SYSTEMATIC REVIEW

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The preventive and carcinogenic effect of metals on cancer: a systematic review

Amir Hossein Khoshakhlagh[1], Mahdiyeh Mohammadzadeh[2,3*] and Agnieszka Gruszecka-Kosowska[4]

Abstract

Background Many studies have investigated the role of metals in various types of malignancies. Considering the wide range of studies conducted in this field and the achievement of different results, the presented systematic review was performed to obtain the results of investigations on the prevention and occurrence of various types of cancer associated with metal exposures.

Methods In this review, research was conducted in the three databases: Scopus, PubMed, and Web of Science without historical restrictions until May 31, 2024. Animal studies, books, review articles, conference papers, and letters to the editors were omitted. The special checklist of Joanna Briggs Institute (JBI) was used for the quality assessment of the articles. Finally, the findings were classified according to the effect of the metal as preventive or carcinogenic.

Results The total number of retrieved articles was 4695, and 71 eligible results were used for further investigation. In most studies, the concentration of toxic metals such as lead (Pb), chromium (Cr (VI)), arsenic (As), cadmium (Cd), and nickel (Ni) in the biological and clinical samples of cancer patients was higher than that of healthy people. In addition, the presence of essential elements, such as selenium (Se), zinc (Zn), iron (Fe), and manganese (Mn) in tolerable low concentrations was revealed to have anti-cancer properties, while exposure to high concentrations has detrimental health effects.

Conclusions Metals have carcinogenic effects at high levels of exposure. Taking preventive measures, implementing timely screening, and reducing the emission of metal-associated pollutants can play an effective role in reducing cancer rates around the world.

Keywords Cancer, Essential elements, Metal carcinogenesis, Heavy metals, Oxidative stress

*Correspondence:
Mahdiyeh Mohammadzadeh
m.mohammadzadeh997@gmail.com
[1] Department of Occupational Health Engineering, School of Health, Kashan University of Medical Sciences, Kashan, Iran
[2] Department of Health in Emergencies and Disasters, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[3] Climate Change and Health Research Center (CCHRC), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran
[4] AGH University of Krakow, Faculty of Geology, Geophysics and Environmental Protection, Department of Environmental Protection, Al. A. Mickiewicza 30, Krakow 30-059, Poland

Introduction

Currently, one of the main causes of morbidity and mortality worldwide is cancer. More than 1 person out of 5 people get cancer [1]. Based on projections, the number of new cancer patients will increase from 14.1 million reported in 2012 to 21.6 million estimated in 2030 [2]. Lifestyle behaviors such as obesity, smoking, and unhealthy diet, genetic changes, chronic diseases, and environmental interactions play key roles in cancer etiopathogenesis [3, 4].

Cancer is a disease caused by the uncontrolled and unnormal cell growth, resulting in the possibility to invade and metastasize any part of the body and formation of a tumor [5]. There are several types of cancer,

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including carcinoma, sarcoma, lymphoma, and leukemia [6]. The causes of cancer are mutations in the genes responsible for cell growth and division control [6]. Among the causes of the mutations, genetic inheritance, hormonal imbalances, and exposure to environmental factors such as certain chemicals can be mentioned [6]. Cancer pathophysiology involves three stages. The first one is caused by the initiation of mutations in the cell DNA leading to the activation of cancer genes and the inactivation of tumor suppressor genes. In the second stage promotion of the mutation cell takes place, which is stimulated by the differentiation and rapid growth of the mutation cell, forming a small cluster of abnormal cells. In the third stage the progression takes place, where abnormal cells continue to divide and grow, forming tumors that invade the surrounding tissue, and spread to other parts of the body through the blood flow or lymph system [6].

Studies have shown that various metals can impact on cancer induction by the same mechanisms, such as manipulating the state of chromatin and gene expression [7] or producing ROS and increasing oxidative stress [8]. Nickel was found to activate the signal pathways induced by hypoxia, mediated by competition with Fe in the prolyl-hydroxylase [8]. Arsenic and Cd have also been shown to compete or replace important metals such as Zn and Ca in proteins as the main mechanisms of cell gene and cell toxicity [8]. Also, As and Cd were found to suppress cell autophagy, which is an important factor in tumor suppression [8]. Considering genetic damage through both oxidative and nonoxidative (DNA adducts) mechanisms, metals were revealed to cause significant changes in DNA methylation and histone modifications, that results in epigenetic silencing or reactivation of gene expression [9]. Moreover, it was revealed in in vitro genotoxicity experiments and animal carcinogenicity studies that metals can cause cocarcinogenic and comutagenic effects as metals are likely to interfere with DNA repair processes [9].

Existing reports estimate that environmental factors, such as insecticides and pesticides, pollutants in air, water, and soil, cause 24% of the global disease burden measured in healthy life years lost and 23% of all types of premature deaths [10]. Studies indicate that the difference in exposure to environmental-related risk factors and the ability to obtain adequate health care increase the environmental burden of the apperance of diseases in developing countries 15 times compared to developed countries [11–13]. Environmental anthropogenic changes, such as water, soil, and air pollution, the growth of industrial activities, agricultural practices, the use of chemical fertilizers and pesticides, and food processing, play an important role in increasing the incidence of cancer by disrupting the balance of trace elements and metals in the environment [14, 15].

The mechanism of toxicity and carcinogenicity of toxic metals is presented in Fig. 1. After entering the body through exposure via digestion, inhalation, and dermal contact, metals can accumulate in the vital organs of the body such as the liver, kidney, and bones [16]. This feature can cause complications caused by the toxic effects of these elements in humans, including digestive system and kidney dysfunction, immune system dysfunction, nervous system disorders, vascular damage, birth defects, skin lesions, and epigenetic processes that lead to cancer [17, 18]. These processes lead to the deactivation of tumor suppressor genes, DNA repair enzymes, the transformation of proto-oncogenes into oncogenes, as well as changes in DNA methylation [19]. Metals also significantly affect the development of malignancies by activating redox-sensitive transcription factors, a protein that signals pathways involved in cell growth, apoptosis, disruption of cycle regulation in cells, as well as cell differentiation [20, 21], histone modifications and non-coding RNA expression [22, 23]. In addition, the initiation and progression of cancer have been found to be related to oxidative stress and the activation of inflammatory mediators. Connecting and activating transporters and cell surface receptors [24], activating metallothioneins [25] and specific enzymes and modulating selected intracellular kinases and phosphatases [26, 27] are other mechanisms of metal carcinogenesis. The following protein kinase: extracellular signal-regulated (ERK1/2) and protein kinase B (PKB or AKT) are the main elements of intracellular signaling that are effective in the cell proliferation regulation process [28, 29] and are sensitive to increasing/decreasing metal concentrations [29].

Although the carcinogenic role of metals has been proven in many studies [30–32], some researchers have reached contradictory results. The results of a recent case–control study showed that there   was an inverse relationship between plasma Se levels and the chance of developing renal cell carcinoma [33]. Also, many studies reported higher concentrations of Mn and Fe in healthy people than in patients with various types of cancer such as lung [34], brain tumors [35], testicular [31], kidney [36], and non-melanoma skin [37].

