REVIEW

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Chromium as a Risk Factor for Breast Cancer: A Meta-Analysis

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Abstract

Background: Chromium (Cr) is a transition metal, natural element. Chromium is the 21st most abundant element in Earth's crust. Cr is found in soil, rocks and living organisms. It may have various oxidation states, from -2 to +6, but most of these states are too unstable to exist in any significant quantities. The purpose of this review and meta-analysis is to critically assess the scientific evidence on the carcinogenic effects of chromium (Cr) and to determine whether there is currently sufficient evidence to suggest that that there is a link between chromium levels in hair and blood serum and breast cancer in women. **Material and methods:** Research on the relationship between heavy metal chromium and the risk of developing breast cancer has been searched in PubMed, EMBASE, Web of Science, Scopus among papers published between January 2000 and September 2020. The search used the following terms (MeSH): breast cancer, women, trace elements, metals, chromium, chemically-induced, hair, serum using additional terms. **Results:** In the second group of comparisons of women from "ecologically clean" districts of Aktobe Region, there were significantly lower indicators of the microelements in tumor tissue. The amount of Fe ranges from 38.46 to 65.39 ug/g (average 49.56±5.81 ug/g), Cu from 2.8 to 6.69 ug/g (average 5.06±1.01 ug/g), Zn from 1.89 to 5.38 ug/g (average 3.88±0.89 ug/g), Cr from zero to 6,1 ug/g (average 2.13±1.29 ug/g), Ni from 0.11 to 0.42 ug/g (average 0.28±0.067 ug/g) и Pb from zero to 0.19 ug/g (average 0.098±0.06 ug/g). **Conclusion:** The article established that women who live or work in ecologically polluted areas or have problems with micronutrient exchange need in-depth screening and more frequent screening for early detection of pre- and breast cancer.

Keywords: Biomarker- breast- chromium- elements- dependencies

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Introduction

Chromium (Cr) is a transition metal, natural element. Chromium is the 21st most abundant element in Earth's crust. Cr is found in soil, rocks and living organisms. It may have various oxidation states, from -2 to +6, but most of these states are too unstable to exist in any significant quantities. The two valence states of Cr are stable: trivalent chromium (Cr (III)) and hexavalent chromium (Cr (VI)) (Wilbur et al., 2012). Depending on the pH value of the solution, chromium can occur primarily as Cr (III) or Cr (VI) (Unceta et al., 2010). Hexavalent Cr (VI) and trivalent Cr (III) can be interconverted (Sharma et al., 2008). Chromium exposure to human is widespread as it is used in many industries including stainless steel welding, chromium plating and ferrochrome manufacturing. Chromium is also occurred in the environment as airborne particles from automotive catalytic converters (Salnikow and Zhitkovich, 2008). The Cr (VI) compounds have a wide range of applications and are used as pigments for textile dyes, paints, inks and plastics, corrosion inhibitors, leather tannins and wood preservatives (Urbano et al., 2012). All Cr (VI) used for industrial goals produced from Cr (III) contained in chromite ores (Ferreira et al., 2019).

The greatest Cr (VI) exposure to human is in the chemical, metallurgical and chromite industries, due to skin contact and inhalation of chromium particles as dust or vapors. In addition, significant exposure occurs during welding, casting and cutting of stainless steel and other chrome metals, and alloys, as in these cases Cr (VI) can be distinguished as a by-product (IARC, 2012). The public, especially those living in close proximity to the chromate industry, is exposed to chromium and its derivatives when inhaling chromium-containing air or drinking contaminated water (Tumolo et al., 2020). In addition, Cr (VI) compounds are components of the

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combustion exhaust gas and are contained in cigarette smoke (Williams et al., 2017). Building destruction is an additional source of environmental pollution as Cr (VI) compounds are present as impurities in cement (Urbano et al., 2012).

Cr (III) compounds are inherently harmless and widely used as dietary supplements (Jeejeebhoy, 1999), although their positive health effects have been questioned by the European Food Safety Agency (EFSA, 2014). Currently, Cr (III) is considered non-carcinogenic due to insufficient evidence of its carcinogenicity to humans and animals. According to the International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (EPA), the compounds Cr (VI) are classified as human carcinogens of Group 1 and Group A (Chen et al., 2019a), respectively. In fact, Cr(VI) compounds exposure has numerous negative health effects, mainly on the skin and respiratory system. It should be noted that the International Agency for Research on Cancer (IARC), National Toxicology Program (NTP) classified Cr (VI) compounds as pulmonary carcinogens (IARC, 1990; IARC, 2013; Report on Carcinogens, 2014).

