-related cancers, such as breast cancer, in most western countries [113]. By contrast, no association was reported between Cd intake and prostate cancer risk in a cohort of Danish men or with other types of cancer in Japan [114,115].

Cr and As have been associated with an increase in lung cancer incidence and bladder and kidney cancer mortality, respectively [116,117]. One study observed that dietary intake of Cr through the consumption of wheat grains was related to an increase in cancer risk in residents of India [118]. Several epidemiological studies have reported a direct association between the exposure of As and keratinocyte carcinoma [73]. By contrast, there is not enough scientific evidence to confirm the association between Cr and Cd exposure with skin cancer [73].

Pb possesses a predisposing function in carcinogenesis through the inhibition of DNA synthesis and repair, oxidative damage, and the interplay with DNA-binding and tumor suppressor

proteins [119,120]. Patients with malignant glioma and testicular cancer have been shown to present higher levels of Pb compared with controls [121, 68].

Some non-essential TE are present in most medicinal herbs and vegetables widely used in Africa. Among them, we found Pb, Ni, Cr, and Cd. One study in both children and adults linked the consumption of medicinal herbs with carcinogenic effects, showing that these heavy metals, when accumulated, can increase cancer risk through oxidative stress produced in body tissues, apoptosis and cellular dysfunction [122]. Another dietary food with a high concentrations of metals (Hg, Pb, Cr, As, Ni, Cd) is canned tuna fish. Several studies have analyzed the metal concentrations in seafood and related their consumption with cancer risk [123].

4. The bidirectional impact of oncology treatments and TE

Drugs currently used in conventional cancer treatments have a narrow therapeutic window and often cause adverse reactions due to their toxicity. Their metabolization by the hepatic cytochrome P450 system results in the formation of toxic products and drug resistance may appear as a secondary effect of ionizing radiation [124]. The adverse effect of drugs is a real clinical problem and some TE in combination with oncology treatments can improve treatment effectiveness and reduce toxicity. One of our previous studies carried out with breast cancer patients showed trace element alterations (B, Cu, Zn and Sr) before RT in comparison with the control group. In addition, Sr and Zn were associated with dermatitis and asthenia, the main toxicological responses to RT [125]. Recent evidence has demonstrated that Se supplementation can protect normal cells from toxicity and enhance the therapeutic effect of chemotherapy in several cancer types [126,127], although the best way to safely supplement patients with TE and the optimum dosages still remain unknown. It has been reported that Zn supplementation reduces both the incidence of mucositis induced by chemotherapy and the disease severity in patients with leukemia [128]. A clinical trial has reported that Zn supplementation in patients with colorectal cancer undergoing chemotherapy reduced fatigue and helped to maintain quality of life [129]. Another report has suggested the use of total parenteral nutrition in patients undergoing chemotherapy in order to maintain nutrient homeostasis (Zn, Mg, Mn, Cu, I, etc.) and improve the treatment outcome [130]. Cu plays an important role in the metastatic cascade and many therapeutic strategies attempt to reduce its concentration through the use of chelators post-chemotherapy or radiotherapy. Another clinical trial reported that depleted Cu levels reduced endothelial progenitor cell markers that are involved in metastasis [131]. On the other hand,

experimental studies in mice with breast cancer treated with Cu chelators, found reduced tumor growth and metastases and increased animal survival [132]. However, the response of Cu chelators is different depending on the primary cancer type [133]. *In vitro* and *in vivo* studies have yielded promising results in relation to other TE such as Li, Mn, Cd, V, suggesting that these metals could be potential candidate for adjuvant therapy in different types of cancer.

