CASE REPORT

Recent updates on analysis of alteration of Zn level in cancer patients

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ABSTRACT

Zn micronutrient is involved in many physiological processes that include enzyme activity, genomic stability, DNA repairing, apoptosis, immunity, neurological function, response to oxidative stress, and cell signaling. The deficiency of trace element Zn may be responsible for the mutation of DNA, tumor genesis, and carcinoma cell production. The Zn level has been found to decrease in cancer patients as compared to the healthy controls. Various cancer such as breast, ovarian, prostate, lung, Ewing, endometrial, brain, and bladder cancer have been correlated with Zn deficiency. The polymorphism may be correlated with the ZINC deficiency in several cancer patients. The polymorphism has been observed in MT2A, Matrix metalloproteinase (MMP)-1, MMP-2, MMP-7, and MMP-13 genes significantly change in the Zn levels in the serum of prostate cancer patients. The genotypes GSTM1 and GSTT1 significantly change the concentration of zinc concentration in lung cancer patients. The presence of polymorphism rs1805502 in the GRIN2B gene within the brain is associated with a notably reduced concentration of zinc in the serum. The results of these studies associated with deficiency of zinc in the body may cause DNA damage, mutation in DNA, and tumor growth. This review article provides a detailed description of the deficiency of the Zn element in cancer patients and polymorphisms in genes encoding zinc-dependent proteins associated with different cancers.

KEY WORDS: Cancer, DNA, Mutation, Polymorphism, Zinc

INTRODUCTION

Cancer is a disease in which some body cells grow out of control and spread to other body parts. Cancer is characterized by the development of abnormal cells as a result of unchecked growth. This further related with aberrant cell proliferation and growth. The tissue masses develop from these cells. Cancer is the second-leading cause of death in the world and many of them related with breast, prostate, brain, bladder, endometrial, lung, and ovarian cancer.[1] The breast is composed of a variety of tissues, from extremely fatty tissue to extremely dense tissue. There is a network of lobes within this tissue. Healthy cells in the breast begin to alter and expand out of control to form a tumor, which is a mass or sheet of cells. A tumor may be benign or malignant. Malignant refers to the ability of a cancerous tumor to develop and metastasize to different body regions.[2] Similarly, a walnut-sized gland, the prostate is situated below the bladder, in front of the urethra, and behind the base of the penis. The urethra, the tube-like passageway that conducts urine and sperm through the use of the penis, is encircled by it. A tumor is created when normal prostate cells undergo a transformation and grow out of control.[3] Another tumor is a brain tumor that is referred to as a primary brain tumor. There are two grades of primary brain tumors: Low grade and high grade. However, a low-grade tumor has the potential to progress to a high-grade tumor. A high-grade tumor has a higher chance of expanding quickly. A cancerous tumor that originated in the breast, lung, or colon before spreading to the brain is

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Access this article online
Website: http://isfcppharmaspire.com
DOI: 10.56933/Pharmaspire.2023.15131
Date of Submission: 01 April 2023
Date of Revision: 10 April 2023
Date of Acceptance: 12 April 2023
referred to as a secondary brain tumor. Another cancer is a bladder cancer which composed of the lower abdomen part and stores pee. It is developed inside the bladder (urothelial cells) and related with kidneys. The endocrine cancer is related with uterus and involved in the development of fatal. The lining of uterus known as endometrium involved in cancer development. The soft-tissue surrounding the bones involved in Ewing sarcoma. It is generally start in the pelvic and leg bones. Less frequently, it begins in the limbs, abdomen, chest, or other soft tissues. The lung which is related with breath in oxygen and exhaust carbon dioxide related with lung cancer. It is also a major cause of fatalities. Ovarian cancer can penetrate and obliterate healthy biological tissue and reproduce swiftly. There are two ovaries in the female reproductive system, one on either side of the uterus. The female reproductive system comprises two ovaries, positioned on either side of the uterus, and they play a role in the development of cancer.

It has been observed that the tumors may or may not be malignant (benign). Furthermore, essential trace elements decreased in cancer; however, other trace element deficiencies may also contribute to cancer. The Zn is involved in various biological reaction and plays an important role in their progress such as immunity, genomic stability, enzymatic activity, genetic variation, function of nerve cell, cell signaling, and response to oxidative stress.

Accumulating evidence has recently indicated an association between zinc deficiency and cancers. Serum Zn level is an accurate biomarker of body Zn status as it well responds to dietary and supplemental intakes. Zinc is known to be a crucial component of DNA-binding proteins with zinc fingers. Zinc is crucial for the operation of transcription factors, antioxidant defense, and DNA repair. Zinc deficiency in the diet can result in single- and double-strand DNA breaks as well as oxidative DNA alterations that raise the chance of developing cancer. In smoking of tobacco inhalation of CO₂ it caused the methylation of Zn which causes the DNA damage and caused cancerous cell growth.

Humans who are zinc deficient have a higher risk of getting carcinoma. Through its impact on angiogenesis and tumor growth, zinc may also be able to prevent cancer. Although the levels of Zn in serum and tissue sample has been determined for the identification of various cancer including colon, bladder, thyroid, breast, oral.

Even though the body only requires minute amounts of zinc, nearly 100 enzymes depend on it to perform essential chemical reactions. It plays a crucial role in the production of DNA, cell proliferation, the synthesis of proteins, the repair of damaged tissue, and the maintenance of a strong immune system. Several biological mechanisms, including cell division, reproduction, and immune function, depend on the concentration of zinc. Due to its involvement in scavenging free radicals and antioxidant capabilities, zinc is needed by more than 300 enzymes and almost 2000 transcription factors, and it is linked to a number of disorders in humans. Literature survey revealed that Zn level decreased in patients with cancer and it was related with DNA damage which further changed the integrity of cell.

