Int. J. Econ. Environ. Geol. Vol. 11 (3) 57-64, 2020
Journal home page: www.econ-environ-geol.org

Open Access
ISSN: 2223-957X

Factors Affecting the Rate of Breast Cancer; Role of Heavy Metals

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Received: *06 May, 2020* ***Accepted:****15 June, 2020*

Abstract: Breast cancer is caused by uncontrolled growth of breast cells. It is more common in women as compared to that in men. The breast cancer may be interlinked with the drinking of alcohol, smoking, sex, hormonal therapy, obesity, family history and age. Various epidemiologic studies suggest the role of metals e.g., nickel (Ni), zinc (Zn), arsenic (As), selenium (Se)and cadmium (Cd)as potential risk factors in breast cancer. Humans are exposed to these metals by means of drinking water, food and air. The oxidative theory suspects that the complexes formed from these metals in vivo, near the location of DNA, catalyze the redox reactions which results in oxidation of DNA. The metals like arsenic (As), chromium (Cr), aluminum (Al), cadmium (Cd) and chromium (Cr)which exist in trace amount are considered as carcinogens for organisms by IARC (International Agency for Research on Cancer). The carcinogenicity of these metals mainly depends upon their chemical structure and oxidation states.

Keywords: Breast cancer; heavy metals; carcinogenicity.

Introduction

Breast cancer is a common women disease that appears in the breast tissues. Its initial symptoms include the protuberances in the breast, shape change of breast, fatty skin, fluid releasing from nipples and red scaly spots of skin (Apantaku, 2000). The in-situ breast cancer is mainly classified into lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) (Giuliano et al., 2017).In USA, breast cancer is the cause of about 48,000 deaths every year, with the report of approximate180,000 new cases annually (Apantaku, 2000). Breast cancer is the most common primary malignancy and the second most common cause of cancer-related mortality among women in the United States (Afifi et al., 2020). Breast cancer is the leading cause of death and the most commonly diagnosed cancer among females. In 2018, about 2.1 million new cases were reported over the world. The highest incidence rate of breast cancer in women has been reported in Belgium, followed by Luxembourg and then Netherlands(Bray et al., 2018). Breast cancer is mostly linked to age; about 7% cases of breast cancer have been reported in women before the age of 40 yearsat global level (Anders et al., 2009). The breast cancer developing risks are: lack of physical exercise, female sex, drinking of alcohol, hormone replacement therapy, obesity, family history and age(Mustafa et al., 2016).

Materials and Methods

The current studies were carried out to review the literature relevant to the symptoms (Palesh et al., 2010) and risk factors (Angahar, 2017; Lakshmi et al., 2012) of breast cancer. The role of physical activity (Friedenreich, 2010), age (Bucholc et al., 2001), family history (Bakhshi et al., 2018; Lakshmi et al., 2012), race (Knaus, 2012), diet (Bandera et al., 2015)(Naseer et al., 2018; Naseer et al., 2019; Rehman et al., 2018; Tahir et al., 2018; Vainio et al., 2002), genetic factor (Antoniou and Easton, 2006; Martin and Weber, 2000), alcohol (Dumitrescu and Shields, 2005; Essex et al., 2014), smoking (Jee et al., 1999; Reynolds et al., 2004), obesity (Byrne et al., 1991; Schapira et al., 1990), **estrogen Level** (Byrne et al., 2013; Yarden et al., 2002), radiations (Land et al., 2003; Mattsson et al., 1993; Preston et al., 2002) and heavy metals (cadmium, chromium, arsenic, lead, nickel, aluminum and zinc) in breast cancer are also reviewed (Alatise andSchrauzer, 2010; Aquino et al., 2012; Cantor et al., 1995; Choe et al., 2003; Chunhabundit, 2016; Cui et al., 2007; Darbre, 2016; Farasani and Darbre, 2015; Florea and Büssel berg, 2011; Franklin and Costello, 2009; Gallagher et al., 2010; Health and Services, 1999; Johnson et al., 2003; Kilic et al., 2004; Liu et al., 2010; Mandriota et al., 2016; McElroy et al., 2006; Romaniuk et al., 2015; Ruiz-Ramos et al., 2009; Saleh et al., 2011; Schrauzer, 2008; Siewit et al., 2010; Sukumar et al., 1983; Sun et al., 2007; Ullah et al., 2019; Ying et al., 2009; Zhitkovich, 2011).