The different toxicity of Cr (III) and Cr (VI) can be explained in terms of their physico-chemical properties. Specifically, their ability to penetrate biological membranes and ultimately cause intracellular damage is determined by their size, structure, and charge. In physiological pH Cr (VI), it exists mainly as chromate anions (CrO 4 2-). Being isostructural sulfate and phosphate anions, chromate anions released from Cr(VI) compounds are easily transported through cell membranes using an anion transport system (O'Brien et al., 2003; Zhitkovich, 2011). In contrast, the larger size and octahedral structure of the ions Cr (III) do not allow them to use this transport system (Mamenko and Portiannyk). Very little of the insoluble salt Cr (III) is absorbed by cells, mainly phagocytosis. Poorly water-soluble chromates with a particle size of less than 5 μm can also be phagocytic and will gradually dissolve in an intracellular medium (IARC, 2013). Thus, Cr (VI) can easily pass through the cell membrane via non-specific anionic sulfate / phosphate carriers. Cr (III) is able to pass through cell membranes by diffusion or phagocytosis, although at much lower levels than Cr (VI) (Valko et al., 2005; Stout et al., 2009).

The purpose of this review and meta-analysis is to critically assess the scientific evidence on the carcinogenic effects of chromium (Cr) and to determine whether there is currently sufficient evidence to suggest that that there is a link between chromium levels in hair and blood serum and breast cancer in women.

Materials and Methods

Research on the relationship between heavy metal chromium and the risk of developing breast cancer has been searched in PubMed, EMBASE, Web of Science, Scopus among papers published between January 2000 and September 2020. The search used the following terms (MeSH): breast cancer, women, trace elements, metals, chromium, chemically-induced, hair, serum using additional terms in Table 1. Language barrier - a selection of articles written in English was made. Also, a search was conducted in the reference lists of found articles to find additional research. The inclusion criteria included original articles describing epidemiological studies that assessed chromium levels in the body's biological environment. The design of the studies included in the review was either case control or cohort research. The primary result in the studies included in the meta-analysis was breast cancer.

The article assesses the relevance of research using a hierarchical approach based on the analysis of the name, abstract and full-text article. The overview flowchart showing the search and selection of literature is shown in Figure 1. A total of articles was found using the search terms mentioned above. The titles of these articles were first reviewed and the articles were deleted on the basis of inclusion and exclusion criteria. The abstracts of the selected articles were then considered; the full texts of the articles at the selection stage were examined if the right to research was uncertain based on the analysis of the reports.

The inclusion criteria were as follows: cohort or case-control study; chromium was considered as a baseline effect and breast cancer as a result; original work in English, which were published and indexed from January 2000 to September 2020. The works had data for meta-analysis or dose-reaction analysis. The exclusion criteria were as follows: there was no link between the «dose-reaction» between chromium and the risk of breast cancer; cytological studies, animal studies, reviews, comments, abstracts; poor quality of the article, transverse studies.

According to the standard data extraction form, all data were extracted independently by three reviewers. The characteristics of the identified work were extracted. There are author's name, year of publication, country of study, design (cohort study or case-control), number of participants in the study (number of cohort participants from cohort studies and number of participants in case groups and control groups in case-control studies), age (average age of group or age interval of participants), special groups identified in the study (stages of breast cancer, groups with mutation BRCA1), source of samples to measure chromium level (chromium serum/plasma, chromium in scalp hair), chromium concentration represented by average with standard deviation (Table 2).

Results

Recently, hair has become a fundamental biological material, an alternative to normal blood and urine, and organ biopsy. Human hair has become an attractive diagnostic material due to the ease of sampling (cut from the back of the head in several places near the skin 3-4 cm of hair according to widely accepted standards, that is, hair without chemical perms and uncrushed). Only 0.3 g of a hair sample is required. In addition, hair is a neutral and stable fabric material and can provide valuable information on the accumulation of trace elements, which is significantly more concentrated in hair than in other biological materials. Thus, hair analysis can provide an indirect screening test for physiological excess or

Table 1. Data Inclusion in the Study

Database	PubMed
Retrieval time	from 16 March 2020 to 31 May 2020
Search area	Materials published between 2000 and 2020
Strategy	Search terms #1 and #2 have been combined with the terms #3-#7
#1 Breast cancer	Breast cancer, breast neoplasms
#2 Women	Women, female
#3 Metals	Metals, heavy metals
#4 Trace elements	Trace elements
#5 Chromium	Chromium
#6 Risk factor	Risk factor, risk factors
#7 Chemically induced	Chemically induced, chemically induced disorders
#8 Hair	Hair
#9 Serum	Serum, Blood Serum, Plasma

deficiency of elements in the body. It is very important to note the influence of diet, gender, age of race, individual nutrition of the body, socio-economic conditions, chemical content in drinking water, geographical location and pollution of the environment on the content of chemical elements in the hair. The main advantage of this method is that it allows monitoring of changes in the state of microelements in the body for a long period of time, much longer than in the case of blood samples. Currently, clinical studies have shown that the levels of some trace elements in the hair (especially potentially toxic elements) are highly correlated with pathological disorders. A growing body of data supports the theory that biochemical analysis of trace elements in hair can be useful in determining a possible risk of cancer progression or progression as a simple biomarker without the need for an invasive biopsy.

Table 2 presents the meta-analysis data on chromium levels in hair and blood of breast and healthy patients.