Zn is a micronutrient involved in many physiological processes that include enzyme activity, genomic stability, apoptosis, immunity, neurological function, response to oxidative stress, and cell signaling. Zn serves as a free radical scavenger and assumes a fundamental role in the initiation of DNA rebuilding enzymes when combined with super oxide dismutase.

In a Chinese case-control study, researchers looked at the independent and combined effects of dietary zinc and selenium intake, as well as polymorphisms of the genes related to oxidative stress (superoxide dismutase 1, superoxide dismutase 2, glutathione peroxidase, and catalase), on the risk of CRC.

Polymorphism

The polymorphism in genetics is related with genetic variation in the population, on which natural selection can operate or refers to the occurrence of two or more variants of a certain DNA sequence in various people or communities. A single nucleotide can vary in polymorphism, which is the most prevalent kind (also called a single-nucleotide polymorphism or SNP). Other polymorphisms can involve longer sections of DNA and be substantially bigger. In the polymorphism, the loss or deficiency of the essential trace elements causes DNA damage because essential trace elements repair the DNA damage. Due to DNA damage, the mutation occurs in the cells of DNA which leads to the growth of the benign tumor or malignant tumor.

Zn polymorphism was described by various scientists in their study. Reszka et al. reported a study where they found lung cancer patients in comparison to control (24.4%), who did not smoke (6.0%). The distribution of GSTM1, GSTM3, and GSTP1 genotypes between the studied groups lacked statistical significance. When compared to the control (43.2%), lung cancer patients (44.1%) were found with a similar prevalence of the GSTM1 genotype. In comparison to lung cancer patients, controls had a substantially greater prevalence of GSTT1 homozygous deletion (GSTT1 null genotype). Between the two groups, there was no difference in the combined GST genotypes which were evaluated as GST both protective, GST either protective and GST neither protective. The activity of GPx and SOD in RBC, as well as Se and Zn concentrations, is significantly lower in lung cancer patients. In another study, Liuzzi and Cousins studied Zn metabolized due to single nucleotide polymorphism which may influence the bioavailability and homeostasis of Zn within cells. Zn homeostatic processes that affect Zn absorption, efflux,
and distribution inside of cells regulate how much zinc is bioavailable. There are two protein families that make up zinc transporters such as the ZIP and ZnT. Metal ion transporters belonging to the SLC39A (ZIP) and SLC30A (ZnT) families, respectively, are included in the ZnT family.[20,21] Furthermore, Białkowska et al. investigated, the associations between prostate cancer in Polish males and changes in serum Zn levels and polymorphisms in MT2A, Matrix metalloproteinase (MMP)-1, MMP-2, MMP-7, and MMP-13.[22] In progression to the polymorphism and associated, Zn level deficiencies various other literature have been published. Where Liu et al. studied the GluN2B subunits of NMDA receptors which encoded by GRIN2B. It is a fairly sized gene with 13 exons, and 400 kb of genomic DNA, and is found on the 12p13.1 chromosome. The medial prefrontal cortex, a crucial part of the brain involved in spatial learning and memory tasks, and the hippocampus have been shown to express the protein GRIN2B at high levels. Results also demonstrated that the risk of dyslexia is altered by polymorphisms of the rs1805502 in the GRIN2B gene.[23]

In a study, Zhu et al. reported MPO G-463A polymorphism prevalence in gastric cancer. It is investigated using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques. The MPO-463G/A genotype distribution was shown to be substantially different between patients and controls (c2 14 7.42, P 14 0.03). According to stratified analyses, the protective impact of the A allele was significant in males and younger patients (age 58 years) (adjusted OR 14 0.42; 95% CI: 0.18–0.94) and not observed in older or female patients. In addition, respondents who lived in rural rather than urban regions had a considerably lower risk (adjusted OR 14 0.41; 95% CI: 0.18–0.95) of polymorphism.[24] Krześlak et al. analyzed 412 samples of prostate cancer tissue, and the MT2A polymorphism was identified using the PCR-RFLP method. Real-time RT-PCR was used to analyze the MT2A gene expression. The genotype of rs28366003 and the level of MT2A expression were significantly correlated. The genotype distribution was shown to be substantially different between patients and controls (c2 14 7.42, P 14 0.03). Research discovered that minor allele carriers, or the risk allele, had lower average mRNA levels than major allele homozygotes. The flamed atomic absorption spectrometer instrument was used to assess the metal levels. The SNP was significantly associated with the levels of Cd, Zn, Cu, and Pb. According Krześlak et al., SNP polymorphism may have an impact on the prostate’s MT2A gene expression, which was linked to certain metal buildup.[25]

Furthermore, Miller et al. described the p53 Y220C mutation caused by protein unfolding, aggregation, and loss of Zn in the DNA binding domain. Miller et al. designed the series of compound that contain iodate phenols and aimed for interaction and stabilization of the p53 Y220C surface cavity and Zn binding fragments and, characterized the Zn affinity by spectroscopic methods with anticancer activity.[26] Rentschler et al. studied that the polymorphism of Zn transporter genes SLC39A8 and SLC39A14 belongs to Zn homeostasis system and modifies Cd concentration in blood and urine. The study found that the Bangladeshi women exhibited higher Ery-Cd and U-Cd than the Andean women, but lower BMI, P-Zn, and plasma ferritin. Bangladeshi women had lower Zn concentration than the Andean women. The Andean groups have weak LD for the SNPs rs4872479 and rs870215 in SLC39A14, while Bangladeshi people did not.[27] Yanar et al. studied the plasma levels of oxidative stress and evaluated with manual colorimetric techniques according to NOS3 genotypes in LC patients and their appropriate controls. Plasma non-protein thiol, Cu, and Zn-SOD levels in LC patients with TT genotypes were considerably greater than those in the control group. Elevated levels of LHP demonstrated statistically significant data as compared to HC in individuals with the GG and GT genotype.[28] The cancerous cell growth described due to deficiency of Zn in Figure 1.