However, many metals, such as copper (Cu), iron (Fe), selenium (Se), strontium (Sr), manganese (Mn), zinc (Zn), and molybdenum (Mo), are essential for life at low concentrations [38]. These metals have protective roles in processes such as chromosome damage and oxidation [38, 39]; and by regulating cell metabolism and DNA, RNA, and protein synthesis, they have preventive effects on cancer [40]. They also act as cofactors for some antioxidants such as superoxide dismutases [41], play a role
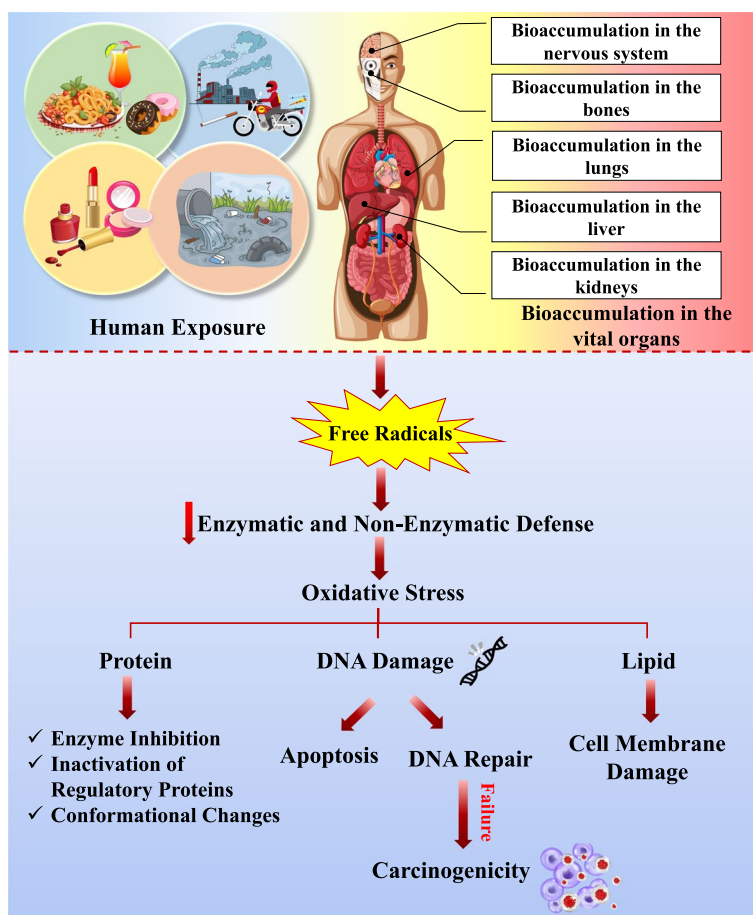
Fig. 1 Mechanism of toxicity and carcinogenicity of metals after human exposure

in cell differentiation and apoptosis, and are essential for all stages of the cell cycle [42]. However, despite the evidence demonstrating their preventive role in cancer [33, 34, 43], if their concentration exceeds the body's homeostatic capacity, they can lead to degenerative conditions and even cancer [44].

The development of knowledge and technology in recent decades has led to the use of various solutions to prevent the spread of metals in the environment and reduce the adverse effects of exposure to these elements. Among these solutions, we can mention using Nanomaterials to reduce the consumption of substances containing heavy metals in the water remediation process [45] and chelating agents and barrier creams to prevent excessive exposure to heavy metals [46]. In addition, global removal of lead from gasoline, control of exposure to As in drinking water in Chile [47], and using bio-filters to remove these elements from wastewater [48] and landfill leachate [49] are among the preventive measures taken in this field. But considering the increasing spread of metals in the environment and the chronic exposure

of people to these toxic elements, it seems that the measures taken are not enough.

Considering the broad exposure of humans to metals, the important role of these elements in cancer causation, and the contradictory results in various studies, our systematic review was performed to retrieve the scientific literature without historical restrictions until May 31, 2024. The main aims of this review were as follows: 1) evaluation of the types and concentrations of metals in the environmental or biological samples of exposed people, 2) investigation of the carcinogenic effect associated with metal concentrations, and 3) estimating the potential role of controlling metal exposures in cancer prevention.

Methods
Study protocol
The presented systematic review complies with the statement of Preferred Reporting Items for Systematic Review and Meta-analyses guidelines (PRISMA) [50] and fully adherence with the protocol that was registered in the

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International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42023397867) on 8 February 2023.

PECO statement

To develop the research question, a Population, Exposure, Comparator, and Outcome (PECO) protocol was used, and the statement is presented in Table 1. In this statement, the exact purpose of the present systematic review, the terms of search, and the inclusion and exclusion criteria of studies related to the impact of exposure to different levels of metals and their impact on cancer occurrence or prevention were specified.

Search strategy and study selection

To access all studies presenting the effects of metals on the prevention or occurrence of cancer in humans, a systematic search without historical restrictions was conducted until May 31, 2024 in the following databases: Scopus, PubMed, and Web of Science for the following keywords: "heavy metal*", "trace element*", "trace metal*", cancer, tumor, carcinogen, cancerogenic, neoplasm, oncogen*, neoplasia*, malignancy.

Criteria of study entering and extracting

In the review performed, studies focused on the effects of metals on cellular and biochemical changes (without examining the metal effect on the cancer appearance) were excluded. In addition, animal studies, books, review articles, conference papers, and letters to editors were omitted. In this systematic review, only original peer-reviewed articles in English were investigated. From the selected studies information on the name of the authors, publication year, study design, country, number of people in the investigated human subpopulation, their age, gender, type of metals, type of environmental and human samples, average metal concentration in samples, and type of cancer were gathered.

Quality assessment

The quality of the investigated studies was evaluated by two researches (M.M. and A.H.Kh.) independently, and the Joanna Briggs Institute (JBI) checklists for cohort studies, case–control studies, and analytical cross-sectional studies were used for this purpose. The JBI checklists assess the risk of bias in studies by asking 8 questions related to sample selection criteria, exposure assessment, confounding factors, and appropriate statistical analysis. According to the percentages assigned to each of the answers in the questionnaire ("yes", "no", "unclear", or "not applicable"), the quality of the articles was determined at 3 levels, namely: 1) Q1 of high quality and low risk of bias (answer "yes" in ≥ 50–75%), 2) Q2 of average quality and unclear risk of bias (answer "unclear" in ≥ 50–75%), and 3) Q3 of low quality and high risk of bias (answer "no" in ≥ 50–75%) [51]. All articles that were of adequate quality were included in the study.

Result synthesis

Meta-analysis as quantitative synthesis was not suitable in this study, as we obtained a too diverse range of study designs and other heterogeneities were found in methodological and contextual aspects. Therefore, the results of the study, which included types of metals, the mean concentrations of metals in the samples, the type of cancer, and the role of metal in the prevention or appearance of cancer (Table S1), were narratively combined. A narrative synthesis was performed in two stages, including (1) initial synthesis using general grouping based on preventive/carcinogenic role and (2) exploration of associations within and between studies to investigate the relationship between metal exposure levels and severity of the outcome.