Results and Discussion

Factors Affecting the Rate of Breast Cancer

The breast cancer is comprised of approximately 22.9% of all cancers (excluding non-melanoma skin cancers) and second most common cause of cancer deaths in women worldwide. The mortality rate due to breast cancer is higher in developing countries although the

developed nations have higher incidence rates (Angahar, 2017; Francies et al., 2020). Breast cancer involves either preventable or non-preventable risk factors. The non-preventable (beyond control) risk factors include medical history, family history and age. The preventable risk factors include the alcohol consumption, physical activity and weight (Lakshmi et al., 2012).

Physical Activity and Family History

Approximately 25% cancer risk is reduced in physically active women as compared to the least active women. Physical activity lowers the risk of breast cancer via multiple interrelated biologic pathways which may involve chronic inflammation, adipokines, insulin resistance, sex hormones and adiposity (Friedenreich, 2010).

Breast cancer occurrences and consequently death proportion rates usually increase with age. About 88% of breast cancers were reported in the women having age over 40 years. The risks of breast cancer development are maximum in women whose menstruation starts in early life or whose menopause period is late (Bucholc et al., 2001).

About 5% of breast cancer cases are due to inherited family problems. If a female possesses one first degree-female relative (daughter, mother, and sister) identified with breast cancer disease, then her breast cancer risk chance is doubled. If two such first relatives have been diagnosed, then the same risk of breast cancer is increased to five times. If breast cancer has been diagnosed in one's father or brother, the risk is much higher(Lakshmi et al., 2012).

Breast cancer in women is a very lethal factor that may cause the risks of physical, cerebral and social health. The treatment by chemotherapy which is an effective treatment method, disturbs the quality of life of patients and damages their brain, social and psychic well-being (Bakhshi et al., 2018).

Race Diet and Genetic Factor

Race is an intrinsic factor increasing the incidence of breast cancer. The breast cancer occurrence rate is higher in non-Hispanic white women than African and American females for many age groups (Knaus, 2012). Diet is considered as a risk factor of many different types of cancers including breast cancer. It is very important to control the sources of fats and red meat of animals because they contain the hormones and other growth factors (Bandera et al., 2015). To use of high fats increases breast cancer incidences. But fruits and vegetables reduce breast cancer incidences. The intake of vitamin D, calcium and phytoestrogens are also effective against breast cancer risks (Vainio et al., 2002). The use of some vegetables and fruits has been found effective against cancer (Naseer et al., 2018; Naseer et al., 2019; Rehman et al., 2018). Some aflatoxins have also been known to cause cancer (Tahir et al., 2018).

The genetic and environmental factors may also contribute to the development of breast cancer. Two breast cancer susceptible genes (BRCA1 and BRCA2) have been recognized. About 5% to 10% cases of breast cancer cases are reported due to changes in these genes. The variation in the number of gene classes is considered as the main reason of breast cancer disease (Martin and Weber, 2000).The other main risk factor for breast cancer is family history, representing that genetic factors are important elements in the development of breast cancer. The susceptibility to breast cancer is intermediated through mutations in many genes (Antoniou and Easton, 2006).

Alcohol, Smoking and Obesity

In most epidemiologic studies, it was found that drinking alcohol is associated with breast cancer. In such cases breast cancer is characterized by various mechanisms such as through mutagenesis by acetaldehyde, perturbation of estrogen metabolism and by inducing oxidative damage or by disturbing folate and carbon metabolism pathways containing single carbon. In human breast tissue, alcohol-metabolizing enzymes are present. From the metabolism of ethanol, reactive oxygen species are produced which may be involved in breast cancer. Genetic polymorphism is very important in enhancing a women breast cancer (Dumitrescu andShields, 2005).

It is clearly evident that all alcoholic beverages are the cause of different types of cancers. Alcohol may increase the risk of breast cancer, throat, mouth, and larynx, liver and bowel cancer in men. The risk of breast cancer is increased with alcohol drinking, the main mechanism through which breast cancer rate is increased by rising estrogen levels. Alcohol can affect the blood level of the estrogen hormone, which further increases the breast risk. Alcohol damages the DNA cells and in this way, breast cancer risk also increases. Women who take 3 alcoholic drinks in a week have a 15% high risk of breast cancer. The risk of breast cancer is increased in women up to 10% for each extra alcoholic drink taken on regular basis(Essex et al., 2014).