**Zinc transporters**

Zinc is an essential element for cellular process which is regulated by zinc transporters. Zinc is regulated by zinc transporters and buffered by metallothionein and glutathione. Zinc is necessary for numerous cellular activities. A variety of zinc-trafficking routes have been identified recently that are connected to signaling cascades, notably those that include the inhibition of protein phosphatase and the downstream activation of mitogen-activated protein kinases and tyrosine kinases.[29] A rising number of studies have been found that ZnTs and ZIPs have a role in a range of malignancies.[30] A common scenario is that these Zn transporters have either altered expression levels or abnormal activity, which in turn contributes to Zn homeostasis regulation in cancer cells or tumor tissues.[31] Despite the fact that no mutation or SNP variant of Zn transporter genes has been reported to be associated with a specific cancer as of yet. At least, five ZnTs and nearly all ZIP transporters are involved in a number of malignancies,

![Figure 1: Chronic Zn deficiency causes DNA damage which leads to cancer cell growth](Image)
The zinc content in pancreatic adenocarcinoma is lower than that in normal pancreatic ductal and acinar epithelium, according to in situ Zn staining pictures of human pancreatic tissues. These alterations in zinc content and ZIP3 expression are thought to occur early in the progression of pancreatic cancer, making the malignant cells more resistant to the cytotoxic effects of zinc. Regarding ZIP4, it is unclear why this gene’s expression is elevated in pancreatic cancer cells and even positively linked with the development of the tumor in a xenograft animal model. Although the precise mechanism is still unknown, a recent study demonstrated that ZIP4 might make pancreatic cancer cells resistant to Zn deficiency-induced apoptosis. Zn transporters participate in both death and growth of cancer cells, as well as their ability to withstand drugs. According to Taylor et al., TamR cells, a tamoxifen-resistant breast cancer cell line derived from MCF7, showed higher levels of Zn and ZIP7. They also demonstrated that TamR cells regained tamoxifen sensitivity by lowering intracellular Zn levels and disrupting EGFR/IGF-I receptor/Src signaling using siRNA that precisely targets the ZIP7 gene to diminish ZIP7 expression. Despite mounting evidence linking deregulated zinc transporters to malignancies, it is still unclear whether the dysfunction of the zinc transporter acts as a “driver” or a “passenger” for tumor genesis or carcinogenesis. It is also unclear whether these effects are caused by the deregulated Zn transporter itself or the ensuing changes in Zn status. With the exception of prostate cancer, the results described in Table 1 seem to show a tendency toward an overexpression of ZIP transporters. It could be a sign that cells need to take in more zinc to keep up with their higher rate of metabolism and proliferation. Multiple processes underpinning the participation of Zn transporters may coexist as Zn status itself, hormones, growth factors, and cellular redox state are also capable of regulating Zn transporters.

Methods were reported for the estimation of Zn generally based on DCP-AES, AAS, FAAS, SP, ICP-MS. These methods were used to analyze the zinc levels in the serum or hair sample.

The literature survey was done through the online database PubMed, Springer, Science Direct, Elsevier, and other sources. In these databases and online journals, different case-control studies of cancer were studied. In the search, there were other terms like polymorphism, and cell lines of cancer were also included such as Zinc levels, trace elements, polymorphism, cancer tumors, and sites of cancer.

No restriction was about of age, gender, and area, and menopausal patients the data, which is not usable, were excluded from the study.

Deficiency of Zn level and related diseases

Zinc is the most included element in the human body. Zn cause cancer due to excessive exposure in our diet and deficiency in our serum or blood (900 mg in dietary exposure per day). Zn is one of the trace elements that play the role of tumor progression in cancer. Zn is considered as an anti-cancer trace element. Zn acts as a repairing the DNA proteins and protects the DNA integrity and stability. Zn plays an important role of the biological progression in cancer tumors. Common reasons cause of deficiency of Zn that includes digestive disorder, chronic stress, medication uses, poor diet, and high toxic exposure. There are common reasons of Zn deficiency in Figure 2.

Treatment of Zn deficiency

To maintain Zn levels, there are no drugs available in the market. In the market, only supplements and nutraceuticals are used for maintain the Zn levels. Diet plays a very important role to maintain Zn levels such as meat, shellfish (oysters), whole grains, dairy products, eggs, and some fruits and vegetables. Daily 20 mg of Zn intake in our body is necessary to maintain the Zn levels. Zn supplements are beneficial in cancer through decreased angiogenesis and inflammatory cytokines induction by increasing apoptosis in cancer cells. These supplements act by inhibiting the NF-kB (nuclear factor-kB), an ancient protein transcription factor that plays critical roles in inflammation, immunity, cell proliferation, differentiation, and survival. Zn plays its role to preserving the proper function of the p53 gene.
Singh, et al.: Zn level in cancer patient

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(tumor suppressor p53) which is present or located in the cell nucleus of the body.[23]

Database of Zinc deficiency

We identify the data of Zinc deficiency through different online sources with the exclusion of duplicity of the database [Figure 3].

Records identified of Zn deficiency which are collected online databases in Science Direct, PubMed, and Google scholar = 25.

Duplicate records of the study which are removed before screening = 5.

Records identified of Zn deficiency which are collected online databases in Science Direct, PubMed, and Google scholar = 25.

Duplicate records of the study which are removed before screening = 5.