The entire process of the present systematic review which was carried out by the research team members shown in Fig. 2. This process includes 7 steps as follows: topic selection, keywords extraction, systematic search, screening and data extraction, evaluating risk of bias, resolving contradictions and ambiguities, and synthesizing results.

Results and discussion
Study selection

The process of articles selection performed in this study is presented in Fig. 3 using a PRISMA flow diagram. Through the systematic search, 4,695 articles were

Table 1 Statement of the Population, Exposure, Comparator, and Outcome (PECO) Protocol in this systematic review

| PECO	Evidence
Population	All people exposed to metals
Exposure	Inhalational, ingestion, and dermal exposure to metals
Comparator	Comparing the concentration of metals in biological samples (including blood, urine, serum, tissue, scalp hair, and nails) of people diagnosed and not diagnosed with cancer
Outcome	The effect of different levels of metals on the development or prevention of cancer
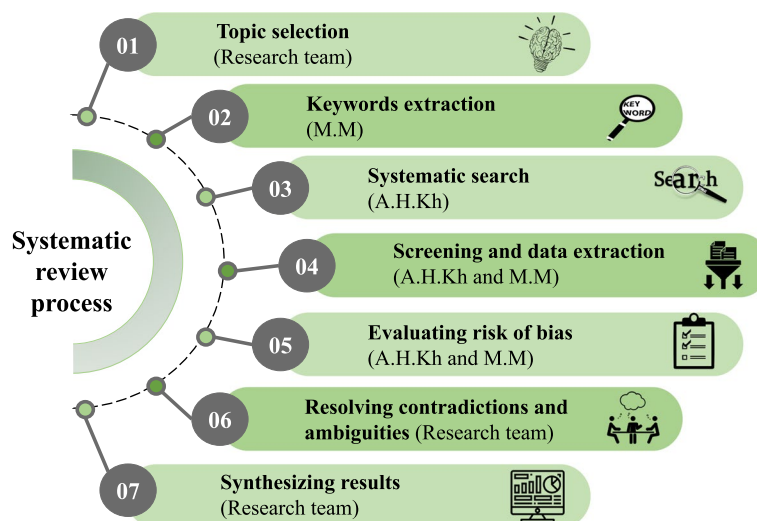
Fig. 2 The seven stages of the systematic review management process

retrieved, of which 1558 were obtained from Web of Science, 2553 from the Scopus, and 584 from the PubMed database. After removing 983 duplicates, 3712 articles were screened by title and abstract. This step resulted in the exclusion of 3556 studies. Then, 156 full texts were subjected to additional check to assess the criteria of the entry and the exit, and quality assessment. Further 85 studies were excluded due to: lack of inclusion criteria ($N=25$), in detail: not metal (7), benign tumor (4), not relevant (11), report on the cumulative effect of various contaminants on cancers (3), not determining and reporting the concentration of metals (self-reports) ($N=34$), failure to report original data ($N=7$), and investigating the effects of metals in cells on a laboratory scale (N=19). Finally, in the current review, we included the total number of articles equal to 66 studies.

The studies in this review included 56 case–control studies [30–36, 52–99], 8 cohort studies [37, 100–106], 7 cross-sectional studies [107–113], and one observational study [114]. They were performed in various countries around the world: 8 in Pakistan, 7 in China, 6 in Taiwan, 5 in Sweden, 5 in USA, 4 in Iran, 6 in Poland, 3 in Turkey, 3 in Tunisia, 3 in Egypt, 2 in Spain, 2 in Romania, 2 in Iraq, 2 in India, 2 in Croatia, and one in Finland-Sweden-Iceland, Japan, Greece, the United Kingdom, New Zealand, United Arab Emirates, Ukraine, Italy, Nigeria, Russia, and Belgium. Four studies investigated metals in the natural environment and 67 in human biological samples such as tissue, serum, urine, blood, hair, and nails. The potential sources of exposure to metals are presented in Fig. 4.

The main analytical methods used to measure element concentrations were the Atomic Absorption Spectrophotometry (AAS) and Inductively Coupled Plasma Mass Spectrometry (ICP-MS). A total of 1,369,887 people were examined in the 66 included studies. Table 2 presents a summary of the included 66 articles (for a complete table, see Table S1).

Toxic metals

The results of the majority of selected studies showed that metals such as Pb, As, Cr, Cd, and Ni act significantly in the development or progression of several types of cancer. Most toxic metals can damage cellular macromolecules such as DNA, RNA, proteins, and lipids by producing superoxide anion radical and hydroxyl radical reactive oxygen species (ROS) through the Fenton reaction and change cellular homeostasis [115]. In addition, oxidative stress caused by metals can induce genetic and epigenetic changes, abnormal cell signaling, increased micronuclei, chromosomal aberrations and mitotic index, and uncontrolled cell growth [116, 117]. In their role as endocrine disrupting chemicals [118], metals cause interference in the estrogen and androgen signaling pathways and affect the expression of genes involved in the growth and secretory function of the prostate gland [119].