5. Focus on TE as a target in cancer

The identification of novel biomarkers for the diagnosis, prognosis or monitoring of cancer follow-up is a priority in cancer research. TE have great potential for use as biomarkers since they can play an important role in many physiological processes, as we have previously discussed. Alterations in TE levels is a common finding among cancer patients and opens the opportunity to find reliable biomarkers. Using machine learning algorithms can help us improve the accuracy of cancer diagnosis and response to cancer treatment. In accordance with the above, the nature of cancer promotes a wide range of plasma alterations in elements such as B, Cu, Zn, among others. Low plasma Zn concentrations have been reported to be a good predictor of colorectal cancer, with a diagnostic accuracy of 80% [134]. Similar results in plasma or serum have been reported in breast, thyroid, and bladder cancer. However, the Zn concentration in malignant breast tissue was reported higher than in benign tissue [135]. In patients with thyroid cancer, decreased serum levels of Zn, Se, and Cu, and increased tissue Zn, Se, and decreased Cu were observed compared to healthy controls [136]. Finally, bladder cancer patients showed higher plasma levels of B, Cd, Cu, Hg, Li, Ni, and Zn than healthy controls. The most predictive elements were Ni and Li with an accuracy of 79 and 77%, respectively [137]. Selecting a biomarker has become an important task in trace element research; however, age, ethnicity and sex are important variables in the analysis to avoid bias and wrong predictions. Therefore, to achieve personalized treatments for better patient outcomes it is necessary to obtain sex-specific biomarkers to improve prediction accuracy. Precision oncology with the help of learning models drastically enhances the way cancer is treated, the way drugs are developed and the clinical outcomes. In this context, real-world datasets can be used to provide clinical decision support tools to improve health outcomes and to minimize the risk of error. Artificial intelligence and learning algorithms will help us to optimize the use of TE and will answer some of important questions, such as when and how to administer the TE and the optimum dosages, etc.

6. Conclusions and further perspectives

Despite the difficulty in providing accurate and reliable evidence for the effects of TE in cancer, these elements seem to play a crucial role in the metabolism of cancer cells. Considering the importance of good dietary habits for maintaining optimal health status, it is easy to think that some TE can be beneficial in protecting us from cancer cells. The approach should take into account the effects of supplementation alone and in conjunction with a food matrix and should observe the changes in the metabolism using a multi-omics approach. Using TE together with conventional oncology treatments to combat cancer could be possible in the near future. In the era of big data, a shift is underway in the world of science as more and more effective tools become available to decipher vast amounts of health-related data. This scenario opens new opportunities for generating evidence and expanding our understanding of oncology research. Therefore, the new science offers a more precise and effective way to find new synergic interaction between TE and conventional treatments, which will unlock a wide variety of choices for treating each cancer type properly.

CRediT authorship contribution statement

Conceptualization, E.R.T., G.B.G., M.A., J.C. and J.J.; writing-original draft preparation, E.R.T., G.B.G., H.C. and J.C.; writing-review and editing, E.R.T., G.B.G., J.C, M.A.; supervision, J.C. and J.J. All authors critically supervised the manuscript and approved the final version.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Figure legends

Fig. 1. Intrinsic and extrinsic factors involved in dietary requirements for trace elements. Physiological (age, sex, genetics, body mass index (BMI), pregnancy and lactation and ethnicity) and extrinsic (soil and geographical location, food preparation and processing, cultural practices and pollution) factors can influence requirements for trace elements due to their influence in

nutrient absorption and utilization. Created with BioRender.com (BioRender, Toronto, ON, Canada). Accessed 03/20/2021.

Fig. 2. The intestinal absorption interaction of trace elements. Diet provides the main source of trace elements; however, their concentration can differ depending on the type of food source. When these elements arrive at the intestinal lumen to be absorbed it may produce some element-element interaction and decrease absorption. Therefore, the dietary pattern will play an essential role in maintaining a correct equilibrium of trace element levels. Created with BioRender.com (BioRender, Toronto, ON, Canada). Accessed 03/20/2021.