![Image](image_url)

**Figure 2:** Common reasons of Zn Deficiency of our daily routine which leads to cancer

Data of records which are usable for this review = 20.

Studies which are suitable for this review = 20.

Reports excluded after screening = 0.

Total research studies and data which are suitable for review = 20.

**COLLECTION OF DATA**

**Breast cancer**

The breast is composed of a variety of tissues, from extremely fatty tissue to extremely dense tissue. There is a network of lobes within this tissue. Each lobe is composed

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**Table 1:** Zn concentration levels in the breast cancer patients compared to controls

<table>
<thead>
<tr>
<th>S. No</th>
<th>First author</th>
<th>Year</th>
<th>Province</th>
<th>Case/ control (N)</th>
<th>Age (years)</th>
<th>Zn (mean±SD) Patients/normal</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ding et al.[45]</td>
<td>2015</td>
<td>China</td>
<td>88/88</td>
<td>45.73+9.84/45.8+8.52</td>
<td>110.96±23.63 μg/dL/113.14±24.17 μg/dL</td>
<td>DCP-AES</td>
</tr>
<tr>
<td>2</td>
<td>Li et al.</td>
<td>2015</td>
<td>China</td>
<td>155/155</td>
<td>-</td>
<td>227±84 μg/dL/308±42 μg/dL</td>
<td>AAS</td>
</tr>
<tr>
<td>3</td>
<td>Karki et al.[55]</td>
<td>2015</td>
<td>India</td>
<td>70/70</td>
<td>-</td>
<td>130.70±2.84 μg/dL/170.15±3.00 μg/dL</td>
<td>SP</td>
</tr>
<tr>
<td>4</td>
<td>Pavithra et al.[56]</td>
<td>2015</td>
<td>India</td>
<td>54/54</td>
<td>47.2±8.1/46.8+8.4</td>
<td>52.26±32.59 μg/dL/79.47±16.44 μg/dL</td>
<td>SP</td>
</tr>
<tr>
<td>5</td>
<td>Karki et al.[55]</td>
<td>2015</td>
<td>India (south)</td>
<td>70/70</td>
<td>-</td>
<td>130.70±2.84 μg/dL/158.36±3.72 μg/dL</td>
<td>SP</td>
</tr>
<tr>
<td>6</td>
<td>Choi et al.[61]</td>
<td>2018</td>
<td>Korea</td>
<td>137/150</td>
<td>-</td>
<td>Median 46 95.00±2.60 μg/dL/Median 48 110.00±20.94 μg/dL</td>
<td>ICP-MS</td>
</tr>
<tr>
<td>7</td>
<td>Choi et al.[61]</td>
<td>2018</td>
<td>Korea East Asia</td>
<td>63/79</td>
<td>-</td>
<td>Median 41 76.00±7.97/Median 47 75.00±13.34 μg/dL</td>
<td>ICP-MS</td>
</tr>
</tbody>
</table>
of lobules, which are tiny, tube-like structures that house milk glands. Milk is transported from the lobes to the nipple through tiny ducts that connect the glands, lobules, and lobes. The areola, the darker region that encircles the nipple, contains the nipple in the center. In addition, the breast is covered in lymphatic and blood arteries. By bringing oxygen and nutrition to the cells as well as eliminating waste and carbon dioxide, blood arteries nurture the cells. Healthy cells in the breast begin to alter and expand out of control to form a tumor, which is a mass or sheet of cells. Numerous studies have found that cancer cells in breast growth by deficiency of the zinc. Breast cancer also causes the deficiency of essential trace elements such as Mg, Mn, or Zn. Feng et al. looked into the connection between breast cancer and serum copper (Cu) and/or zinc (Zn) levels. The serum Cu to Zn ratio (Cu/Zn) may or may not be related to breast cancer risk. Therefore, using a meta-analysis, they assessed the serum Cu and Zn levels as well as the Cu/Zn in breast cancer. In the online databases of PubMed, CNKI, and Wanfang, studied reported serum Cu and/or Zn concentrations in breast cancer patients and controls from 1991 to 2020. Thirty six qualifying studies involving 5747 female cases were included in the study. Zn concentrations were statistically lower in breast cancer patients than in healthy controls (HC), this difference was not significant. The findings suggest that decreased Zn and elevated blood levels of Cu and Cu/Zn may be linked to an increased risk of breast cancer. Breast cancer and benign breast illnesses may be distinguished by these three factors that have the potential to distinguish between

Figure 3: Flow chart of Zn deficiency database. The data are found in online survey in PubMed, Springer, and Science direct
A walnut-sized gland, the prostate is situated below the bladder, in front of the urethra, and behind the base of the penis. The urethra is the tube-like passageway that conducts urine and sperm through the use of the penis. The key role of the prostate is to produce seminal fluid, the liquid in semen that nourishes, shields, and aids in the motility of sperm. A tumor is created when normal prostate cells undergo a transformation and grow more rapidly. Comparing prostate cancer to other cancers, it is a little different. This is due to the fact that many prostate cancers do not readily spread to other body areas. Some forms of prostate cancer grow very slowly and may go years or even decades without showing any signs or issues. Prostate cancer is frequently treatable for a very long time, even when it has spread to other body parts. Costello et al. have described the connection between prostate cancer with several trace elements and how they lead to malignant cells. Microbeam synchrotron radiation X-ray fluorescence emission technique was applied for quantitative analysis of the trace elements. Concentration of the Se, Mn, Fe, Cu, and Zn was correlated with different patients. Saleh et al. described the variations of the trace elements such as Zn, Cu, Mn, and Fe with several metabolic disorders, cellular growth disturbance, mutation, and tumor genesis. The study was performed in Saudi Arabia for the presence of trace element levels in prostate cancer patients. In this study, serum levels of selenium, copper, manganese, zinc, and iron were measured in 22 prostate male cancer patients and 30 healthy subjects. Serum levels of Zn, Se, and Mn were decreased in prostate cancer patients as compared to the HC groups as other side, the Fe and Cu levels were higher in prostate cancer patients as compared to the healthy groups. The study noticed between some trace elements disturbance and prostate cancer: Ozmen et al. have shown the pro or antioxidant qualities of trace metals as well as the anti-carcinogenic and antioxidant effects of Vitamins A, C, and E. In patients with prostate cancer, they measured the amounts of the anti-oxidant Vitamins A, C, and E, selenium, MDA, and trace metals Fe, Ni, Zn, Co, and Cu. The study was performed in 41 subjects who had 20 prostate cancer patients and 20 controls. Serum levels of trace elements were observed by AAS. Only serum levels of Se were determined by the fluorometric method or serum levels of vitamins and MDA were determined by the HPLC. Serum levels of Vitamins A and E were higher in prostate cancer patients as compared to controls. Serum levels of Vitamins A, C, and E, and Se and Zn were lower in prostate cancer patients when it has spread to other body parts.
patients significantly as compared to the controls.\cite{52} The data of prostate cancer studies are represented in Table 2.