It has been known that cigarette is a cause of cancer (Madigan et al., 1995). There is more chance of breast cancer developing in cigarette-smokers, verifying the function of cigarette in breast cancer (Reynolds et al., 2004). More than 80 different cancer generating substances are present in tobacco smoke. When smoke passes through the lungs, it enters into the bloodstream and is drawn throughout the body (Jee et al., 1999).

Obesity is also closely related to breast cancer. The incidences of breast cancer risk are increased by 18%

for every addition of 5 kg/m^2 in body weight. The risk may also be increased due to high level of circulating estrogen (Byrne et al., 1991). It has been considered that the extra production of estrogen by obese females increases more effect on mammary epithelial cells. The non-protein part of estrogen available on the breast is responsible for the development of breast cancer. As the women attain weight in the upper part of the body including shoulders, nape of the neck, abdomen and in lower part of body such as on buttock and thigh then metabolic and hormonal irregularities are noted in obesity. The decreased level of sex hormone binding proteins and increased levels of non-protein bound-estrogen in females having obesity can increase the risk of breast cancer (Schapira et al., 1990).

Estrogen Level, BRCA1 and Radiation

The age at menopause, reproductive history, breastfeeding, menarche and utilization of exogenous estrogen can increase the risk of breast cancer. In various cases, non-genetic breast cancer happens in menopausal women who keep more expression of the estrogen receptor. Estrogen has a minimum of two roles in breast cancer growth: (i) metabolism of estrogen may change or produce DNA- breaking free radicals and (ii) estrogen through its hormonal activity can proliferate cells in cancerous and precancerous lesions. Additionally, estrogen-receptor is an essential part of breast carcinoma, other mechanisms also take part in the generation of breast cancer. Mutation of BRCA1 increases the incidences of breast cancer to 51% but about 85% by the period of 50 and 70 years. It also generates the ovarian cancer risk to 23% and 63% by the age of 50 and 70 years (Yarden et al., 2002)

Metalloestrogens are small metalloids or metals ions acting as endocrine disruptors by stimulating the action of estrogens. Two classes of metal loestrogens have been identified: the first-class includes antimony, oxyanions, arsenite, selenite, vanadate and nitrite; second class is comprised of bivalent-cations like cadmium, copper, cobalt, nickel, calcium, mercury, tin, chromium and lead. In the lack of estradiol, the estrogen receptor is activated by Metalloestrogens; hence these metals can increase the risk of breast cancer development when there is direct exposure to them. Over the last 50-60 years, a significant increase of Metalloestrogens in the environment has occurred. Many metalloestrogens have a long biological half-life. The half-life of cadmium is between 10 to 30 years and it may retain in body and breast mammary tissues. Numerous studies explain that the exposure to cadmium (Cd) is the risk of breast cancer(Byrne et al., 2013).

It is recognized that exposure of the breast to ionizing radiation elevates the relative risk of breast cancer, particularly in younger women (Mattsson et al., 1993). Women who are less than 20 years old are at high risk of radiation than those at older ages. The women who are more than 50 years old are not so much at risk of breast cancer (Preston et al., 2002). About 70,165 breast cancer cases were reported in women due to mixed gamma and neutrons radiation levels associated with Japanese atomic bomb (Land et al., 2003).

Role of Heavy Metals in Breast Cancer

Many epidemiologic studies suggest metals as potential risk factors of breast cancer. These metals include nickel (Ni), zinc (Zn), cadmium (Cd), selenium (Se) and arsenic (As), which naturally exist in the environment. These metals get exposure to the human beings by means of drinking water, food and air (Florea and Büsselberg, 2006; Iqbal et al., 2019; Silvera and Rohan, 2007). Further studies confirmed that age-related breast cancer deaths in various countries are directly related with the dietary intake of Zn, Cd, Cr, Sn and As while they are inversely associated with dietary ingestion of Se due to anti-carcinogen properties of selenium (Schrauzer, 2009). Many studies have reported that breast cancer patients have irregular levels of Cd, Zn Se, and Cu (Saleh et al., 2011).