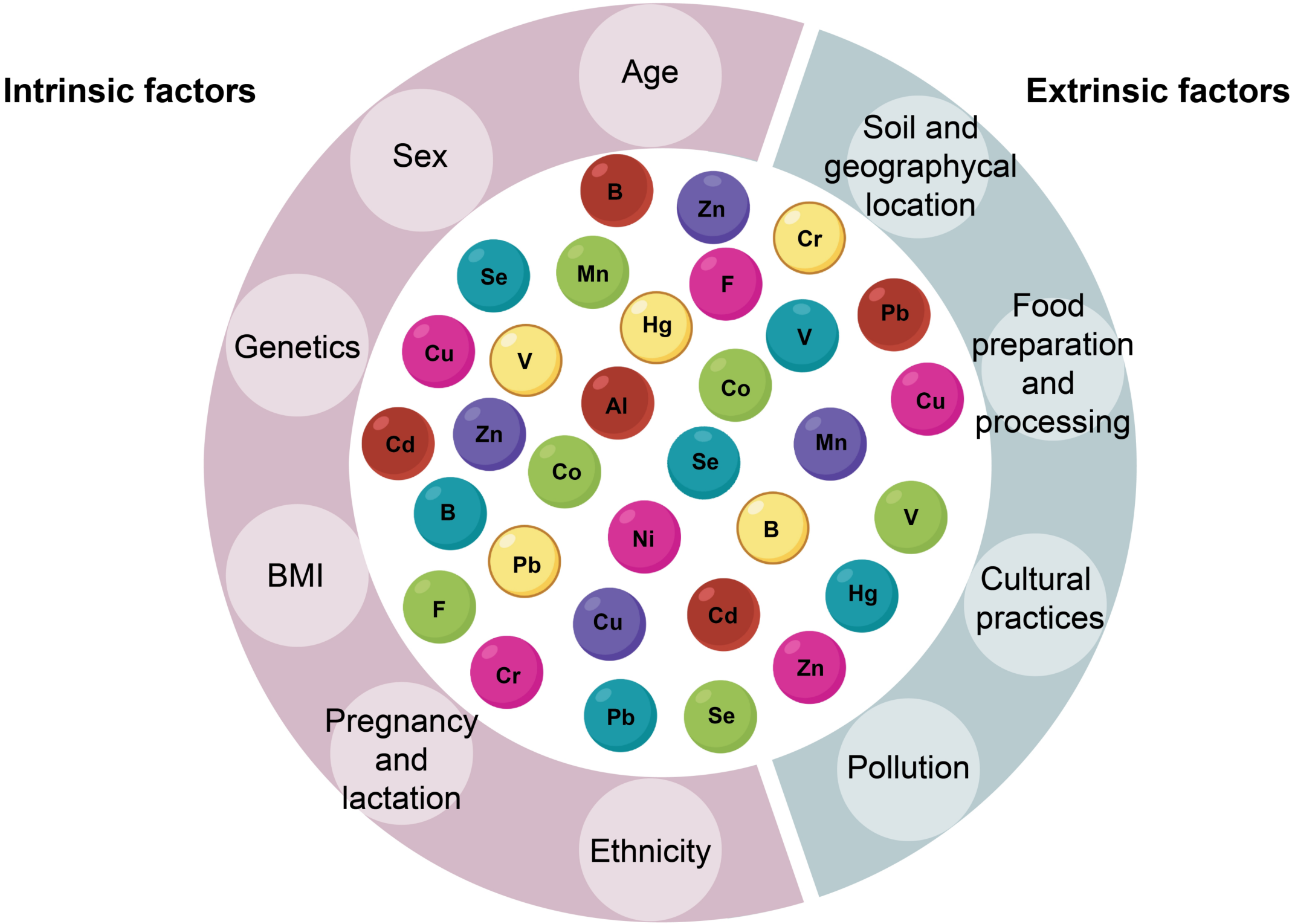
Fig. 3. Deregulation of the levels of trace elements and associated cancers. An imbalance (excess or insufficiency) in trace element levels is associated with different types of cancer. Created with BioRender.com (BioRender, Toronto, ON, Canada). Accessed 03/20/2021.