### Brain tumor

An initial brain tumor is referred to as a primary brain tumor. There are two grades of primary brain tumors: Low grade and high grade. However, a low-grade tumor has the potential to progress to a high-grade tumor. A high-grade tumor has a higher chance of expanding quickly. A cancerous tumor that originated in the breast, lung, or colon before spreading to the brain is referred to as a secondary brain tumor. Metastatic cancer or brain metastasis is other names for secondary brain tumors.\cite{4} Leptomeningeal metastases or neoplastic meningitis are the terms used to describe cancer that has spread to the meninges and cerebrospinal fluid. People who have leukemia, lymphoma, melanoma, breast cancer, or lung cancer are more likely to develop this illness.\cite{4} Haşimoğlu et al. described the close connections between the majority of trace elements and the processes that lead to tumor formation. They studied quantitatively serum zinc levels in individuals with primary brain tumors and linked with serum zinc levels. In this study, serum zinc levels of 35 healthy volunteers serving as the control group and 33 patients with brain tumors were examined. Atomic absorption spectrophotometry was used to measure the amounts of metals. Patients with primary brain tumors showed lower serum zinc levels than the control group ($P = 0.05$). Results showed that tumor etiology, tumor typology, and prognosis may be influenced by the serum zinc levels of individuals with brain tumors.\cite{53} The data of brain tumor studies are represented in Tables 3 and 4.

### Bladder cancer

The cells (urothelial cells) that line the inside of the bladder are responsible for the development of bladder cancer.\cite{5} When bladder cells experience DNA changes (mutations), bladder cancer starts to spread. The DNA of a cell carries instructions that direct the cell’s actions. A tumor created by the aberrant cells can penetrate and obliterate healthy body tissue. The aberrant cells have the potential to separate over time and spread (metastasize) throughout the body.\cite{13} Golabek et al. reported the role of trace elements in bladder tumor genesis and cell carcinoma. They studied the relationship between cancer and trace elements. The study included the patient group and control group. The samples of serum were examined by the AAS. The study was correlated to the tumor stage and control group. Result of the study was found that the Cu concentration of the bladder cancer tissue, and the Zn concentration in the serum and bladder tissue of the patients were decreased as compared to the HC. The serum Cu/Zn ratio was significantly higher in the bladder cancer patients as compared to the controls.\cite{46} Mazdak et al. studied the role of trace elements in cancer. They investigated the influence of the occurrence and recurrence of bladder cancer through oxidative processes. The serum concentrations of iron (Fe), copper (Cu), and zinc (Zn) in bladder cancer patients were compared to those of healthy people. After adjusting for age, sex, and smoking behaviors, this cross-sectional study included 58 healthy volunteers and 51 bladder cancer patients. Samples were taken the next day after a 24-h fast. Flame atomic absorption spectroscopy was used to measure the amounts of Fe, Cu, and Zn, and the Student’s t-test was used to compare the results. Result of this study was found in significantly increase serum levels of Cu and Cu/Zn in bladder cancer patients than in the control group.

#### Table 2: Zn concentration levels in prostate cancer patients as compared to controls

<table>
<thead>
<tr>
<th>S. No</th>
<th>First author</th>
<th>Year</th>
<th>Province</th>
<th>Case/Control</th>
<th>Age (years)</th>
<th>Zn (mean±SD) patients/normal</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saleh et al.\cite{57}</td>
<td>2011</td>
<td>Saudi Arabia</td>
<td>40/52</td>
<td>68.2±5.2/66.4±6.5</td>
<td>0.51±0.09/0.82±0.19 (μg/mL)</td>
<td>ICP-MS</td>
</tr>
<tr>
<td>2</td>
<td>Ozmen et al.\cite{52}</td>
<td>2006</td>
<td>-</td>
<td>20/21</td>
<td>-</td>
<td>0.456±0.121/0.278±0.084 (μg/mL)</td>
<td>FAAS</td>
</tr>
</tbody>
</table>

#### Table 3: Zn levels in patient and control according to age

<table>
<thead>
<tr>
<th>S. No</th>
<th>First author</th>
<th>Case/control</th>
<th>Zn (mean)</th>
<th>P-value</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Haşimoğlu et al.\cite{53}</td>
<td>33/35</td>
<td>0.28±19.52/76.69±8.14</td>
<td>0.03</td>
<td>FAAS</td>
</tr>
</tbody>
</table>