Cadmium is a metallic element which exists in the environment due to weathering of cadmium bearing rocks and volcanic activity. It may also be released from various industrial products such as plastic stabilizers and coating processes, batteries, phosphate fertilizers and also from fuel vehicles combustion and tire outfit(Health and Services, 1999). The in vivo and in vitro studies have shown that Cd can behave like a metalloestron (Cantor et al., 1995). Moreover, Cd also creates other estrogen-type effects, such as enhancing the uterine weight, modification of the uterine lining, increase of the epithelial density in mammary glands and also enhances the cell proliferation and aneuploidy (Johnson et al., 2003).

It has been recognized by the US Environmental Protection Agency that main source of cadmium is food and tobacco burn (Siewit et al., 2010). Cadmium is a universal carcinogenic contaminant and possesses numerous biological effects leading to breast cancer (Gallagher et al., 2010 and (McElroy et al., 2006). There is significant risk of breast cancer by increased concentration of urinary cadmium (Siewit et al., 2010). Cadmium affects many cellular processes such as differentiation, proliferation and apoptosis (Siewit et al., 2010). Cadmium also acts as an estrogen disruptor, that motivates the action of estrogen-receptor-α (ER-α) and increases the growth of mammary and uterine tissues (Schrauzer, 2008). Cadmium modifies gene expression and disturbs the transcription activity pattern altering intracellular signals (Sun et al., 2007).

The DNA is also effected by Cr(VI), because it forms Cr-DNA adduct as a results of mutation and chromosomal breakage (Zhitkovich, 2011). Acute chromium toxicity will increase the incidence of different types of human cancers. It is observed that reduction of Cr(VI) to its lower oxidation states and its

free radical reactions are very carcinogenic (Kilic et al., 2004). Multiple tissues such as intestine, esophagus, testes, stomach, prostrates and lungs are affected by chromium exposure (Chunhabundit, 2016).

Arsenic (As) exposure is one of the strongest environmental carcinogen and is related to increased threats of different kinds of cancer (Ullah et al., 2019; Ying et al., 2009). The presence of As in drinking water increases the incidence of human cancer in lung, kidney, liver, bladder and skin (Ruiz-Ramos et al., 2009). Little concentration of As_2O_3 also creates carcinogenic effects after its term exposure (Liu et al., 2010). Even though, arsenic trioxide is also part of traditional Chinese medicine (Liu et al., 2010). In clinical practice, it is used to cure hematologic malignancies (Florea and Büsselberg, 2011).

Breast cancer is associated with industrialization that contaminates the air, soil, and water by lead (Pb) and many more metals that cause risk factors for humans. Low concentration of Lead (0.5 ppm) in drinking water can increase the growth of mammary murine tumors in female C3Hmice infected by virus. It also promotes the tumor growth rate. High amount of lead is observed in blood and head hair samples of newly investigated breast cancer patients. The level of Pb in hair samples were directly linked to the sizes of tumors (Alatise andSchrauzer, 2010).

Like Cd, nickel can also bind to ERα, generate cell proliferation and induce aneuploidy. However, many studies of cellular, animal and molecular level are needed to explain the exact mechanism of breast cancer pathogenesis through chronic nickel exposure. More structural research studies are needed to confirm the function of nickel as a metalloestrogens (Aquino et al., 2012).

Aluminum exposure is closely related to cause breast cancer. Mice were exposed to $AlCl_3$resulting in malignant growth in mammary gland epithelial cells and the same effects were seen on the samples of human breast tissues (Darbre, 2016). Another research has also shown that exposure of Al to human breast cells has a tendency to produce uncontrolled growth (Mandriota et al., 2016). In an experimental study, it was observed that aluminum acts as a metal estrogen that behaves as an agonist for the estrogen receptor and shows a well-known breast cancer risk (Mandriota et al., 2016). To minimize the exposure of aluminum to humans, it is necessary to use reverse osmosis filtration. This technique is very efficient to reduce the level of aluminum from copper mining waste (Farasani and Darbre, 2015).

Zinc is a component of various enzymes taking part in the chemical processes within the living cells including lactic, carbonic anhydrase, glutamic alkaline phosphatase and alcoholic dehydrogenase. This metal element also takes part in the activation of many enzymes. It is also liable for uncontrolled growth leading to cancer. Zinc accumulation also causes breast cancer. Zinc is essential for cell proliferation and it accumulates in mammary tumors and promotes tumor growth (Sukumar et al., 1983). Zinc, in minute quantity is very important for the normal functioning of cells. It acts as a cofactor for the structure and function of widespread range of cellular proteins such as enzymes, transcription factors and structural proteins. It regulates the immune system, gene expression, cell proliferation, growth and also controls apoptosis in malignant cells (Franklin and Costello, 2009).