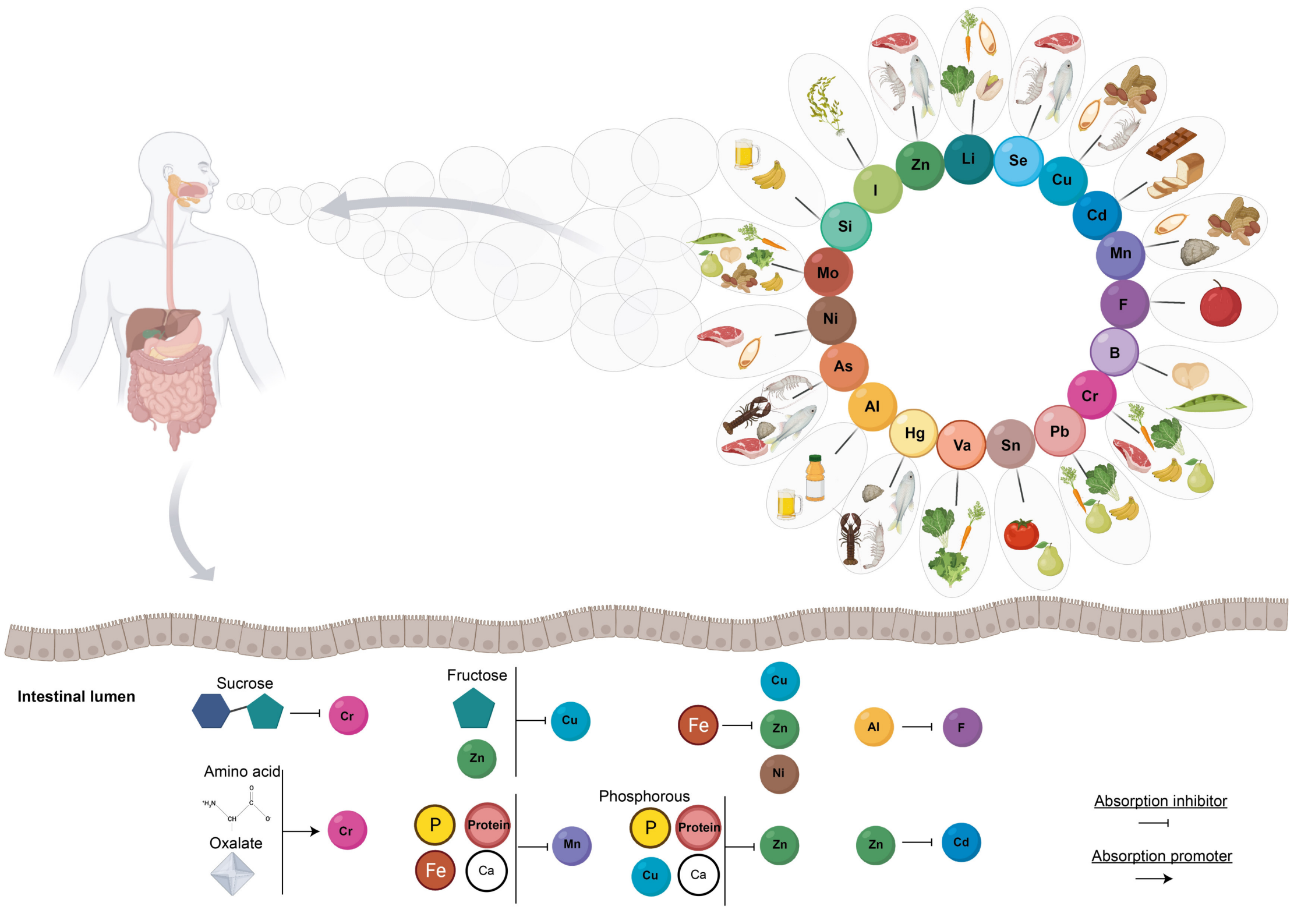
Fig. 4. The imbalance of trace elements implicated in cancer development or prevention. Trace element imbalance can be caused by a poor-quality diet, affecting the immunological response against cancer cells. Specifically, disturbance in trace element homoeostasis worsen the ability to recognize and destroy developing cancer cells, promoting their growth. Created with BioRender.com (BioRender, Toronto, ON, Canada). Accessed 03/20/2021.