The determination of the microelement composition of IDC breast cancer tissue of women from "polluted" areas by atomic absorption spectrophotometry established that the ferrum content ranges from 60.24 to 69.63 ug/g (average 65.23±2.42 ug/g), copper from 2.83 to 9.11 ug/g (average 5.98±1.62 ug/g), chromium from 1.45 to 3.66 ug/g (average 2.56±0.62 ug/g), zinc from 2.84 to 6.4 ug/g (average 4.44±0.99 ug/g), lead from zero to 0.6 ug/g (average 0.11±0.089 ug/g) and nickel from 0.08 to 0.52 ug/g (average 0.3±0.06 ug/g). In the second group of comparisons of women from the "ecologically clean" districts of Sumy Region, there were significantly lower

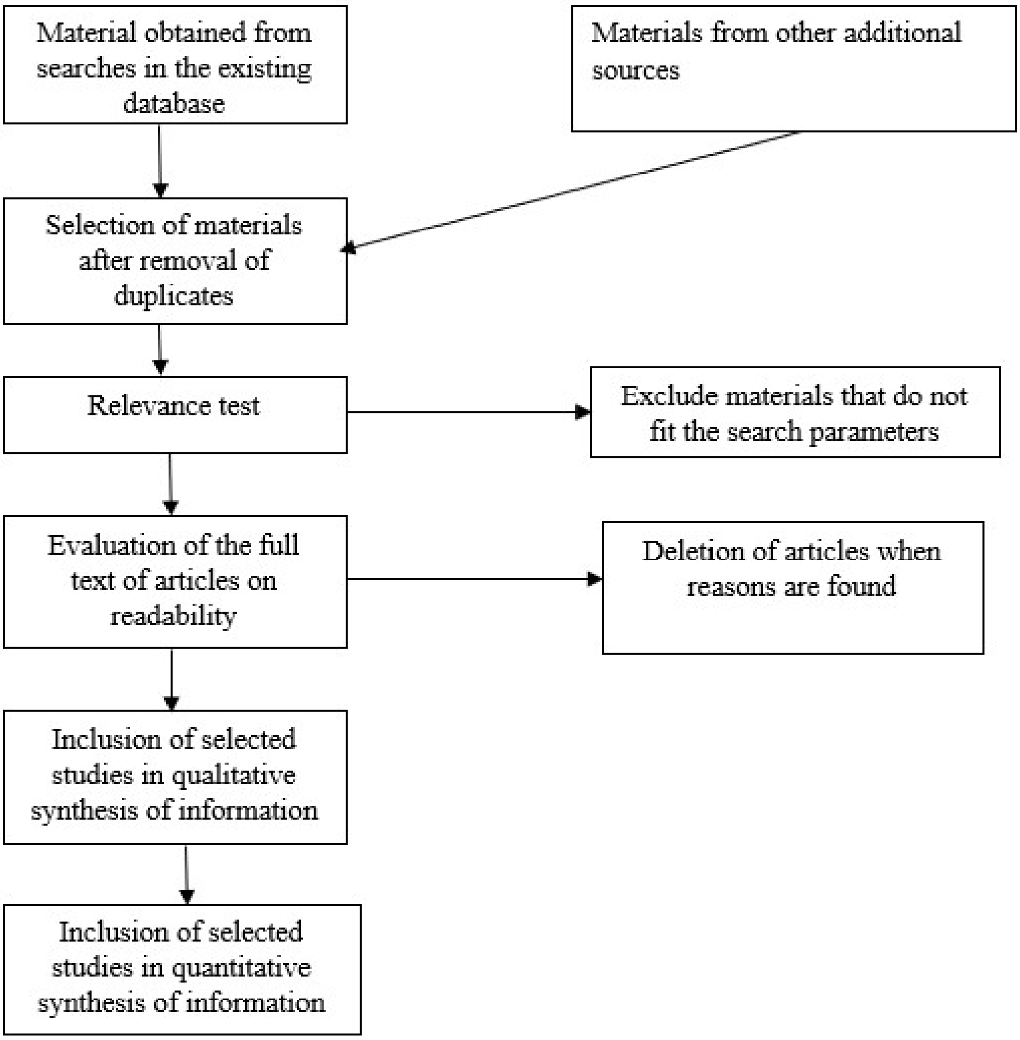

Figure 1. Overview Flowchart Showing Search and Selection of Literature

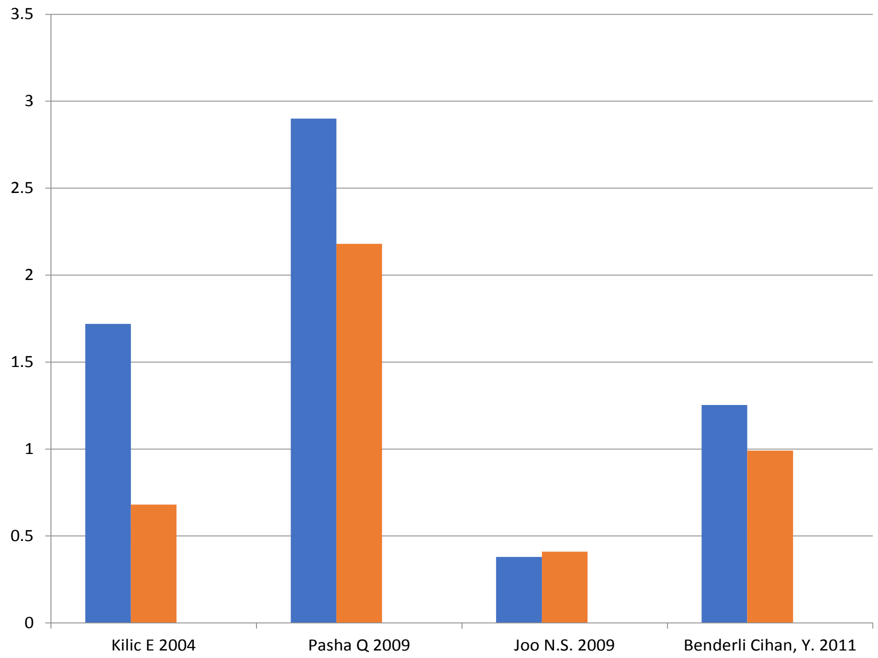

Figure 2. Chromium Content in Hair in Women with Breast Cancer and Healthy

levels of the microelements in tumor tissue. The amount of Fe ranges from 38.46 to 65.39 ug/g (average 49.56±5.81 ug/g), Cu from 2.8 to 6.69 ug/g (average 5.06±1.01 ug/g), Zn from 1.89 ug/g to 5.38 ug/g (average 3.88±0.89 ug/g), Cr from zero to 6.1 ug/g (average 2.13±1.29 ug/g), Ni from 0.11 to 0.42 ug/g (average 0.28±0.067 ug/g) and Pb from zero to 0.19 ug/g (average 0.098±0.06 ug/g).

