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‘‘BPA (Bisphenol A) Exposure As An Environmental Risk Factor – A Cross Sectional Study on Breast Cancer Among the Bangladeshi Female Population.’’

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Abstract The project work was a preventive message to Bangladeshi women that BPA was a major environmental risk factor in causing breast cancer. Therefore, it was clear from our findings that young, job-holding, and married urban women were more likely to suffer from breast cancer. Compared to the average values of BPA (4.0 ng/ml) from control adult females, i.e., noncancerous patients, the average BPA in the serum of cancer patients was 4 to 7 times higher (17.0 to 34.0 ng/ml) under different age groups. Complications of breast cancer were statistically significant with the concentration of BPA in the patient's blood serum. Higher levels of BPA increased the severity of tenderness in the affected breast and physical weakness. Therefore, they would have been concerned about using plastic materials to reduce the risk of breast cancer. All over the world, the emergence of these diseases mobilised science in new ways to think in different dimensions to solve the problem.

Keywords: *Breast cancer, Bisphenol A, Plastic materials, Environmental factors, Nipple destruction, Chemo-resistance, cytokine*

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1. Introduction

Breast cancer is a world-wide leading cancer of women. In addition, there are large geographical differences in the incidence rates of breast cancer. Particularly, Asian populations show a lower incidence of breast cancer than Western countries. [1,2] Citing the IARC report, Head of the Cancer Epidemiology Division at the National Cancer Research Institute, Dr. Md. Habibullah Talukder Ruskin, said some 12,764 women are diagnosed with breast cancer in Bangladesh every year, and 6,844 of them succumb to the disease. According to Global Cancer Statistics, every year, 2,088,849 women suffer from breast cancer worldwide, reports UNB. The widely spread microplastic component and endocrine disruptor BPA is a hazardous material recognised for a long time. Bisphenol A (BPA) is a pollutant, classified as an endocrine-disrupting chemical compound with oestrogenic properties. Their exposure in the early stages of neonatal life leads to an increase in the size and weight of breast tumours and induces cellular changes in the tumoral immune microenvironment, where cytokines play a key role. Breast cancer is the leading cause of death in productive women between 20 and 50 years old and the most prevalent cancer in women worldwide. In 2020, 2.3 million women were newly diagnosed with this disease, and 685,000 deaths were