#### Table 4: Zn concentration in serum in patients gender comparison

<table>
<thead>
<tr>
<th>S. No</th>
<th>Group</th>
<th>gender</th>
<th>Case/control</th>
<th>Zn (mean±SD)</th>
<th>P-value</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient</td>
<td>Male</td>
<td>17</td>
<td>65.78±17.86</td>
<td>0.18</td>
<td>FAAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>16</td>
<td>75.06±20.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control</td>
<td>Male</td>
<td>19</td>
<td>80±7.18</td>
<td>0.01</td>
<td>FAAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>16</td>
<td>72.75±7.62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In contrast, participants with bladder cancer had significantly lower serum zinc levels than those in the control group ($P < 0.05$). The study found a correlation between the level of trace elements and the development of bladder cancer, suggesting that rising serum Cu levels and falling serum levels of Zn and Fe may be significant factors in the development of bladder cancer. Data of the Bladder cancer due to Zn concentration are represented in Table 5.

### Endomaterial cancer

One type of cancer that starts in the uterus is endometrial cancer. The pear-shaped, hollow pelvic organ known as the uterus where fetal development takes place. Uterine cancer is another name for endometrial cancer. Uterine sarcoma is one of the other cancers that can develop in the uterus, however, it is considerably less prevalent than endometrial cancer. Mutation in the cells of DNA in endometrium causes the lining responsible for the growth of cancer cell. When a mutation occurs, healthy cells become aberrant and responsible for cancer. It has been reported that the development of cancer may be related with the deficiency of Zn and DNA damage. The following studies showed that the endometrial cancer causes the deficiency in the serum levels of zinc that can lead to other diseases. Atakul et al. evaluated serum copper (Cu) and zinc (Zn) levels in correlation to the metabolic profile and clinic pathologic characteristics of endometrial cancer patients. The population included 45 controls and 47 endometrial cancer-positive women. Each subject’s clinical and pathological characteristics, metabolic profile, and serum copper and zinc levels were examined. Cu and Zn levels were found lower in endometrial cancer patients (Cu mean 3.72 ± 2.15 mg/L, median 3.54 [0.41–9.16] mg/L, and Zn mean 1.83 ± 0.71 mg/L, median 1.77 [0.71–4.02] mg/L) than in controls (Cu mean 6.06 ± 1.79 mg/L, median 6.32 [2.95–9.05] mg/L, and Zn mean 2.48 ± 0.89 mg/L, median Cu/Zn ratio was also greater in controls compared to patients with endometrial cancer (0.85 1.96 vs. 2.57 0.73). Both Cu and Zn levels demonstrated an age-related positive connection when cancer patients were assessed independently. The results of the investigation revealed that as compared to controls, women with endometrial cancer exhibit changed serum Cu and Zn levels. Data of the endometrial cancer due to Zn deficiency are represented in Table 6.

### Ewing’s sarcoma

Ewing sarcoma is an uncommon kind of cancer that develops in the soft tissue surrounding the bones or in the bones themselves. Ewing sarcoma can develop in any bone; however, it typically starts in the pelvic and leg bones. Less frequently, it begins in the limbs, abdomen, chest, or other soft tissues. The gene EWSR1 mutation causes cancer. The mutation occurs due to DNA damage and DNA damage occurs due to the deficiency of Zn. Chanhoon et al. studied a very uncommon type of cancerous tumor called Ewing’s sarcoma. It develops in bones or the soft tissue next to the bones, like cartilage or nerves. It frequently affects people between the ages of 10 and 20 and had a high rate of cure. Assessment of hazardous (cadmium [Cd]) and important trace (zinc [Zn]) elements was performed in biological samples (scalp hair and blood) from 87 Ewing sarcoma patients, with ages ranging from 7 to 19 years. Age-matched, healthy (referent) volunteers’ biological samples ($n = 62$) were also examined for specific metals for comparative investigation. With the aid of a microwave oven, the biological sample matrices were oxidized using a 2:1 mixture of HNO3 (65%) and H2O2. Atomic absorption spectrometry was used to analyze the oxidized biological samples to determine their composition. Zn levels were found to be lower in the scalp hair and blood samples of several Ewing sarcoma patients, ranging from (45.9–141.2 g/g) and (0.65–3.12 mg/l) and (246–265 g/g) and (6.40–7.25 mg/l), respectively, than in the biological samples of referent persons. The Cd levels in various types of Ewing sarcoma patients’ scalp hair and blood samples were found to be higher, ranging from 2.70 to 5.60 g/g and 2.46 to 5.64 g/l, respectively, than the biological samples of controls (1.49–1.79 g/g and (1.52–1.90 g/l), respectively. As a result, the Ewing’s sarcoma patients have significantly had lower Zn levels than controls. Data of the Ewing sarcoma cancer due to Zn deficiency are represented in Table 7.

#### Table 5: Zn concentration in Bladder Cancer in different samples as compared to controls

<table>
<thead>
<tr>
<th>S. No</th>
<th>First Author</th>
<th>Case/control (N)</th>
<th>Sample</th>
<th>Zn (mean±SD) Patients/controls</th>
<th>Method</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mazdak et al.[46]</td>
<td>32/63</td>
<td>Serum</td>
<td>96.62±17.39 μg/L/121.93±16.67 μg/L</td>
<td>FAAS</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Golub et al.[47]</td>
<td>36/15</td>
<td>Bladder tissue</td>
<td>18.044 ng/g/16.611 ng/g</td>
<td>AAS</td>
<td>0.055</td>
</tr>
<tr>
<td>3</td>
<td>Golub et al.[47]</td>
<td>36/15</td>
<td>Serum</td>
<td>0.924 μg/L/1.201μg/L</td>
<td>AAS</td>
<td>0.03</td>
</tr>
</tbody>
</table>