A statistically valid difference has been established between the accumulation of VM in two tissue groups ($p < 0.05$). The total number of VMs in the first group ranges from 71.36 to 84.86 ug/g (average 78.63±3.47 ug/g), and in the second group from 51.21 to 73.2 ug/g (average 61.02±5.77 ug/g). As we can see, the content of the above elements in the comparison group is 22.4% less than their number in the research tissue sample. Comparing the average VM levels in tumor tissue between the two groups, it is found that the amount of Fe in the comparison group is less by 24% (p=0.001), Cu – by 15.4% (p=0.002), Cr – by 16.8% (p=0.016), Zn – by 13.8% (p=0.005) This confirms the fact that with the injection of increased amounts of VM into the body of women with food and water, they are deposited in the tissues of macro-organism, including tumor tissue of breast.

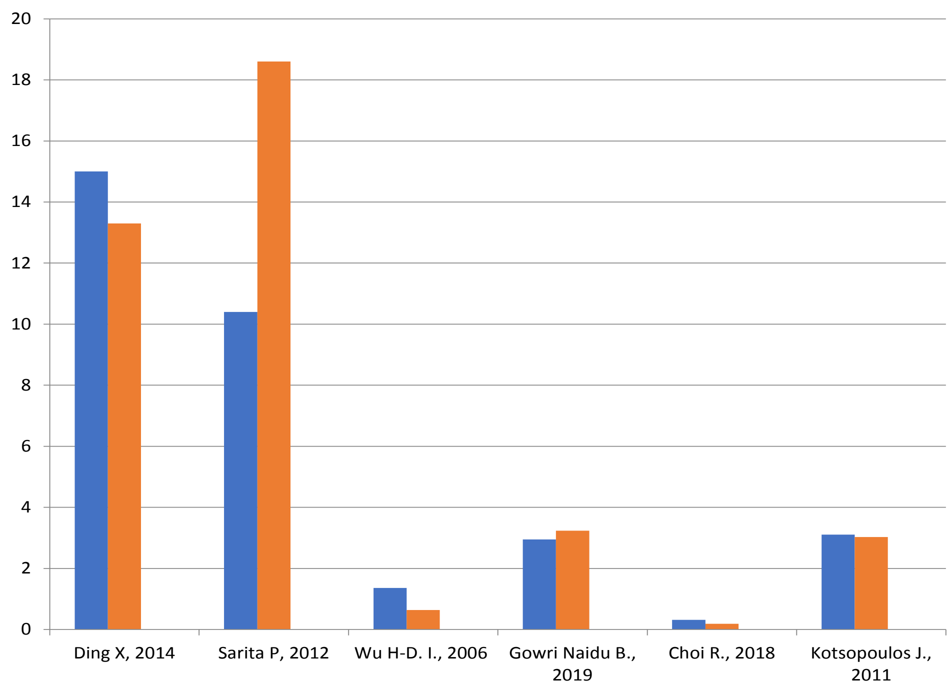

Figure 3. Blood Chromium Content in Women with Breast Cancer and Healthy

Table 2. Chromium Content in Hair and Blood in Patients with Breast Cancer and Healthy