Metals like Cd, Pb, As, Ni, and Cr(VI) compete with essential elements in the formation of ligands with enzymes and other proteins, including calcium-substituted lead, zinc-substituted cadmium, and aluminum-substituted mentioned with most of the rare elements [120]. These substitutions cause disturbances in important biochemical reactions, antioxidant imbalance, and adverse effects on various hormonal activities and the functioning of essential enzymes [121]. Gaman et al. (2021) reported that some metals can cross the
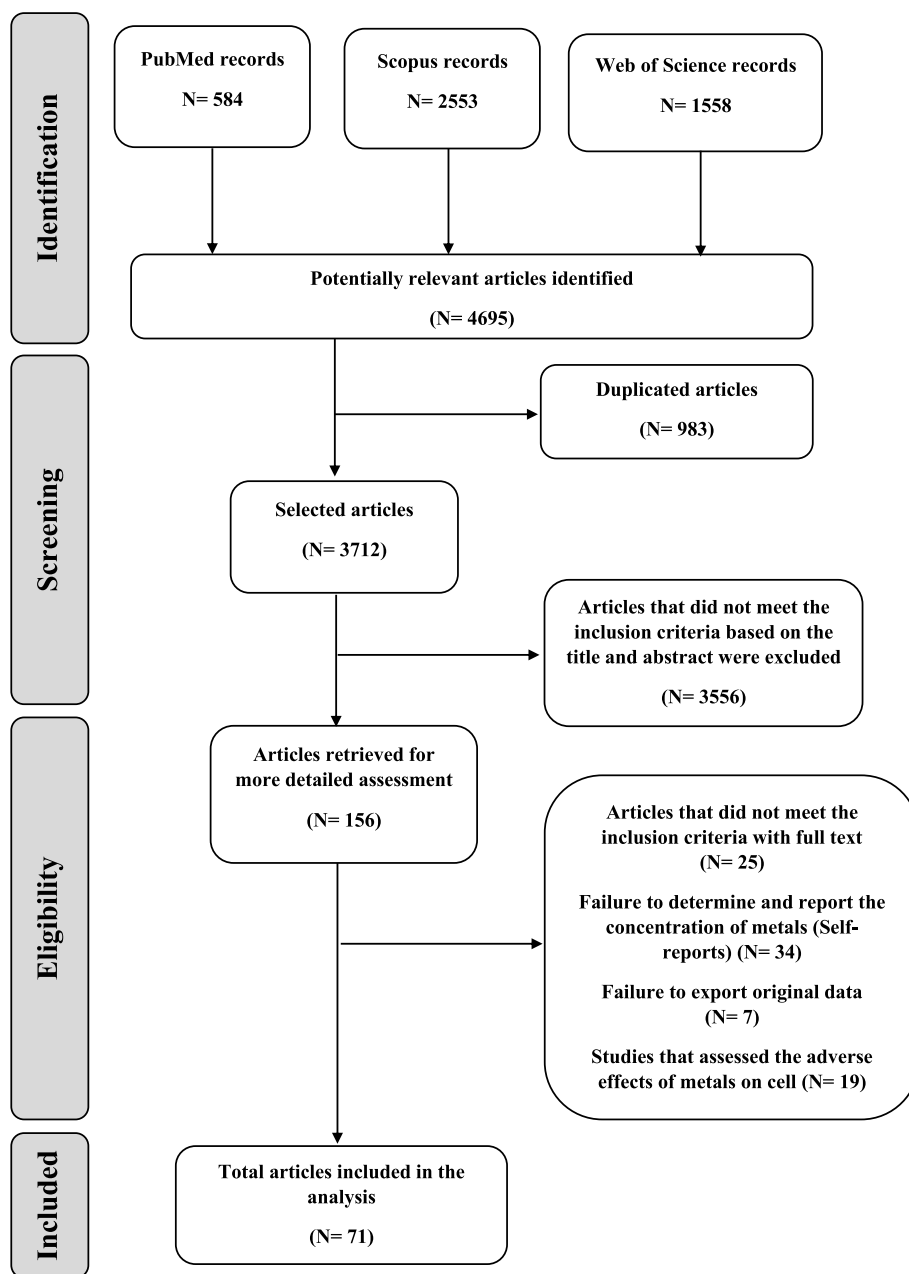
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Fig. 3 PRISMA flow diagram of the literature search

blood–brain barrier through this replacement, accumulate in neurons and other brain cells, and potentially cause brain malignancies [35]. Despite the sensitivity of the placental barrier to toxic substances [122], metals can pass through the placental barrier by deceiving the transport proteins in the cell membrane of the placenta and causing important biochemical changes during fetal development [123]. The toxicity of each metal depends on its physicochemical characteristics, as well as on the

biological properties of the target cells, in addition to the dose and duration of exposure [124].

The results of this systematic review showed that most of the examined people were elderly (>60 years). Therefore, the age of exposed people can also play an important role in various malignancies [125]. The aging process in humans is associated with significant changes in cells, including telomere wear, genomic instability, epigenetic changes, cell aging, quantitative and qualitative changes in protein spectra, mitochondrial dysfunction, change
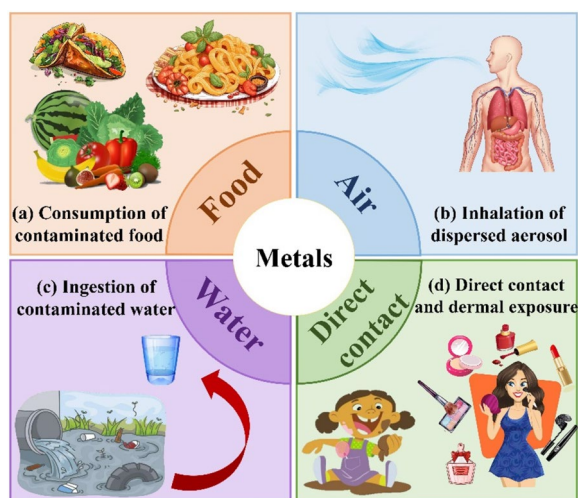
Fig. 4 Environmental sources of exposure to metals based on studies included in this systematic review

in intercellular communication, and exhaustion of stem cells [125].

Cadmium

Studies show that an increase of 1 µg of Cd in urine, increases the risk of lung cancer by 1.25 times [94]. A case–control study in the Italian population showed that a 1.11-fold increase in Cd in the diet doubles the incidence of melanoma [126]. Men et al. (2020) showed that the concentration of Cd in the urine of breast cancer patients was almost twice that of the control population [89], which was consistent with the results of a previous epidemiological study [127]. Also, the study conducted by Abdul Qayyum et al. (2019) reported double the levels of this metal in the blood and scalp hair of patients with lymphoma [30]. Meanwhile, some researchers concluded that the levels of Cd in patients with stomach cancer were 1.37 times higher than those of the control group [91]. Although the difference in the concentration of this element between the group of patients and healthy people reported in [30] was higher than that of [91], the highest levels of Cd (case group) in these two studies were equal to 25.04 µg/dL and 344.6 µg/dL, respectively. In addition, the results of a recent case–control study showed that the Cd concentration in the whole blood of testicular cancer patients was 1.57 times higher than that of the control group [31]; which was consistent with the results obtained by Chang et al. (2016) [80]. The study examining the impact of heavy metals in urothelial carcinoma, revealed that the urinary concentration of Cd in patients were 1.52 times (1.53 µg/g CR) higher than in healthy people [80].

Many studies have proven the role of Cd in human lung, kidney, liver, breast, hematopoietic system, bladder, stomach, prostate, and pancreas cancers [128, 129]. Cadmium is a toxic metal with a long biological half-life, having low excretion levels related to the absence of efficient elimination mechanisms [130]. This element is spread in the environment through various sources, including industrial applications as stabilizers in PVC products, Ni–Cd batteries and pigments, fossil fuel combustion, use of phosphate fertilizers, electronic waste recycling, smoking, and volcanic activities and can cause chronic human exposure [131, 132].

Cadmium affects several cellular processes including cell cycle progression, proliferation, differentiation, DNA replication, and apoptosis [133], which may play a major role in Cd genotoxicity [134]. This process is also true for other diseases caused by exposure to Cd such as lung, prostate, or breast cancer [135], as well as non-cancerous diseases such as diabetes and cardiovascular diseases [136]. It can also replace essential elements like Fe, Cu, and Zn in various cytoplasmic and membrane proteins and cause oxidative stress through the Fenton reaction [90]. Chronic exposure to Cd, in addition to inhibiting the activity of superoxide dismutase, which is known as one of the strongest antioxidant enzymes [137], also causes dysplastic lesions in the gastric glands [138].