Prevention of Cancer

Epidemiological studies demonstrate that cancer can generally be prevented by more consumption of edible fruits and green leafy vegetables, avoiding from smoking and the effective control of infections. Other factors include the avoidance from intense sun exposure, increasing the physical activity and controlling the drinking of alcohol and to some extent red meat. An extensive reduction in the cases of breast cancer can possibly be achieved by modifications in the sex hormones level. Mechanistic studies of carcinogenesis reveal a significant role of endogenous oxidative damage to DNA which can be balanced by proper repair and defense mechanism. The cell division rate is most important factor as it governs the probability of altering DNA lesions to mutations and effects on growth, inflammation, cytotoxicity and hormones (Ames et al., 1995).

Conclusion

Breast cancer may be interlinked with the drinking of alcohol, smoking, sex, hormonal therapy, obesity, family history and age. Heavy metals and their metal compounds exhibit immense toxic effects on humans due to their carcinogenic properties. On one side, heavy metals cause pathogenesis of breast cancer, while on the other side they also prompt apoptosis and cytotoxicity in breast cancer cells. Therefore, awareness regarding carcinogenic mechanism of toxic metals is important. Industries releasing untreated wastewater into rivers, canals and streams containing different carcinogens heavy metals (Pb, Cd, Cr, Hg and As etc.) should install waste water treatment plants. Different ailments such as breast cancer, sexual, cerebral and neural diseases are likely to be caused by these toxic heavy metals. Educational programs are needed to promote the awareness of risks related to the exposure of toxic heavy metals in most affected areas.

References

Afifi, A. M., Saad, A. M., Al-Husseini, M. J., Elmehrath, A. O., Northfelt, D. W. Sonbol, M. B. (2020). Causes of death after breast cancer diagnosis: A US population-based analysis. *Cancer,* **126** (7), 1559-1567.

Alatise, O. I. Schrauzer, G. N. (2010). Lead exposure: a contributing cause of the current breast cancer epidemic in Nigerian women. *Biological Trace Element Research*, **136** (2), 127-139.

Ames, B. N., Gold, L. S. Willett, W. C. (1995). The causes and prevention of cancer. *Proceedings of the National Academy of Sciences*, **92** (12), 5258-5265.

Anders, C. K., Johnson, R., Litton, J., Phillips, M. Bleyer, A. (2009). *Breast cancer before age 40 years.* Paper presented at the Seminars in oncology.

Angahar, L. (2017). An overview of breast cancer epidemiology, risk factors, pathophysiology, and cancer risks reduction. *MOJ Biol Med*, **1**(4), 92-96.

Antoniou, A. C. Easton, D. (2006). Models of genetic susceptibility to breast cancer. *Oncogene*, **25** (43), 5898.

Apantaku, L. M. (2000). Breast cancer diagnosis and screening. *American Family Physician*, **62** (3), 596-602.

Aquino, N. B., Sevigny, M. B., Sabangan, J. Louie, M. C. (2012). The role of cadmium and nickel in estrogen receptor signaling and breast cancer: metalloestrogens or not? *Journal of Environm ental Science and Health, Part C*, **30** (3), 189-224.

Ataollahi, M., Sharifi, J., Paknahad, M. Paknahad, A. (2015). Breast cancer and associated factors: a review. *Journal of Medicine and Life*, **8** (4), 6-11.

Bakhshi, R., Bahreini, M., Mirzaei, K. Kiani, J. (2018). The Effect of Group Counseling on the Quality of Life in Patients with Major Thalassemia Referred to the Thalassemia Treatment Center in Bushehr. *Pajouhan Scientific Journal*, **16** (3), 11-19.

Bandera, E. V., Chandran, U., Hong, C.-C., Troester, M. A., Bethea, T. N., Adams-Campbell, L. L., Haiman, C. A., Park, S.-Y., Olshan, A. F. Ambrosone, C. B. (2015). Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast Cancer Research and Treatment*, **150** (3), 655-666.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A. Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, **68** (6), 394-424.