Table 1. Dietary trace elements recommendations and nutrient interactions.

Element	Nutrient interaction	Dietary Recommendations
Arsenic	Not stablished	Not stablished
Aluminum	Not stablished	26.5mg/day (Estimated Average Daily Intake)
Boron (UL)	Not stablished	**Adult:** 20mg/day **Adolescent (14 to 18):** 17mg/day **Adolescent (9 to 13):** 11mg/day **Children (4 to 8): 6** mg/day **Children (1 to 3): 3**mg/day **Infants (0-12 months)**: not possible to establish
Cadmium	Decrease absorption: Zinc	0.83μg/week/kg body weight (Provisional Tolerable Weekly Intake)
Chromium (Adequate Intake AI)	Decrease absorption: Sugar and phytate. Increase absorption: amino acids and oxalate.	**Adults (>51 years):** 30μg /day (Men) 20μg /day (Women) **Adult:** 35μg /day (Men) and 25μg /day (Women) **Adolescent (14 to 18):** 35μg /day (Men) and 24μg /day (Women) **Adolescent (9 to 13):** 25μg /day (Men) 21μg /day (Women) **Children (4 to 8): 1**5 μg /day **Children (1 to 3):** 11 μg /day **Infants** (7-12 months): 5.5 μg /day **Infants** (0-6 months): 0.2 μg /day
Copper	Decrease absorption: Zinc, Iron and Fructose	**Adult:** 900μg /day **Adolescent** 890 μg /day **Children (9 to 13):** 700μg /day **Children (4 to 8):** 440 μg /day **Infants**: 340μg /day
Fluoride	Decrease absorption: Aluminum	5mg/kg body weight (Probable Toxic Dose)
Iodine	Not stablished	**Adult (>18):** 150 μg /day (Men) **Adolescent (14 to 18):** 150 μg /day (Men) and 24μg /day (Women) **Adolescent (9 to 13):** 120μg /day (Men) 21μg /day (Women) **Children (4 to 8):** 90 μg /day **Children (1 to 3):** 90 μg /day
Lead	Decrease absorption: Calcium	12.5μg/day
Lithium	Not stablished	Not stablished
Manganese (Adequate Intake AI)	Decrease absorption: Calcium, Iron and Phosphorus.	**Adult:** 2.3mg/day (Men) and 1.8mg/day (Women) **Adolescent (14 to 18):** 2.2mg/day (Men) and 1.6mg/day (Women) **Adolescent (9 to 13):** 1.9mg/day (Men) 1.6mg/day (Women) **Children (4 to 8): 1.**5 mg/day **Children (1 to 3):** 1.2mg/day

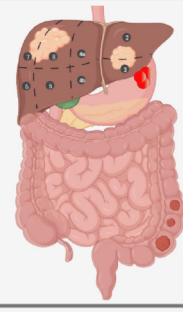
		Infants (7-12 months): 0.6mg mg/day **Infants** (0-6 months): 3 μg /day
Mercury	Not stablished	Not stablished
Molybdenum	Decrease absorption: Tungsten but is not considered significant in human nutrition.	**Adult:** 45μg /day **Adolescent (14 to 18): 43**μg /day **Adolescent (9 to 13):** 34μg /day **Children (4 to 8): 22**μg /day **Children (1 to 3): 17**μg /day **Infants** (0-12 months): not possible to establish
Nickel	Decrease absorption: Iron	**Adult:** 1mg/day **Adolescent (14 to 18):** 1mg/day **Adolescent (9 to 13):** 0.6mg/day **Children (4 to 8): 0.3** mg/day **Children (1 to 3): 0.2** mg/day **Infants** (0-12 months): not possible to establish
Selenium	Not stablished	**Adult:** 45μg /day **Adolescent** 55μg /day **Children (9 to 13):** 40 μg /day **Children (4 to 8): 30**μg /day **Infants**: 20μg /day
Silicon	Not stablished	Not stablished
Tin	Not stablished	Not stablished
Vanadium **Tolerable Upper Intake Level (UL)**	Not stablished	**Adult:** **Adolescent (14 to 18):** not possible to establish **Adolescent (9 to 13):** not possible to establish **Children (4 to 8):** not possible to establish **Children (1 to 3):** not possible to establish **Infants** (0-12 months): not possible to establish
Zinc	Decrease absorption: Iron, Calcium, Phosphorous, Copper, Folate and Protein.	**Adult:** 11mg/day (Men) and 8mg/day (Women) **Adolescent:** 11mg/day (Men) and 9mg/day (Women) **Children (9 to 13):** 8mg/day **Children (4 to 8):** 5 mg/day **Infants**: 2 mg/day