Studies have shown that Cd creates a key step in the initiation of cancer and tumor stimulation by disrupting E-cadherin at cell junctions [139]. This mechanism has been reported to accelerate cancer growth by activating proto-oncogenes and genes involved in cell proliferation, reducing p53 function, and inhibiting DNA methylation, causing the clonal expansion of damaged and mutated cells [140]. Studies have shown that increased oxidative stress caused by exposure to Cd may cause cancer [141]. Zhang et al. (2016) in an epidemiological study concluded that the concentration of Cd in prostate tissue and plasma from patients with prostate cancer is substantially higher compared to healthy individuals [142]; this is consistent with the study of Zimta et al. (2019) [143]. However, a recent meta-analysis did not find any epidemiological evidence of the effect of Cd exposure in the general or occupational population with an increased risk of prostate cancer [144]. Epidemiological studies indicate that exposure to this heavy metal can increase the risk of lung cancer [145]. Based on available evidence, a doubling of Cd concentration leads to an approximate 68% increase in the relative risk of lung cancer [146]. Chronic exposure to Cd causes a significant decrease in the amount of glomerular filtration [147] and kidney and bladder cancer [82]. However, some recent studies did not find any relationship between occupational exposure to Cd and kidney cancer [36]. The study of Madrigal et al.

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Table 2 Main characteristics of the studies included in this systematic review

Reference	Title	Study design	Country (city)	Number of samples (N)	Sex	Age	Sample	Concentration	Type of cancer
[87]	Evaluation of role of heavy metals in causation of colorectal cancer	Case–control	India (Kolkata)	Case = 50 Control = 100 Total = 150	Men and women	≤14–50	Tissue	**Case [ppm]:** As = 0.144 Pb = 2.108 **Control [ppm]:** As = 0.130 Pb = 1.82	Colorectal cancer
[89]	Evaluation of heavy metals and metabolites in the urine of patients with breast cancer	Case–control	China (Tengzhou)	Case = 106 Control = 38 Total = 144	Men and women	50.56	Urine	**Case [µg/L]:** Cd = 9.3 As = 20 Cr = 175 Hg = 4 Pb = 0.2 **Control [µg/L]:** Cd = 4.8 As = 28 Cr = 168 Hg = 24 Pb = 76	Breast cancer
[90]	Study of trace metal imbalances in the scalp hair of stomach cancer patients with different types and stages	Case–control	Pakistan (Islamabad)	Case = 95 Control = 91 Total = 186	Men and women	45	Scalp Hair	**Case [µg/g, dry weight]:** Zn = 186.1 Pb = 15.80 Fe = 40.39 Cu = 10.65 Cr = 6.294 Mn = 3.709 Cd = 0.961 **Control [µg/g, dry weight]:** Zn = 184.2 Pb = 15.51 Fe = 57.16 Cu = 10.50 Cr = 4.349 Mn = 5.606 Cd = 1.720	Stomach cancer

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Table 2 (continued)

Reference	Title	Study design	Country (city)	Number of samples (N)	Sex	Age	Sample	Concentration	Type of cancer
[92]	Importance of elements, vitamin D levels, and DNA damage in patients with asbestosis and mesothelioma	Case–control	Turkey (Konya)	Case = 34 Control = 27 Total = 61	Men and women	Case = 60.24 ± 15.24 Control = 54.18 ± 9.89	Blood	**Case [µg/L]:** Al = 7.37 Cr = 0.90 Co = 0.93 Ni = 1.12 Cu = 1,301.33 Zn = 951.38 As = 5.40 Se = 10.29 Cd = 23.28 Pb = 24.48 **Control [µg/L]:** Al = 3.87 Cr = 0.64 Co = 0.67 Ni = 0.89 Cu = 1,051.14 Zn = 1,054.67 As = 3.41 Se = 11.27 Cd = 19.45 Pb = 22.89	Mesothelioma

Table 2 (continued)

Reference	Title	Study design	Country (city)	Number of samples (N)	Sex	Age	Sample	Concentration	Type of cancer
[93]	Human serum elements' levels and leukemia: A first pilot study from an adult Greek cohort	Case–control	Greece (Athens)	Case = 133 Control = 66 Total = 199	Men and women	20—≥70	Serum (median)	**Case]µg/L]:** As = 3.2 Ba = 0.35 Cd = 0.48 Co = 0.92 Cr = 1.2 Cs = 0.74 Cu = 1295 Ni = 1.1 Pb = 72 Rb = 100 **Control]µg/L]:** As = 1.5 Ba = 0.35 Cd = 0.1 Co = 0.08 Cr = 0.05 Cs = 0.58 Cu = 922 Ni = 0.05 Pb = 0.05 Rb = 164	Leukemia
[96]	Plasma nickel levels correlate with low muscular strength and renal function parameters in patients with prostate cancer	Case–control	Spain (Valencia)	Case = 46 Control = 46 Total = 92	Men	Case = 72.24 Control = 74.63	Plasma	**Case [µg/L]:** Ni = 4.97 **Control [µg/L]:** Ni = 3.59	Prostate Cancer
[97]	Association between urinary lead and female breast cancer: A population-based cross-sectional study	Case–control	USA-National	Case = 210 Control = 2585 Total = 922,795	Women	Case = 65.71 Control = 49.95	Urine	**Case [µg/L]:** Pb = 0.48 **Control [µg/L]:** Pb = 0.37	Breast Cancer
[113]	Assessment of cadmium (Cd) and lead (Pb) blood concentration on the risk of endometrial cancer	Cross-sectional	Poland (Szczecin)	110	–	–	Blood	**[mg/L]:** Cd = 0.0028 Pb = 0.2440	Endometrial Cancer

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(2019) also revealed that the decrease in kidney function associated with occupational exposure to Cd differs according to gender and the presence of comorbidities, that is, diabetes mellitus and high blood pressure [148].

Lead

Lead is a key player for esophageal and stomach cancers [112], brain tumors [35], kidney [33], thyroid [91], and testicular cancer [31]. Metal plating industries, mines, paints, cosmetic products, batteries, electronic waste, and the combustion of fossil fuels containing Pb are among the most important sources of Pb emission in the environment [149]. Increasing levels of this element in the environment can increase levels of human exposure and cause adverse health effects.

So far, many studies have investigated the effect of Pb concentration on various types of malignancy [31, 92, 93]. In their study, Tariba Lovaković et al. [31] investigated the effect of heavy metal levels on testicular cancer and concluded that Pb levels in the whole blood of patients (30 µg/L) were 1.25 times those of healthy people (23.9 µg/L). In addition, the results of a case–control study in Pakistan showed that stomach cancer sufferers have 1.8 times more Pb in their blood [91]; which was consistent with the results of the study by Sarkar et al. (2020) [87]. In this research, 150 tissue samples (case = 50, control = 100) were evaluated in terms of the concentration of this element and showed that the Pb levels in the case group were 1.15 times higher than those in the control group [87]. Similar results were observed with other studies on thyroid cancer [86], breast cancer [84], and bladder carcinoma [82].