Bucholc, M., Łepecka-Klusek, C., Pilewska, A. Kanadys, K. (2001). Women's opinion of the risk of breast cancer. *Ginekologia Polska*, **72** (12A), 1460-1464.

Byrne, C., Brinton, L. A., Haile, R. W. Schairer, C. (1991). Heterogeneity of the effect of family history on breast cancer risk. *Epidemiology*, 276-284.

Byrne, C., Divekar, S. D., Storchan, G. B., Parodi, D. A. Martin, M. B. (2013). Metals and breast cancer. *Journal of Mammary Gland Biology and Neoplasia*, **18** (1), 63-73.

Cantor, K. P., Stewart, P. A., Brinton, L. A. Dosemeci, M. (1995). Occupational exposures and female breast cancer mortality in the United States. *Journal of Occupational and Environmental Medicine*, **37** (3), 336-348.

Choe, S.-Y., Kim, S.-J., Kim, H.-G., Lee, J. H., Choi, Y., Lee, H. Kim, Y. (2003). Evaluation of estrogenicity of major heavy metals. *Science of the Total Environment*, **312** (1-3), 15-21.

Chunhabundit, R. (2016). Cadmium exposure and potential health risk from foods in contaminated area, Thailand. *Toxicological research*, **32** (1), 65.

Cui, Y., Vogt, S., Olson, N., Glass, A. G. Rohan, T. E. (2007). Levels of zinc, selenium, calcium, and iron in benign breast tissue and risk of subsequent breast cancer. *Cancer Epidemiology and Prevention Biomarkers*, **16** (8), 1682-1685.

Darbre, P. D. (2016). Aluminium and the human breast. *Morphologie*, **100** (329), 65-74.

Dumitrescu, R. G. Shields, P. G. (2005). The etiology of alcohol-induced breast cancer. *Alcohol*, **35** (3), 213-225.

Essex, H. N., White, I. R., Khadjesari, Z., Linke, S., McCambridge, J., Murray, E., Parrott, S. Godfrey, C. (2014). Quality of life among hazardous and harmful drinkers: EQ-5D over a 1-year follow-up period. *Quality of Life Research*, **23** (2), 733-743.

Farasani, A. Darbre, P. (2015). Effects of aluminium chloride and aluminium chlorohydrate on DNA repair in MCF10A immortalised non-transformed human breast epithelial cells. *Journal of Inorganic Biochemistry*, **152**, 186-189.

Florea, A.-M. Büsselberg, D. (2006). Occurrence, use and potential toxic effects of metals and metal compounds. *BioMetals*, **19** (4), 419-427.

Florea, A.-M. Büsselberg, D. (2011). Cisplatin as an anti-tumor drug: cellular mechanisms of activity,

drug resistance and induced side effects. *Cancers*, **3** (1), 1351-1371.

Francies, F. Z., Hull, R., Khanyile, R. Dlamini, Z. (2020). Breast cancer in low-middle income countries: abnormality in splicing and lack of targeted treatment options. *American Journal of Cancer Research*, **10** (5), 1568-1591.

Franklin, R. B. Costello, L. C. (2009). The important role of the apoptotic effects of zinc in the development of cancers. *Journal of Cellular Biochemistry*, **106** (5), 750-757.

Friedenreich, C. M. (2010). Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms *Clinical Cancer Prevention* (pp. 125-139): Springer.

Gallagher, C. M., Chen, J. J. Kovach, J. S. (2010). Environmental cadmium and breast cancer risk. *Aging*, **2** (11), 804-814.

Giuliano, A. E., Connolly, J. L., Edge, S. B., Mittendorf, E. A., Rugo, H. S., Solin, L. J., Weaver, D. L., Winchester, D. J. Hortobagyi, G. N. (2017). Breast cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA: a cancer journal for clinicians*, **67** (4), 290-303.

Health, U. D. o. Services, H. (1999). Agency for Toxic Substances and Disease Registry: Toxicological profile for Lead (update) PB/99/166704. *Atlanta: US Department of Health and Human Services*.

Iqbal, M., Muneer, M., Hussain, S., Parveen, B., Javed, M., Rehman, H., Waqas, M. Abid, M. A. (2019). Using Combined UV and H_2O_2 Treatments to Reduce Tannery Wastewater Pollution Load. *Polish Journal of Environmental Studies*, **28** (5), 1-7.