#### Table 6: Zn concentration levels of endo-material cancer patients

<table>
<thead>
<tr>
<th>S. No.</th>
<th>First author</th>
<th>Age (years)</th>
<th>Case/Control</th>
<th>Sample</th>
<th>Zn (mean)</th>
<th>Method</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atakul et al.[46]</td>
<td>57.8±8.4/51.1±9.1</td>
<td>47/45</td>
<td>Serum</td>
<td>1.77 mg/ml/2.23 mg/ml</td>
<td>AAS</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 7: Zn concentration in Ewing Sarcoma patients as compared to controls

<table>
<thead>
<tr>
<th>S. No</th>
<th>First author</th>
<th>Province</th>
<th>Subtypes</th>
<th>Stages</th>
<th>Case/control</th>
<th>Sample</th>
<th>Zn (mean±SD) patients/control</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chanihoo et al[58]</td>
<td>Pakistan -2020</td>
<td>Extra-ossos Ewing sarcoma</td>
<td>T-1</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>137±9.05 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-2</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>125±7.82 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-3</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>95.8±8.05 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-4</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>74.9±6.92 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<tr>
<td></td>
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<td></td>
<td>Peripheral primitive neuroectodermal tumor</td>
<td>T-1</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>109±6.39 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>T-2</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>86.2±4.92 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>T-3</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>68.5±3.95 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>T-4</td>
<td>62/62</td>
<td>Scalp hair</td>
<td>48.3±4.92 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<td>Askin tumor</td>
<td>T-1</td>
<td>62/62</td>
<td>Blood</td>
<td>132±7.50 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<td></td>
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<td></td>
<td></td>
<td>T-2</td>
<td>62/62</td>
<td>Blood</td>
<td>119±6.28 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<td></td>
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<td></td>
<td></td>
<td>T-3</td>
<td>62/62</td>
<td>Blood</td>
<td>83.4±5.02 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
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<td>T-4</td>
<td>62/62</td>
<td>Blood</td>
<td>62.8±4.95 μg/g/254±17.5 μg/g</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td>2</td>
<td>Chanihoo et al[58]</td>
<td>Pakistan -2020</td>
<td>Extra-ossos Ewing sarcoma</td>
<td>T-1</td>
<td>62/62</td>
<td>Blood</td>
<td>2.95±0.32 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-2</td>
<td>62/62</td>
<td>Blood</td>
<td>2.95±0.32 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-3</td>
<td>62/62</td>
<td>Blood</td>
<td>2.20±0.29 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
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<td>T-4</td>
<td>62/62</td>
<td>Blood</td>
<td>1.69±0.42 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
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<td>Peripheral primitive neuroectodermal tumor</td>
<td>T-1</td>
<td>62/62</td>
<td>Blood</td>
<td>2.32±0.19 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
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<td>T-2</td>
<td>62/62</td>
<td>Blood</td>
<td>1.90±0.25 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
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<td></td>
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<td></td>
<td>T-3</td>
<td>62/62</td>
<td>Blood</td>
<td>1.27±0.31 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-4</td>
<td>62/62</td>
<td>Blood</td>
<td>0.72±0.12 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-1</td>
<td>62/62</td>
<td>Blood</td>
<td>1.45±0.36 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T-2</td>
<td>62/62</td>
<td>Blood</td>
<td>2.05±0.20 mg/l/6.86±0.95 mg/l</td>
<td>Microwave and digestion</td>
</tr>
</tbody>
</table>
Lung cancer

Report showed that there are vast data available for mortality due to lung cancer.[4] Smoking of tobacco, inhalation of CO, may be responsible for methylation of Zn which causes DNA damage and cancerous cell growth. Several literature surveys revealed that lung cancer may be associated with Zn deficiency. Wang et al. studied the records which are associated with the Zn levels in plasma and lung cancer. This study resulted that Zn serum levels in lung cancer patients were significantly lower than that in controls.[49] Jin et al. studied the trace element’s effect on genetic polymorphisms on lung cancer. The study was based on a hospital case–control. Face-to-face interviews were used to complete the epidemiology questionnaires, RFLP-PCR was used to screen for gene polymorphisms, an atomic absorption spectrophotometer was used to detect serum trace metal levels, and logistic regression models were used to evaluate the data. The risk variables for NSCLC were a high serum copper level (>1500 ng/mL) or a high serum copper/zinc ratio (>1) (5OR = 3.10, 11.03, respectively), while the risk ratios for NSCLC for greater serum Zn (>1200 ng/mL), Se (>50 ng/mL), or Cr (>600 ng/mL) were all significantly less than 0.20 (all P = 0.01). The chance of CYP1A1 variations carriers with higher serum Zn, Se, or Cr levels is 0.18, but it was 3.38, 12.59, or 0.18 for those with higher serum Cu or Cu/Zn ratio levels. Results indicated the fascinating pathophysiology of lung cancer, suggesting that CYP1A1 or GSTM1 polymorphisms may dramatically affect the relationships between levels of blood trace metals (Cu, Zn, Se, or Cr) and NSCLC.[49] Zn concentration in lung cancer patients is represented in Table 8.