Furthermore, Chrysochou et al. (2021) observed that the serum Pb level in leukemia patients was 154 times higher than that of healthy individuals [93], which is consistent with the results of the study by Guzel et al. [150]. Guzel et al. (2012) indicated that the blood and prostatic Pb levels in patients with prostatic intraepithelial neoplasia are significantly higher than those with benign prostatic hypertrophy (BPH) [150]. Studies have found a positive correlation between Pb and Al elements with increased levels of methylated MGMT and methylated MLH1, DNA repair enzymes [88], which is consistent with the results obtained by Scanlon et al. (2017). This study points to an effective role for metals in silencing the MLH1 promoter and in initiating the carcinogenesis process [151]. Devóz et al. (2017) showed that occupational exposure to Pb causes changes in DNA methylation and gene expression regulation in exposed workers [152]. The BRAF and KRAS genes are important in the process of the RAS/RAF/MAPK signaling pathway and in this way can regulate cell growth, differentiation, proliferation and apoptosis in malignant and non-malignant cells [153].

In a study, Talaat Abd Elaziz et al. (2020) investigated the effect of occupational exposure to heavy metals on colorectal cancer in industrial workers in Egypt and concluded that compared to unexposed tissues, there was a statistically significant increase in the expression of the BRAF and KRAS genes in malignant tissues [88]. This relationship has a positive correlation with methylated repair enzymes MLH1 and MGMT and exposure to Pb and Al metals [88]. Some researchers reported that mutations in the KRAS and BRAF genes in patients with colorectal carcinoma play a role in disease progression and response to treatment [154]. Until now, many epidemiological studies have shown a relationship between workers' exposure to inorganic Pb and lung, kidney, and brain cancers [155, 156], but no correlation was found with prostate cancer [95]. Several factors potentially account for the differences in the studies, including genetics, sex, exposure dose, duration of exposure, bone accumulation over time, and also the number of people examined in each study.

Arsenic

Arsenic is very relevant because groundwater and drinking water supplies can exceed the Maximum Contaminant Level Goal (MCLG) of 10 µg/L (USAEPA) and indicate a health risk [31, 86, 92]. In the USA, around 7% of the wells contain As above the MCLG [157]. Sarkar et al. (2020) revealed that the mean level of As in the group of patients with colorectal cancer vs healthy people was 2.12 ± 1.04 and 1.43 ± 0.73 ppm, respectively, and this difference was statistically significant [87]. Also, exposure to this element at a sufficient dose and for a suitable period, by creating a dose–response relationship between As and cancer, leads to the progression of carcinogenesis [82]. In addition, the evaluation of serum levels of Cd and As with bladder cancer indicates that As levels in patients are 1.48 times those of healthy people [32]. Chrysochou et al. (2021) reported a 1440-fold difference in serum As concentration in Leukemia patients compared to the control group [93]. The results of this research were consistent with the study conducted by Chang et al. (2016) [80].

Furthermore, Chrysochou et al. (2021) showed that there is a strong relationship between As, Cd, Ni, and Pb in patients with chronic leukemia compared to the control group [93] and the twofold levels of As increase the risk of thyroid cancer 5.35 times [86]. Arsenic alters the transcription process in gene-related actions, inhibits glutathione, decreases antioxidant defense mechanisms, and increases free radicals [158, 159]. Talaat et al. (2011) [159] showed that Kindlin-2 protein is expressed in the stromal element of transplanted and archival samples of human bladder cancer associated with As. Prostate tissues are a target of As [105, 160]. Some studies do not

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support the relationship between As in prostate cancer and breast cancer [89, 95]. There are significant differences in tissue As concentrations. The reason could be the difference in the type of cancer and the accumulation of these metals in different tissues according to the biological characteristics of the involved cells [124]. Malandrino et al. (2020) [161] showed that the concentration of many elements such as As in thyroid tissue was higher than in sternothyroid muscle and subcutaneous neck fat, which could be a good explanation for this difference.

Today, there are many natural and human sources for exposure to As, which can increase the risk of various types of cancer in exposed people. Among the most important of these sources, the industries of metal smelting, fossil fuel combustion, coal power plants, industrial wastewater, pesticides, mining, and volcanic activities [162] are mentioned.

Nickel

In this review, 23 studies examined the relationship between Ni levels and cancer, and 78% of the studies reported elevated concentrations of this metal associated with several cancers. Concentrations of Ni in serum were different in acute and chronic leukemias vs the control group (22 and 2.2 times, respectively) [93]. These results are consistent with studies conducted in the breast [84], thyroid [91], bladder [82], lymphoma [30], prostate [96], and brain [35]. Lovaković et al. (2021) also showed that the total blood/serum Ni concentration of patients with testicular germ cell tumors (TGCT) was significantly higher than that of healthy subjects [31]. Nickel has various carcinogenic mechanisms, including induction of DNA changes, reduction in lymphocyte telomere length, inhibition of intercellular transfer mechanisms, inhibition of nucleotide excision maintenance, oxidative stress and DNA methylation, and endocrine disruptor.

Despite the evidence confirming the carcinogenicity of Ni, some studies have reported results different from those mentioned [31, 85, 94]. The accumulation and effects of Ni are different according to the type of cell/tumor [163]. Lee et al. (2022) in a recent case–control study in Taiwan showed that urinary Ni levels in patients with lung cancer were 8.72 µg/g CR, in patients with other malignancies were 5.9 µg/g CR, and in healthy subjects 11.63 µg/g CR [94]. The results of their study were consistent with the research conducted by Tariba Lovaković et al. (2021) [31]. Tariba Lovaković et al. in the study of the relationship between exposure to low levels of metals and testicular cancer concluded that although the urinary levels of Ni in healthy people are higher than in patients, this concentration was opposite in whole blood and serum samples [31]. The reason for this difference can be related to the physicochemical

characteristics and the absorption and metabolism process of each metal in different target tissues.

In addition, increasing levels of exposure to Ni from volcanic activity, wild forest fires, windblown dust, fossil fuel combustion, commercial and industrial applications such as electroplating, stainless steel, battery manufacturing industries, industrial waste, stainless steel kitchen utensils, dental or orthopedic implants, tobacco, and cheap jewelry can increase the risk of various types of malignancies [164, 165].

Chromium

In this systematic review, 87% of Cr studies associated with cancer reported higher concentrations in cancer patients than in controls [93, 112]. The results of examination of the metal imbalance in the blood of patients with thyroid cancer showed that the levels of this element in the case group were 1.28 times those of the control group (757.9 vs 588.8 µg/dL) [91]. In addition, Afzal et al. (2020) achieved similar results in the study of stomach cancer [90]. The investigation of the effect of heavy metals on breast cancer progression also reported a 2.6-fold difference between sick and healthy people [54], which is consistent with the results of the study by Abdel-Gawad et al. (2016) [82] and Chang et al. (2016) [80]. Qayyum and Shah (2019) investigated the average Cr contents in blood and hair from lymphoma patients versus healthy controls and found a significant difference, 59.43 µg/dl vs 34.95 µg/dl, respectively [30].