Jee, S. H., Ohrr, H. Kim, I. S. (1999). Effects of husbands' smoking on the incidence of lung cancer in Korean women. *International Journal of Epidemiology*, **28** (5), 824-828.

Johnson, M. D., Kenney, N., Stoica, A., Hilakivi-Clarke, L., Singh, B., Chepko, G., Clarke, R., Sholler, P. F., Lirio, A. A. Foss, C. (2003). Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. *Nature Medicine*, **9** (8), 1081-1084.

Kilic, E., Saraymen, R., Demiroglu, A. Ok, E. (2004). Chromium and manganese levels in the scalp hair of normals and patients with breast cancer. *Biological Trace Element Research*, **102**(1-3), 19-25.

Knaus, P. (2012). Invasion des Raufussbussards Buteo lagopus im Winter 2010/11 in der Schweiz. *Ornithol. Beob*, **109**, 229-248.

Lakshmi, R., Athira, R., Mary, J. T. Vijayalakshmi, S. (2012). Breast cancer risk factors: preventable and non-preventable. *International Research Journal Of Pharmacy*, **3** (10), 48-52.

Land, C. E., Tokunaga, M., Koyama, K., Soda, M., Preston, D. L., Nishimori, I. Tokuoka, S. (2003). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. *Radiation Research*, **160** (6), 707-717.

Liu, Y., Hock, J. M., Sullivan, C., Fang, G., Cox, A. J., Davis, K. T., Davis, B. H. Li, X. (2010). Activation of the p38 MAPK/Akt/ERK1/2 signal pathways is required for the protein stabilization of CDC6 and cyclin D1 in low-dose arsenite-induced cell proliferation. *Journal of Cellular Biochemistry*, **111** (6), 1546-1555.

Madigan, M. P., Ziegler, R. G., Benichou, J., Byrne, C. Hoover, R. N. (1995). Proportion of breast cancer cases in the United States explained by well-established risk factors. *JNCI: Journal of the National Cancer Institute*, **87** (22), 1681-1685.

Mandriota, S. J., Tenan, M., Ferrari, P. Sappino, A. P. (2016). Aluminium chloride promotes tumorigenesis and metastasis in normal murine mammary gland epithelial cells. *International Journal of Cancer*, **139** (12), 2781-2790.

Martin, A.-M. Weber, B. L. (2000). Genetic and hormonal risk factors in breast cancer. *Journal of the National Cancer Institute*, **92** (14), 1126-1135.

Mattsson, A., Rudén, B.-I., Hall, P., Wilking, N. Rutqvist, L. E. (1993). Radiation-induced breast cancer: long-term follow-up of radiation therapy for benign breast disease. *JNCI: Journal of the National Cancer Institute*, **85**(20), 1679-1685.

McElroy, J. A., Shafer, M. M., Trentham-Dietz, A., Hampton, J. M. Newcomb, P. A. (2006). Cadmium exposure and breast cancer risk. *Journal of the National Cancer Institute*, **98** (12), 869-873.

Mustafa, M., Nornazirah, A., Salih, F., Illzam, E., Suleiman, M. Sharifa, A. (2016). Breast Cancer: Detection Markers, Prognosis, and Prevention. *IOSR Journal of Dental and Medical Sciences*. 15(8). 73-80.

Naseer, S., Hussain, S., Naeem, N., Pervaiz, M. Rahman, M. (2018). The phytochemistry and medicinal value of Psidium guajava (guava). *Clinical Phytoscience*, **4** (1), 1-8.

Naseer, S., Hussain, S. Zahid, Z. (2019). Nutritional and Antioxidant Potential of Common Vegetables in Pakistan. *RADS Journal of Biological Research & Applied Sciences,* **10** (1), 36-40.

Palesh, O. G., Roscoe, J. A., Mustian, K. M., Roth, T., Savard, J., Ancoli-Israel, S., Heckler, C., Purnell, J. Q., Janelsins, M. C. Morrow, G. R. (2010). Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center–Community Clinical Oncology Program. *Journal of Clinical Oncology,* **28** (2), 292-298.

Preston, D. L., Mattsson, A., Holmberg, E., Shore, R., Hildreth, N. G. Boice Jr, J. D. (2002). Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiation Research,* **158** (2), 220-235.

Rehman, A., Hussain, S., Javed, M., Ali, Z., Rehman, H., Shahzady, T. G. Zahra, A. (2018). Chemical composition and remedial perspectives of *Hippophae rhamnoides linn*. *Postepy Biologii Komorki,* **45** (3), 199-209.