Original author	Year	Country	Sample source	Method for determining Cr	Stage breast cancer	Women with breast cancer			Control (women's health)			Type of investigartion
						Middle age	N	Cr (mean ± SD)	Middle age	N	Cr (mean ± SD)	
Ding et al.	2014	China	Serum	ICP-AES	Not reported	45.73±9.84	88	15.0±5.4	45.29±8.52	84	13.3±5.4	Case-control
Kilic et al.	2004	Turkey	Hair	GFAAS	3	53±9	26	1.72±0.67	55±7	27	0.68±0.32	Case-control
Sarita et al.	2012	India	Serum	PIXE	Not reported	from 30 to 75	21	10.4 ± 3.9	from 25 to 62	30	18.6 ± 7.8	Case-control
Pasha et al.	2010	Pakistan	Hair	FAAS	Not reported	30.2–65.4	33	2.90±0.57 μg/g	30.3–62.7	35	2.18±0.24μg/g	Case-control
								Used SE			Used SE	
Wu et al.	2006	China	Serum	ICP-AES	Not reported	---	25	1.36±0.26 μg/L	---	26	0.64±0.20 μg/L	Case-control
Joo et al.	2009	Korea	Hair	LC/MS Liquid Chromatography Mass Spectrometry	Not reported	47.1±9.6	40	0.38±0.014 μg/g	47.8±5.1	144	0.41±0.009 μg/g	Case-control
Naidu et al.	2019	India	Serum	SRXRF Synchrotron radiation-based X-ray fluorescence	Not reported	55 ± 7	40	2.95 ± 0.50 μg/g	49 ± 5	40	3.24 ± 0.74 μg/g	Case-control
Choi et al.	2018	Korea	Serum	ICP-MS	---	46.0 (40.0–53.0)	150	0.22 (0.12–0.54) μg/L	48.0 (43.0–56.0)	137	0.21 (0.12–0.51) μg/L	discovery cohort.
Choi et al.	2018	Korea	Serum	ICP-MS	---	41.00 31.00–48.00	79	0.32 (0.14–4.05) μg/L	47.00 43.00–53.75	63	0.19 (0.10–0.31) μg/L	Validation Cohort
Benderli Cihan et al.	2011	Turkey	Hair	ICP-MS	Stage III	50.3±8.8	52	1.253 ±0.891 μg/g	47.4±10.1	52	0.991 ±0.950 μg/g	Case-control
Kotsopoulos et al.	2011	Poland	Serum	ICP-MS	BRCA1 mutation	1,962.8 (1,943.4–1,988.4) range	48	3.11 (2.12–6.00) μg/L	1,962.9 (1,943.2–1,988.5) range	96	3.03 (2.12–4.19) μg/L	Case-control

In the beast, without nidi and in distant metastases, the number of investigated elements was lower than in the primary tumor site. Correlation (r=0.62, p <0.05) between accumulation of VM in areas of neoplasia and the degree of malignancy of breast cancer was established. The fact of increase of microelements concentration in IDC breast cancer tissue with progression of carcinogenesis can be explained by violation of mechanisms of regulation of VM absorption and utilization by tumor cells. Increased anaplasia of cancer cells leads to inhibition of enzyme synthesis, which is involved in the maintenance of intracellular homeostasis of epitheliocytes. On the other hand, the increased number of microelements stimulates this imbalance by maintaining a sinister VM influence over the course of the malignant process. The determination of the elemental composition of the tumor tissue by atomic absorption spectroscopy shows the total amount of microelements per gram of the examined tissue, but it does not allow the investigation of the content of these elements in the different structural components of the tumor. In order to determine the spatial features of the localization of accumulation of microelements in the cancer tissue, a study of the chemical composition of IDC breast cancer was carried out, which was determined by an energy dispersion method on a raster electron microscope.

The process of determining the chemical composition of the breast tissue took place in two functional modes. There is local scanning of the surface of the drug at different levels of image enlargement and focal scanning, taking into account the microelemental composition in parenchymatous on stromal components of the tumor.

Figure 2 presents data on the chromium content of hair in women with breast cancer (blue) and healthy.

Experimental and epidemiological studies provide evidence that micronutrient levels in biological substrates may be associated with the risk of breast cancer. However, the relationship between the level of chromium in the blood serum and other biological substrates and breast cancer remains relatively unknown. The results show that exposure to heavy metals, including chromium, may affect blood lipid levels and some low molecular metabolites, which may in turn contribute to the development of breast cancer. In this study, Cr levels of blood serum were found to be 3.24 times higher in patients with breast cancer than in the control group.

Figure 3 presents data on blood chromium levels in women with breast cancer (blue) and healthy women.

According to meta-analysis, the relationship between exposure to Cr (VI) and mortality from breast cancer was not significant. The case-control study compared the levels of 15 trace elements in the women's serum with breast cancer and healthy control to assess whether the levels of trace elements in the blood serum are related to the risk of breast cancer. Women with breast cancer had borderline high levels of Cr (p = 0.052) compared to the control group.

Discussion

In many studies since the 1930s, the relationship between chromium and cancer has been documented, with chromium-6 being a well-known human carcinogen, which may lead to various health problems during breathing and drinking water (Stohs et al., 2000).