Chromium levels can increase in the environment through mining, steel and metal alloy industries, paint production, wood and paper processing, burning coal ash, or the use of municipal waste for energy production and second generation fertilizer production [166]. Chromium is present in contaminated drinking water [167], and its effects other than oncological, include an endocrine disrupting capacity [168]. Das et al. (2015) reported mitochondrial-dependent apoptosis in male somatic cells and spermatogonial stem cells by hexavalent Cr(Cr (VI)), a pathway for reproductive abnormalities and infertility. Paternal exposure to heavy metals and solvents increases the risk of their sons developing a testicular germ cell tumor (TGCT) [169]. However, some previous evidence shows that there is no statistically significant risk between paternal exposure to heavy metals/welding fumes and boys suffering from TGCT, which requires more and more extensive studies to reach a definitive result [170]. A recent case–control study proved that maternal exposure to Cr increases the chance of Tenosynovial Giant Cell Tumor (TGCT) occurrence in male children [171]. Krstev et al. (2019) reported in a meta-analysis that occupational exposures to pesticides, Cr (VI), polycyclic aromatic hydrocarbons, diesel fumes,

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metal fabrication environments, vehicle batteries, flight personnel, jobs causing circadian disruption, firefighters, sewage and petroleum and gasoline workers increase the risk of prostate cancer [172]. In vitro and in vivo studies show that even exposure to low doses of Cr (VI) can affect the epithelial-mesenchymal pathway (EMT), cause the growth and migration of prostate cancer cells, and follow the progress of tumor and metastasis [173]. Rafnsson et al. (1997) reported the cancer incidence of an Iceland cohort of 1172 masons exposed to wet concrete aerosols and Cr (VI) exposures associated with cement. These masons had an increase in lung cancer with a standardized incidence ratio (SIR) of 1.69 and 1.77 after 30 years of work [174].

Mercury (Hg)

In this systematic review, 11 studies investigated the effect of Hg levels on thyroid [58, 86], breast [68, 89], lung [76, 94, 109], prostate [95], brain tumor [35], and other types of cancers [105]. The results showed that 62.5% of the case–control studies conducted in this field confirmed higher levels of Hg in the biological samples of patients compared to healthy people. Pizent et al. (2022) investigated the role of metal exposure in prostate cancer and concluded that the mean Hg levels in blood/serum of the case group were 2.43 times that of the control group [95]. In addition, some researchers have reported a two-fold difference in the concentration of this metal in the urine of healthy people and those with thyroid cancer, confirming the existence of a direct relationship between exposure to heavy metals and the development of malignancies [86]. The results of these studies were consistent with the   investigations conducted by Binkowski et al. (2015) [76] and Alatise et al. (2010) [68].

Cement, iron and steel, gold, and chloro-alkali industries, non-ferrous metal smelting, dental amalgam, forest fires, and volcanoes are among the main sources of Hg release in the environment and exposure of humans to this dangerous element [175]. Some laboratory studies concluded that Hg causes hypomethylation and hypermethylation of G protein signaling; therefore, it can act as a driving force for tumor growth [176]. One of the most important mechanisms in pathologies caused by Hg is oxidative stress [177]. Mercury has a strong ability to deplete intracellular thiols (especially glutathione) and bind to thiol groups on proteins. Although the exact mechanism of ROS production by Hg is not yet known, it seems that this mechanism depends on the physical and chemical form of the element [95]. For example, the detection of Hg in blood reveals exposure to organic methylmercury (MeHg) associated with eating seafood or inhaling elemental mercury vapor [95]. Studies have shown that the high affinity of this organic compound for selenohydryl groups, thiols, and selenides can disrupt the structure and function of antioxidant enzymes and proteins [178].

Although many researchers have proven the role of exposure to Hg in various types of malignancies, some studies have reached contradictory results. The results obtained from the study by Lee et al. (2022) showed that the urinary Hg concentration in patients with lung cancer was measured at 1.57 μg/g CR, while in healthy subjects urinary Hg concentration was equal to 2.3 μg/g CR [94]. In addition, a case–control study conducted in China showed that urinary Hg levels in the control group (24 μg/L) were 6 times higher than those with breast cancer (4 μg/L) [89]. The results of these two studies were consistent with the research conducted by Gaman et al. (2019) [35]. In this study, the concentration of Hg in tissue-blood samples from healthy people was higher than in patients with brain tumors [35].

The difference in the results of this section can be considered related to the difference in the type of biological sample examined and the duration of Hg detection (according to the Hg half-life). Studies have shown that Hg is distributed and accumulated in most vital organs, mainly in the central nervous system and kidneys [179]. Blood Hg concentration decreases with a half-life of nearly 50 days [180]. Researchers reported that 90% of this element is excreted through feces and only 10% through urine [181, 182].

Essential elements

Some of the metals such as Co, Cu, Fe, Mn, Cr (III), Zn, Se, and Mo also have a protective role in the processes of chromosome damage and oxidation [38, 39] and are vital for the body in low concentrations. Metals play key roles in antioxidant defense, hemoglobin and energy production in the aerobic respiration process, preserving normal nerve and muscle function, and aiding the immune system [183]. Some of these essential metals are also an integral part of antioxidant enzymes such as selenoenzymes, glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) and are effective in maintaining sufficient amounts of metallothionein (MT), reducing ROS, and subsequently, oxidative DNA damage [184]. In addition, they can act as cofactors of DNA repair proteins and as essential components of ribonucleotide reductase in DNA synthesis and help in nucleotide acid metabolism [185].

The researchers showed that the increase in the concentration of essential elements in the body follows a U-shaped dose–response relationship. Accordingly, at very low doses of essential micronutrients, a high level of complications will occur (known as "deficiency"), which

will decrease as the dose increases. In addition, very high doses also have the potential to cause high levels of side effects, which decrease as the dose is reduced. When the deficiency is removed by increasing the dose and no adverse reactions are detected, the organism reaches a state of homeostasis. Generally, Co, Cu, Fe, Mg, Mn, Mo, Se, and Zn are accepted as essential metals, each of which has a unique deficiency point and toxicity. This is happening while there is no deficiency and homeostasis area in the dose–response curve in toxic elements. In this situation, depending on the measured endpoint, the shape of this curve may be an inverted U or J shape. According to studies, if endpoints are related to growth, longevity, fertility, or cognitive function, the response is inverted U-shaped and in the case of disease, it is seen as J-shaped [186].

The results of the present study showed higher concentrations of these metals in the healthy control group than in the case group, which supports their preventive role in the onset and progression of cancer. Case–control studies indicate an inverse relationship between plasma Zn level and the risk of cancers of the lung [34], cervix [59], lung [34, 78], prostate [74, 75], thyroid [91], mesothelioma [92], and lymphoma [30] cancers. Under physiological conditions, Zn prevents the formation of free radicals, participates in the cellular immunity of T lymphocytes, and prevents tumor growth [187]. Zinc also plays a role in the antiangiogenic activity of endostatin cell proliferation and intracellular signaling pathways, and the serum level reduction can increase the risk of cancer [43].