Reynolds, P., Hurley, S., Goldberg, D. E., Anton-Culver, H., Bernstein, L., Deapen, D., Horn-Ross, P. L., Peel, D., Pinder, R. Ross, R. K. (2004). Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *Journal of the National Cancer Institute,* **96** (1), 29-37.

Romaniuk, A., Lyndin, M., Moskalenko, R., Kuzenko, Y., Gladchenko, O. Lyndina, Y. (2015). Pathogenetic mechanisms of heavy metal effect on proapoptotic and proliferative potential of breast cancer. *Interventional Medicine and Applied Science,* **7**(2), 63-68.

Ruiz-Ramos, R., Lopez-Carrillo, L., Rios-Perez, A. D., De Vizcaya-Ruíz, A. Cebrian, M. E. (2009). Sodium arsenite induces ROS generation, DNA oxidative damage, HO-1 and c-Myc proteins, NF-κB activation and cell proliferation in human breast cancer MCF-7 cells. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis,* **674** (1-2), 109-115.

Saleh, F., Behbehani, A., Asfar, S., Khan, I. Ibrahim, G. (2011). Abnormal blood levels of trace elements and metals, DNA damage, and breast cancer in the state of Kuwait. *Biological Trace Element Research,* **141** (1-3), 96-109.

Schapira, D. V., Kumar, N. B., Lyman, G. H. Cox, C. E. (1990). Abdominal obesity and breast cancer risk. *Annals of Internal Medicine,* **112**(3), 182-186.

Schrauzer, G. (2008). Interactive effects of selenium and cadmium on mammary tumor development and growth in MMTV-infected female mice. A model study on the roles of cadmium and selenium in human breast cancer. *Biological Trace Element Research,* **123** (1-3), 27-34.

Schrauzer, G. (2009). Selenium and selenium-antagonistic elements in nutritional cancer prevention. *Critical reviews in biotechnology,* **29** (1), 10-17.

Siewit, C. L., Gengler, B., Vegas, E., Puckett, R. Louie, M. C. (2010). Cadmium promotes breast cancer cell proliferation by potentiating the interaction between ERα and c-Jun. *Molecular Endocrinology,* **24** (5), 981-992.

Silvera, S. A. N. Rohan, T. E. (2007). Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes & Control,* **18** (1), 7-27.

Sukumar, S., Notario, V., Martin-Zanca, D. Barbacid, M. (1983). Induction of mammary carcinomas in rats by nitroso-methylurea involves malignant activation of H-ras-1 locus by single point mutations. *Nature,* **306** (5944), 658.

Sun, X., Fontaine, J.-M., Bartl, I., Behnam, B., Welsh, M. J. Benndorf, R. (2007). Induction of Hsp22 (HspB8) by estrogen and the metalloestrogen cadmium in estrogen receptor–positive breast cancer cells. *Cell Stress & Chaperones,* **12** (4), 307-319.

Tahir, N. I., Hussain, S., Javed, M., Rehman, H., Shahzady, T. G., Parveen, B. Ali, K. G. (2018). Nature of aflatoxins: Their extraction, analysis, and control. *Journal of Food Safety,* **38** (6), e12561.

Ullah, H., Hussain, S. Ahmad, A. (2019). Study on Arsenic Poisoning by Worldwide Drinking Water, its Effects and Prevention. *International Journal of Economic and Environmental Geology,* **10** (2), 72-78.

Vainio, H., Kaaks, R. Bianchini, F. (2002). Weight control and physical activity in cancer prevention: international evaluation of the evidence. *European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP),* **11**, S94-100.

Yarden, R. I., Pardo-Reoyo, S., Sgagias, M., Cowan, K. H. Brody, L. C. (2002). BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. *Nature Genetics,* **30** (3), 285-289.

Ying, S., Myers, K., Bottomley, S., Helleday, T. Bryant, H. E. (2009). BRCA2-dependent homologous

recombination is required for repair of Arsenite-induced replication lesions in mammalian cells. *Nucleic Acids Research*, **37** (15), 5105-5113.

Zhitkovich, A. (2011). Chromium in drinking water: sources, metabolism, and cancer risks. *Chemical Research in Toxicology*, **24** (10), 1617-1629.