Penetrate with the cells, Cr (VI) undergoes a series of metabolic changes and forms intermediate forms of Cr, including Cr (V) and Cr (IV), and finally recovers to Cr (III) (Zhitkovich, 2011; Zhitkovich, 2005). Studies have shown that solubility plays a key role in the carcinogenicity of Cr (VI), with the most potent carcinogens being water insoluble or «solid» compounds. The genotoxic mechanism of action of these particles involves the extracellular release of the soluble anion Cr (VI), which penetrates the cells and causes DNA damage (Xie et al., 2004). Molecular mechanisms involving oxidative stress and DNA damage are considered the main ways in which Cr (VI) manifests its carcinogenic effects. Active oxygen forms (AFCs) are formed during Cr (VI) reduction, resulting in oxidative DNA damage. Intermediate products Cr (V), Cr (IV) and final product Cr (III) cause Cr-DNA adducts and genomic changes (Stout et al., 2009). The formation of AFC causes cellular damage caused by Cr (VI), such as DNA damage, cytotoxicity and tumor development (Zhitkovich, 2011; Zhitkovich, 2005; Chen et al., 2019b). It is known that Cr (III), (IV), (V) and (VI) produce intracellular AFCs. Ascorbic acid and glutathione are capable of detecting and reducing Cr (VI) to Cr (III), thereby producing free radicals such as hydroxyl radicals, and intermediate compounds damaging DNA such as Cr (V) and Cr (IV) (Zhitkovich, 2011; Chen et al., 2019b; Arita and Costa, 2009; Jomova and Valko, 2011). It is recognized that Cr (VI) can cause DNA damage after intracellular repair by interacting with proteins and amino acids or directly with DNA, causing single-stranded and double-stranded DNA breaks (Zhitkovich, 2011; DeLoughery et al., 2015). Ovesen et al., (2014) presented evidence that prolonged exposure to low concentrations of Cr (VI) could cause DNA damage.

Numerous studies have shown that Cr (VI) is capable of altering gene expression and causing malignant tumors to develop using multiple epigenetic mechanisms (Ferreira et al., 2019). Wang et al., (2018) has found that chronic Cr (VI) exposure is associated with epigenetic dysregulation by increasing the expression of related histone-lysing methyltransferases, which play an important role in Cr (VI) -induced cell transformation. Another study confirmed that Cr (VI) can form protein-Cr-DNA adducts and inhibit tumor growth suppressor genes, as well as disrupt CTCF binding (11-zinc protein) and nucleosome distance (VonHandorf et al., 2018). Some epidemiological studies show that the carcinogenic potential of some toxic metals and chromium, including, may include epigenetic changes such as suppression of DNA repair and tumor-suppressing genes (Ali et al., 2011; Kondo et al., 2006; Takahashi et al., 2005; Martinez-Zamudio and Ha, 2011). Systemic toxicity associated with Cr has been documented for the respiratory and lung system, gastrointestinal tract, skin and kidneys (Wilbur et al., 2012).

The main way of exposure to Cr, unrelated to professional activities, is to take a person inside. In occupationally exposed persons, Cr ingestion is most likely via inhalation or dermal absorption (Wilbur et al., 2012). Adverse effects on the respiratory tract and lungs caused by exposure to Cr include asthma, bronchitis and respiratory tract irritation (Khan et al., 2013), as well as ulcers and nasal septum perforation (Gibb et al., 2000). The effect of chromates and bichromates can be contact dermatitis (Lejding et al., 2018), skin burns, blisters and skin sores have also been noted. Gastrointestinal effects, including chronic dyspepsia, gastric ulcers and gastritis, have been reported after occupational exposure to Cr (Wilbur et al., 2012; Beyersmann and Hartwig, 2008). Prolonged exposure to this element may cause damage to the liver and kidneys, blood circulation and nervous system (Abdulrahman et al., 2012). In addition, according to the results obtained by White et al., (2020) in the Sister Study, the level of chromium in the nails is associated with the later age of menopause.

However, in a study conducted by Qayyum and Shah (2014), in which chromium levels were determined in hair from head cancer lung and healthy control, higher chromium concentrations were obtained in control group subjects than in lung cancer patients. Pasha et al., (2007), which used the same biological material, in contrast, found an inverse correlation: in cancer patients of different localizations, the level of this metal was higher. A number of studies have shown an increased risk of laryngeal cancer in workers exposed to hexavalent chromium compounds (Hall et al., 2020; Wozniak et al., 2016). It has also been established that Cr (VI) promotes the development of sinus and sinus cancer in workers exposed to occupational exposure (d'Errico et al., 2009). Although hexavalent chromium has been recognized as a human respiratory carcinogen, there is currently insufficient data to conclude conclusively that Cr (VI) is a peroral carcinogen. In saliva, acidic environment of stomach and blood Cr (VI) is restored to non-toxic Cr (III) (Proctor et al., 2002).

Meta-analysis conducted by Beaumont et al. (2008), showed an increase in stomach cancer risk (Relative Risk = 1.27; 1.18-1.38) in workers exposed to Cr (VI) and an increase in stomach cancer mortality (Rate Ratio = 1.82; 1.11-2.91) in chrome-contaminated regions. A meta-analysis conducted by Welling et al. (2015) also suggested that Cr (VI) has a carcinogenic effect in the development of stomach cancer. However, the case-control study O'Rorke et al., (2012) found no link between chromium levels in toenails and the risk of esophageal development of Barrett and esophageal adenocarcinoma.