Intrinsic factors
Extrinsic factors
Age
Sex
Genetics
BMI
Pregnancy and lactation
Ethnicity
Soil and geographycal location
Food preparation and processing
Cultural practices
Pollution
B
Zn
Cr
Se
Mn
F
Hg
Pb
V
Cu
V
Co
Al
Cu
Cd
Zn
Mn
Co
Se
B
B
V
Ni
Pb
Hg
F
Cu
Cd
Cr
Zn
Pb
Se


Zn
Li
Se
Cu
Cd
Mn
F
B
Cr
Pb
Sn
Va
Hg
Al
As
Ni
Mo
Si
I
Intestinal lumen
Sucrose
Cr
Fructose
Cu
Zn
Fe
Cu
Zn
Ni
Al
F
Amino acid
Oxalate
Cr
P
Protein
Fe
Ca
Mn
Phosphorous
P
Protein
Cu
Ca
Zn
Zn
Cd
Absorption inhibitor
Absorption promoter

Gastrointestinal and/or liver cancers

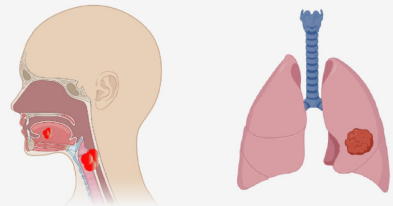
Cr Cu Cu/Zn ratio Se Pb



Mn

Oral, laryngeal, esophageal and/or lung cancers

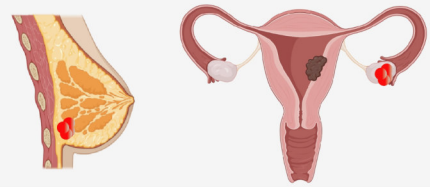
Cu Cr Cd Se Pb As Ni



Zn

Gynaecological cancers

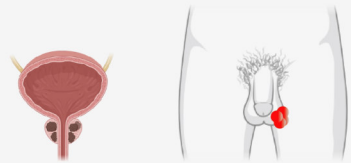
Cu Cd Cu/Zn ratio