Ovarian cancer

A cell growth that develops in the ovaries is called ovarian cancer. The cells can penetrate and obliterate healthy biological tissue and reproduce swiftly. There are two ovaries in the female reproductive system, one on either side of the uterus. The ovaries, which are each roughly the size of an almond, produce progesterone and estrogen in addition to eggs.[50] No study found the causes of ovarian cancer but due to ovarian cancer, the zinc deficiency occurs in the body. Various studies proof that the ovarian cancer can cause deficiency of the essential trace element zinc. Yaman et al. studied that the Zn and Cu concentrations were circulating in ovarian tumor. Data were collected by 20 case/control studies including 699 patients with ovarian tumors, 567 patients with benign ovarian lesions, and 1194 controls were selected. Genetic tools of 21 single nucleotide polymorphisms (SNPs) linked with circulating zinc and 25 SNPs associated with circulating copper were developed using a two-sample MR technique. Their ovarian cancer genetic correlations were taken from a genome-wide association analysis of 25,509 cases and 40,941 controls. Examined ovarian cancer patients had lower Zn concentration than the controls and high concentration of Cu in ovarian cancer patients than the controls. The study was found to be although there were higher levels of circulating copper and lower levels of zinc in ovarian cancer patients, only the zinc concentration showed a suggested causal relationship, indicating that more research on zinc therapies for ovarian cancer could have a clinical benefit.[21]

Other findings

This review first demonstrates the link between cancer and serum Zn where significant difference between the patients and the controls was analyzed. Zn is also an essential trace elements for human nutrition that is an integral part of the enzyme system and deficiency of the Zn causes sexual immaturity and stunting the growth. The Zn is essential trace element which regulates the normal cell functions and deficiency causes different disease states. Due to its involvement in the activation of several enzymes, the trace metal zinc has significant biological impacts on DNA and RNA synthesis and cell division.[25] Białkowska et al. reported in case–control research intended to determine the serum zinc levels in Polish males may serve as a meaningful indicator of prostate cancer risk. Białkowska et al. examined the potential association between prostate cancer risk and polymorphisms in various Zn-dependent genes (MT2A, MMP-1, MMP-2, MMP-7, and MMP-13). Białkowska et al. studied prostate cancer patients’ serum where Zn levels were found substantially greater than those of controls (P = 0.01). Furthermore, he demonstrated that a higher incidence of prostate cancer is linked to higher Zn levels. Prostate cancer risk was also raised by one of the examined SNPs, rs11568818 in MMP-7 (P = 0.03).[22] Liu et al. studied the interaction between GRIN2B genetic polymorphism and urinary zinc levels in relation to the risk of dyslexia and found out the polymorphism in GRIN2B,

Table 8: Zn concentration in Lung cancer patients as compared to controls

<table>
<thead>
<tr>
<th>S. No</th>
<th>First author</th>
<th>Province</th>
<th>Patients/control</th>
<th>Age (years)</th>
<th>Sample</th>
<th>Zn concentration (mean±SD)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cobanoglu et al,[41]</td>
<td>Turkey -2010</td>
<td>30/20</td>
<td>54±8.29</td>
<td>Serum</td>
<td>0.539±0.225 μg/dL/ 2.051±0.298 μg/dL</td>
<td>AAS</td>
</tr>
<tr>
<td>2</td>
<td>Jin et al,[49]</td>
<td>China -2011</td>
<td>154/154</td>
<td>34.9±21.3</td>
<td>Serum</td>
<td>0.673±0.47 μg/mL/ 1.27±0.442 μg/mL</td>
<td>AAS</td>
</tr>
<tr>
<td>3</td>
<td>He et al,[49]</td>
<td>China -2011</td>
<td>104/122</td>
<td>38–69</td>
<td>Serum</td>
<td>9.08±1.44 μmol/L/ 16.44±1.69 μmol/L</td>
<td>AAS</td>
</tr>
<tr>
<td>4</td>
<td>Cheng et al,[15]</td>
<td>China -2011</td>
<td>197/93</td>
<td>-</td>
<td>Serum</td>
<td>0.9±0.3 μmol/L/ 1.12±0.56 μmol/L</td>
<td>AAS</td>
</tr>
</tbody>
</table>
rs1805502, altered the relationship between zinc levels and the likelihood of developing dyslexia. Children with the rs1805502 mutation had much lower risk of dyslexia when their zinc levels were higher.[23] Rentschler et al. have found that intrinsic variants of the Zn-transporter genes SLC39A14 (rs4872479 and rs870215) and SLC39A8 (rs10015145 and rs233804) associated with the kinetics of Cd. Verified in other groups, the correlations between SLC39A14 and SLC39A8 and Cd may be significant in explaining variance in Cd toxicity in bone and kidney.[27] Zinc plays crucial roles in cellular metabolism and tumor cells have high levels of malignant metabolic activity; this could be one explanation for why they consume more zinc than normal cells.[23] Shetty et al. (2015) found that patients with oral pre-cancer and oral malignancy had considerably lower salivary Zn levels.[62]

CONCLUSIONS

Our review showed the polymorphism of MT2A, MMP-1, MMP-2, MMP-7, and MMP-13, MPO G-463A to G and p53 Y220C increase the cancer risk. Consequently, the monitoring of different genotypes polymorphism could be identified the highest risk of cancer. Deficiency of the Zn in serum causes damage DNA integrity and progression of carcinoma cells. It has been found the Zn serum levels insufficient in cancer patients as compared to healthy subjects. The literature survey revealed the connection of Zn level with Zn polymorphism and cancer. By controlling the Zn level how we can be controlling the development cancer still be a topic for future research.

ACKNOWLEDGMENTS

The authors have no acknowledgments to declare.

AUTHOR CONTRIBUTION

The literature search involved all of the authors. Alamjot Singh: Oversaw the group, data extraction, manuscript drafting, and categorization of the manuscripts, and writing review. Komal Dagar: Gathering data, analyzing it, and creating tables. Vivek Asati: Authoring the text, collecting and analyzing the data, supervision, and editing review.

AUTHOR DECLARATION

The authors declare that there are no conflicts of interest regarding to the publication of this paper.

SOURCES OF SUPPORT

There are no funding sources for this article.

REFERENCES