Hara et al., (2010) has found that exposure to Cr (VI) can increase the risk of developing brain cancer and malignant lymphoma. According to Iaia et al., (2006), exposure to Cr (VI) increases mortality from lung cancer, bladder and pancreas cancer, myeloid leukemia and endocrine gland tumors among skin workers. Cr (VI) is thought to be associated with an increased risk of lung, laryngeal, bladder, kidney, testicles, thyroid and bone cancer (Donato et al., 2016). Deng et al., (2019) meta-analysis has provided evidence that Cr (VI) can cause cancer of the respiratory system, oral cavity and throat, prostate and stomach in humans. In addition, the incidence and risk of cancer death were largely related to the concentration of Cr (VI) in the air and the duration of exposure.

Metallurgical workers exposed to Cr (VI) have been found to have an increased incidence of bladder cancer (IARC, 1990). The study Wise et al., (2016) describes an increase in chromosome instability after chronic exposure to chromates, which is believed to be the mechanism of chromate-induced bladder cancer. Together, these results suggest that Cr (VI) may act as a carcinogen after ingestion.

Among the various types of cancer in women, breast cancer is the most common malignant neoplasm and breast cancer incidence is increasing in many countries (Chen et al., 2020; Golubnitschaja et al., 2016). For women, breast cancer was the most common cancer in 143 countries and the most common cause of cancer death in 112 countries (Fitzmaurice et al., 2019). In 2018, the breast cancer of women on incidence ranked first place in the world among oncological diseases – 24.2%, and first in the world in mortality – 15.0% (Ferlay et al., 2019).

A number of factors are linked to the development of breast cancer, including genetic background, diet, lifestyle, obesity, smoking, alcohol consumption and pollution (Florea and Büsselberg, 2011; Jevtic et al., 2010). Factors such as early menstruation and late menopause, old age, hereditary mutations, type 2 diabetes and prolonged exposure to estrogens correlate with increased risk of breast cancer. Among these known factors, increased estrogen levels are considered the main risk factor (Feng et al., 2018; Kulkoyluoglu-Cotul et al., 2019). Several studies have shown that some metals, such as Cd, Cu, Fe, Zn, Co, Cr, Pb, Al, Hg, Sn, As and Ni, activate estrogen receptors and stimulate estrogen gene expression and the proliferation of breast cancer cells (Lappano et al., 2017; Florea and Büsselberg, 2011).

Revealing the imbalance of the main elements in patients with breast cancer compared to healthy people can serve as a vital biomarker for early diagnosis of malignant breast cancer. Experimental and epidemiological studies provide evidence that micronutrient levels in biological substrates may be associated with the risk of breast cancer. However, the relationship between the level of chromium in the blood serum and other biological substrates and breast cancer remains relatively unknown.

The results of Li et al., (2020) show that exposure to heavy metals, including chromium, can affect blood levels of lipids and some low-molecular metabolites, which in turn may contribute to the development of breast cancer. In this study, serum levels of Cr were found to be higher in patients with breast cancer compared to the control group by a factor of 3.24.

According to meta-analysis Deng et al. (2019) the link between exposure to Cr (VI) and mortality from breast cancer was not significant. In a study, the case-control of Ding et al., (2015) compared serum levels of 15 trace elements in women with breast cancer and healthy control to assess whether levels of trace elements in the blood serum are related to the risk of breast cancer. Women with breast cancer had borderline high levels of Cr ($p = 0.052$) compared to the control group.

Quantitative elemental analysis of hair from scalp women with stage III breast cancer and control group was used by Kilic et al., (2004) to detect a possible link between breast cancer and chromium level. A comparison of the mean chromium content of breast cancer patients with the control group showed a significant increase in chromium content ($p < 0.05$) in patients with breast cancer.

In a study by Raju et al., (2006) chromium concentration was higher ($p<0.05$), Wilcoxon rank criterion) in breast cancer than in normal tissue. Excess micronutrient levels observed in breast cancer may be the cause or consequence of breast cancer. A possible mechanism for the development of breast cancer is that elevated levels of Cr could lead to the formation of free radicals or other active oxygen forms (ROS) that cause changes in DNA, producing genetic changes. On the other hand, elevated concentrations of elements in breast cancer tissues may also be a consequence of cancer. Tumors, due to uncontrolled and rapid growth, consume significant amounts of essential nutrients, including trace elements. The result is increased blood supply of tumors and increased concentration of elements in tumors.

Sarita et al., (2012) research has provided evidence that serum Cr levels have been reduced ($P<0.005$) in patients with breast cancer compared to control group. Most microelements exhibit a distribution different from normal, as evidenced by large values of dispersion, standard error, and asymmetry.