Zn

Prostate and/or testicular cancers

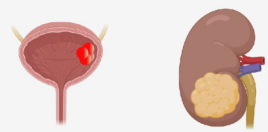
Cd Pb Cu/Zn ratio



Zn Mn

Bladder and/or renal cancers

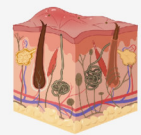
Cd Cu/Zn ratio As Cr



Zn

Skin cancer

Se As

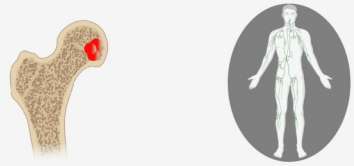


Brain cancer

Pb

Osteosarcoma and/or Non-Hodgkin Lymphoma

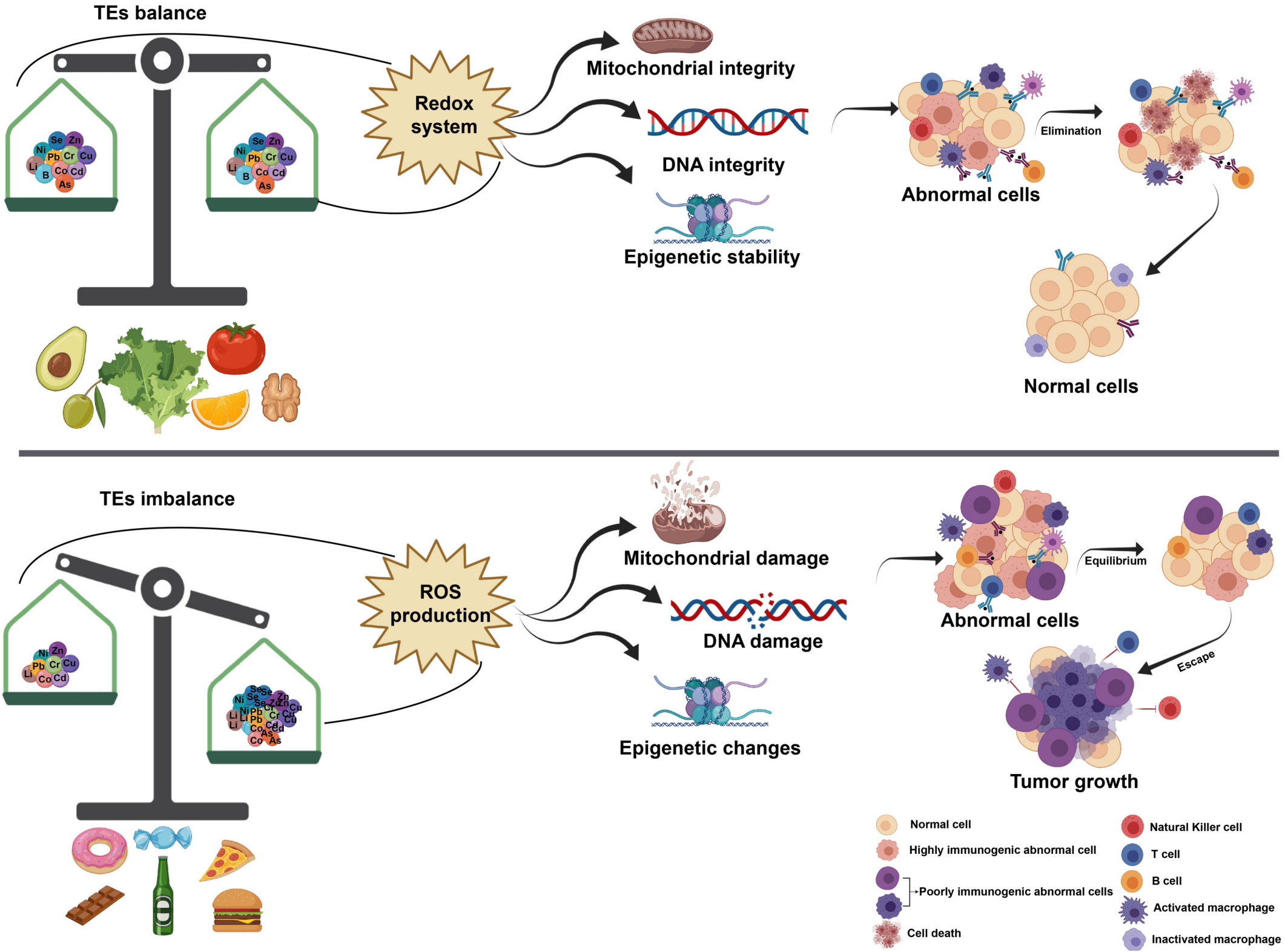
Cu



Mn

High levels

Low levels


TEs balance
Redox system
Mitochondrial integrity
DNA integrity
Epigenetic stability
Abnormal cells
Elimination
Normal cells
TEs imbalance
ROS production
Mitochondrial damage
DNA damage
Epigenetic changes
Abnormal cells
Equilibrium
Escape
Tumor growth
Normal cell
Highly immunogenic abnormal cell
Poorly immunogenic abnormal cells
Cell death
Natural Killer cell
T cell
B cell
Activated macrophage
Inactivated macrophage