Selenium is an important micronutrient for cancer prevention, which can effectively treat kidney cancer by inhibiting the proteins hypoxia-inducible factor 1- and 2-alpha (HIF 1α and HIF 2α) and the nuclear factor erythroid 2- (Nrf2) [188]. According to the studies, the presence of permissible concentrations of Se (230–250 ng/mL of blood) reduces the risk of cancer [189]. The results of the study by Hsueh et al. (2021) showed that higher plasma Se levels significantly reduce the chances of renal cell carcinoma (RCC) [33], which was consistent with the results of Bock et al. (2018). Chitta et al. (2013) showed that Se can reduce As toxicity by changing cytotoxicity, genotoxicity, and oxidative stress [190]. It also reduces the Cd oxidative stress by reducing serum malondialdehyde and increasing the activity of superoxide dismutase and glutathione peroxidase [191]. The mechanism of the Se effect against the reduction of As and Cd toxicity may be through Se-related antioxidant enzymes or the activation of the Nrf2 pathway [192].

Many studies in the present review showed that the concentration of Mn in the control group was higher than in the case group [31, 34, 35, 94, 112]. Manganese is also considered as an essential micronutrient for

intracellular activities. Some studies have shown that nanoparticles of compounds of Mn suppress oxidative stress and DNA damage by imitating several enzymes [193]. It also acts as a cofactor for antioxidants such as Mn superoxide dismutase (MnSOD), which play a role in antioxidant defense [194]. Sohrabi et al. (2021) reported in a cross-sectional study that the Mn content in cancerous tissues is lower than in adjacent healthy tissues [112], which supports this mechanism.

Copper is an essential element and an integral constituent of various metalloenzymes. Studies have determined that the normal range of this element is 700–1400 ng/mL of blood [189]. Marzano et al. (2009) investigated various types of Cu complexes as possible antitumor agents [195]. Both decreased or increased Cu levels are associated with genetic disorders of Cu metabolism and with high environmental exposure resulting in severe pathologies [196]. Available reports indicate that the lack of trace elements such as Fe, Zn, and Cu is related to bladder cancer [197, 198].

The high concentration of Fe in healthy people compared to patients in some studies suggests a potential effect of Fe in preventing the occurrence or progression of cancer [34–36, 66, 81, 90]. Fonseca-Nunes et al. (2015) showed that higher serum Fe and ferritin is inversely related to the risk of stomach cancer [199]. Cook et al. (2012), however, reported that Fe metrics were not associated with neither gastric cardia or non-cardia cancers when taking into account the roles of Helicobacter pylori and gastric atrophy [200]. Puliyel et al. (2015) discussed Fe toxicity in children and adults undergoing treatments for neoplastic processes and the importance of transferrin saturation (TS), associated with toxic free Fe, and showed that high TS is associated with cancer development and indeed, lowering free Fe decreases the risk [201]. Cook et al. (2012) also obtained similar results [200]. Also, the investigations conducted revealed that the level of Fe in cancerous tissues was lower compared to healthy tissues [201], which could be due to the lower absorption of this metal in cancerous tissue. Fe is a vital micronutrient for oxygen transport and oxidative metabolism [202]. Deficiency of Fe, for example in Fe-deficient anemia, has a serious impact on physical and cognitive function with a severe reduction in quality of life [203]. It can also cause side effects such as increased DNA damage, decreased antioxidant defense, decreased enzyme activity, and subsequently increased genomic instability [203].

Trivalent cobalt (Co (III)) and chromium (Cr (III)) also participate in many biological mechanisms as essential elements. Cobalt constitutes the central atom of cobalamin (vitamin B12), and is also considered an important nutrient to maintain testicular function and normal

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fertility [204]. This element impacts DNA synthesis and cell division and participates in purines and pyrimidine production as a cofactor of methionine synthase [205]. Based on its capacity, Cr can be classified into an essential or toxic group. Trivalent chromium has an effective role in the metabolism of carbohydrates, proteins, and fats. However, Cr (VI) is classified as a toxic metal due to its angiogenic and carcinogenic activities [206, 207]. Bibi et al. (2020) investigated the imbalance of metals in the blood of thyroid cancer patients versus healthy individuals [91]. Concentrations of Pb (774.6 vs. 416.2 µg/dL), Cr (757.9 vs. 588.8 µg/dL), Cd (472.5 vs. 344.6 µg/dL) and Ni (360.5 vs. 200 µg/dL) were higher in cancer patients, while Co was higher in controls (2073 vs. 977 µg/dL).

There is a complex balance among essential elements in the prevention and progression of cancer, and several other factors, such as genetic protector and detrimental mechanisms, and the environment play a key role in the final outcomes [42, 44, 93].

Strengths and limitations

The strength of the present study is that it is the first systematic review that examines two opposite effects of metal exposure on carcinogenesis. This study provides new information on the toxicity of metals, their carcinogenic properties, and, on the other hand, their preventive properties against cancer at different doses. Furthermore, the selected studies were retrieved by a comprehensive systematic search, without restrictions on publication date, study type, or country of investigation. Adopting this approach allowed the highest number of relevant articles to be entered without the loss of scientific data. However, the limitation of this study was the lack of access to the full text of some articles and limiting the database search to studies in the English language only.

Gaps and recommendations

A comprehensive review of published studies shows the existence of some gaps in this important area of health, including the lack of information on some heavy metals. According to the available evidence, most studies published in this field have investigated the concentration of metals in only one type of biological sample, which may lack sufficient accuracy and representation. For example, measuring the levels of some metals in urine samples can reflect short-term exposure. Therefore, depending on the physicochemical characteristics and the unique absorption and metabolism processes of each metal in target tissues, detecting element levels only in one type of biological body sample may not be a suitable measure to reflect internal exposure levels for all types of metals. Therefore, more detailed studies are recommended to cover this important gap.

It is also recommended to design more prospective cohort studies with independent replications to investigate the role of prenatal exposure to toxic metals in the individual's incidence of various types of cancer during the years after birth. Investigating the unique characteristics and activities of vital body organs such as the thyroid, brain, and kidney, which can make them more susceptible to the carcinogenic activity of some toxic metals, seems necessary.

Considering the slow process of removing toxic metals from the body, it seems that using methods to accelerate this process can play an effective role in reducing the accumulation of these elements in the target organs and preventing adverse health effects. The surveys conducted indicate that few clinical trial studies have been conducted in this field [208]. Therefore, it is recommended to design and implement more clinical studies to achieve an effective method.

Conclusions

The presented review indicated that chronic exposure to metals, even in low concentrations, can be a potential risk factor for various types of cancer. The main elements found in the biological samples of the patients included Pb, Cr (VI), As, Cd, and Ni and these elements were identified in many studies. Generally, the levels of these metals in clinical cases were higher than in controls, which demonstrates the carcinogenicity of these metals. In addition, the investigation of the effect of essential metals such as Se, Zn, Fe, and Mn on the occurrence of adverse health effects revealed that low concentrations of these elements indicated anticancer properties and that their high concentrations could be the cause of biological toxicity. Therefore, according to the biological accumulation property of heavy metals in the vital organs of the body, regular monitoring of toxic metal concentrations in biological and clinical samples is recommended to identify possible sources of their exposure. In addition, authorities should adopt stricter laws to control and reduce metal emissions into the environment and to protect workers. This will significantly reduce the risk from dermal, inhalational, and ingestion exposure pathways from these metals and will play an effective role in reducing the cancer occurrence.

Supplementary Information

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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