The Pasha et al., (2010) study found that the average level of Cr did not differ significantly in scalp hair samples in three groups: women with malignant breast lesions, women with benign breast tumours and healthy women. However, the distribution of the level of Cr by quartile revealed its maximum spread in the scalp hair of groups with malignant and benign neoplasms of the breast. In addition, strong correlation coefficients have been established between Co and Cr, Cd and Cr in the hair from the scalp of women with malignant breast tumors, while Cr and Pb showed a strong correlation in hair from the scalp of women with benign breast tumors.

The “case-control” study conducted by Wu et al. (2006), compared serum levels of 13 microelements in 3 groups: women with breast cancer, women with benign breast tumors and healthy control. The level of chromium in the serum of women of the first two groups (with breast tumours) was significantly higher ($p<0.01$) compared to the group of healthy women. In a “case-control” study conducted by Joo et al., (2009) in Korea, the levels of Cr and other sixteen trace elements in the scalp hair of women with breast cancer and women from the control group were compared. There were no statistically significant differences in chromium concentration in the hair between the two groups.

In the study Naidu et al., (2019) trace elements in the serum of breast cancer patients and healthy control were determined by the method SRXRF (Synchrotron radiation-based X-ray fluorescence, X-ray fluorescence-based synchrotron radiation). The results revealed significantly reduced levels of Cr in serum in patients with breast cancer compared to healthy subjects ($p < 0.05$).

Choi et al., (2018) study examined the level of chromium and other six trace elements in the blood serum in Korean women with breast cancer compared to the control group of healthy women. The determination of trace elements in the serum was carried out in the primary and verification (validation) cohorts. There are no significant differences in chromium levels between women with breast cancer and control groups, nor between groups of patients with breast cancer (subgroups divided by breast cancer stages and subgroups of women with and without breast cancer).

Olaiya et al., (2019) determined the level of trace elements, including chromium in the breast tissues (the most malignant neoplasm and normal, not affected by cancer of the tissue) of women with breast cancer in Nigeria. Chromium was found in small amounts and there was no discernible difference between its levels in malignant and normal tissues.

In a prospective study, Benderli Cihan et al., (2011) compared the level of 36 elements in the hair from the head in patients with stage III breast cancer and healthy women control group. Compared to the control group, breast cancer patients had higher levels of chromium in their hair ($p < 0.05$), and other heavy metals showed similar results. Thus, a statistically significant difference in the level of toxic trace elements in the hair was determined between the two groups, indicating accumulation of heavy metals in patients with breast cancer.

In a study conducted in Poland, the case-control of Kotsopoulos et al., (2012) assessed the relationship between the level of trace elements, including Cr, in plasma and breast cancer among carriers of BRCA1 mutation. There were no significant differences in plasma chromium levels between women with breast cancer and the control group.

In conclusions, in the environment, salts of heavy metal in the tissue of infiltrating ductal breast cancer are increasing the content of heavy metal ions ($p < 0.05$), which in the second group is 22.4% less than in the first one, which causes a more aggressive course of malignant process. The content of Fe in the tumor tissue in the “ecologically-polluted” areas is 24% more than in the “ecologically clean” areas ($p=0.001$), the content of Cu – by 15.4% ($p=0.002$), Cr – b y 16.8% ($p=0.016$), Zn – by 13.8% ($p=0.005$), Pb – by 1.0.0.0.0. The energy-dispersion spectrometry results confirm the elemental composition of the neoplastic tissue. The heavy metal content is higher in the parenchyma component of the tumor than in the stroma ($p < 0.05$). Increased accumulation of Fe, Zn, Cu, Cr, Ni and Pb in tumor tissue affects the genetic material of cells of infiltrating ductal breast cancer, manifesting in blocking receptor transcription, pathological methylation of DNA and progressive increase in its fragmentation ($p < 0.05$), which negatively affects the course of the malignant process.

Heavy metals accumulate in breast tumor tissue, through intracellular mediators stimulate pathological biomineralization and vascularization processes, stabilize prognostically adverse proteins, destabilize the genetic material and block the activity of prognostic-favorable receptors, which leads to progression of carcinogenesis in the breast. Women who live or work in ecologically polluted areas or have problems with micronutrient exchange need in-depth screening and more frequent screening for early detection of pre- and breast cancer. In their treatment, it is necessary to pay attention to the possibility of accumulation of heavy metal ions in the breast tumor tissue, which can be prolonged to stimulate the progression of the malignant process.

The identified pathological biomineralization and intensive inflammatory infiltration around the infiltrating ductal breast cancer during histological research consider prognostic-unfavorable factor of the neoplastic process. For correct assessment of the flow and prognosis of infiltrating ductal breast cancer in patients living in "ecologically polluted" regions, it is advisable in immunohistochemical research, in addition to expression of receptors to estrogen, progesterone, epidermal growth factor, p53 and Ki-67, pay attention to the need to identify other prognostically important receptors in breast tumor tissue (bcl-2, hsp90, VEGF).

Author Contribution Statement

GB, VK, AA, ZT, GU: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing -review & editing.

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Ethics approval and consent to participate

Not applicable

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Study registration

The study has been prepared accordantly to the MOOSE checklist for meta-analysis, but it was not registered in any data set.

Conflict of interests

The authors declare that they have no conflict of interest.

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