registered globally. [3] Breast cancer is also an economic burden because it is the leading cause of lost disability-adjusted life-years (DALYs) worldwide among any other type of cancer. Breast cancer is a heterogeneous disease where tumours can localise in different areas in the breast, like the lobules, ducts, and connective tissue. [4] Specifically, lobular carcinoma is classified as the most common and invasive subtype. Early detection is crucial in achieving long-term survival. In clinical practice, the diagnosis of mixed invasive ductal and lobular carcinoma (IDC-L) is usually followed by uncertainty across the prognosis and response to systemic treatments. [5] Unfortunately, breast cancer cells can migrate to distant sites along the body, especially the lung, liver, bone, and brain, in a process known as metastasis, which is the leading cause of death; less than 20% of breast cancer patients with distant metastasis survive after five years. [6,7] Tumour progression and metastasis are highly influenced by the tumour microenvironment (TME). On this site, communication among tumour cells, tumour stromal cells, and immune cells are essential components. [8] In the beginning, tumour cells and stromal cells secrete soluble factors such as cytokines, chemokines, and growth factors, modifying cell-cell or cell-ECM (extracellular matrix) interactions and disrupting the normal epithelial rganization. [9] This intercellular communication requires a complex network between stromal and immune cells. [10] This organisation favours the proliferation, migration, and differentiation of tumour cells, suppresses the immune cells, and degrades ECM, which sooner or later will lead to a more invasive tumour that can break the connective tissue and astasize. [11] Breast cancer aetiology is associated not only with levels of specific hormones or their receptors, but importantly with more general environmental factors. Human industrial activity has provoked a colossal release of environmental chemicals tintothe atmosphere for decades, many of them with an unknown toxic effect on human health. Additionally, several daily use products, like plastic food and beverage containers, sunscreen, cosmetics, and cleaning products, aloamongnmany othersontain toxic chemicals. [12,13] Moreover, several epidemiological studies have provided strong evidence that associates toxicants with an increased risk of developing cancer in later stages of life. The possibility to develop a more aggressive type of breast cancer coincides with landmark events. For example, changes during prenatal, pubertal, pregnancy, and menopausal periods, where breast tissue suffers several changes in structure and function, and is more susceptible to specific environmental chemicals. [14] The endocrine-disrupting chemicals (EDC) are very important environmental chemical compounds because they can affect the hormone balance and the endocrine system. [15] The mechanism of action of EDC relies on binding to hormone receptors such as oestrogen (ER) or androgen (AR) receptors, where they interrupt the functions of endogenous steroid hormones. Bisphenol A (2,2-Bis propane), known as BPA, is a synthetic chemical widely used in daily used products, from polycarbonate plastics to epoxy resins and dental sealants, and it is contained in food packaging, baby bottles, medical devices, and personal care products, among others. [16] BPA has been classified as an EDC with ooestrogenic character since it can bind to oestrogen receptors, triggering signalling pathways, even when its affinity is lower than the endogenous ligand, 17 β-estradiol. [17] BPA is a compound that can be easily released from the plastics due to incomplete polymerisation or hydrolysis of the polymers that confirm the material; its detachment can be induced by high temperatures, acidic conditions, or enzymatic processes. [18] The main source of exposure to BPA in humans and animals is through food and beverages contained in materials where detachment from the matrix has occurred, and it can be ingested, inhaled, and introduced by dermal exposure, dental sealants, or injections. [19] Despite the Food and Drug Administration (FDA) and the European Food Safety Agency (EFSA), which calculated that the tolerable daily intake of BPA is 50 μg/kg/day, it has been estimated that exposure to BPA per food package was higher in children from 1–2 months of age. [20] Exposure to BPA at tolerable concentrations or below is related to unfavourable effects on the health of humans and rodents. [21] The nature and magnitude of BPA's adverse effects depend on the dose, the course of exposure, and the developmental stage in which exposure occurs. Exposure to BPA can occur as early as during gestation, according to reports of BPA presence in amniotic fluid, foetal serum, and breast milk. [22,23] In this regard, there is an existing concern about the effects that BPA could exert on a developing organism, including the immune system. [24] Several studies indicate that oestrogen and progesterone stimulate the expression of the vascular endothelial growth factor (VEGF) in breast cancer and umors. [24] VEGF is a key angiogenic factor that stimulates endothelial cells to proliferate and migrate, allowing tumours to progress easily. [25] In breast cancer, VEGF expression is increased depending on the microenvironment compared with normal mammary glands. [26,27] Previously, we have shown that after 25 days of injection, mice exposed to BPA presented no major endocrine alterations, developed larger tumours, a higher proportion of regulatory T lymphocytes, together with decreased expression of TNF-α, IFN-γ, and the M2 macrophage marker Fizz-1. Furthermore, the cytometric analysis revealed differences in the expression of oestrogen receptor (ER-α) in T lymphocytes, macrophages, and NK cells, both associated with exposure to BPA and tumour development. [28] Therefore, we decided to assess whether exposure to BPA in a critical development period affects not only tumour size but also lung metastasis and cytokine expression pattern in umors. Our results demonstrated that BPA administered during the neonatal period evoked an increase in lung metastasis and intratumoral cytokine pro-inflammatory patterns during adult life. Considering the increasing prevalence of hormone-related cancer associated with exposure to BPA, we are interested in studying the relationship between BPA exposure and the risk of breast cancer in Bangladeshi women subjects. To the best of our knowledge, there is no such study performed on Bangladeshi women patients.

2. Materials and Methods

For the cross-sectional analytical study, 55 symptomatic

patients were referred by a gynaecologist to diagnose breast cancer in **LabAid Cancer Hospital Ltd., Dhaka**. Five female adults with no complications were used as a healthy control subject. The study period was September 2022 to February 2023. Patients were selected first purposively who meet the inclusion criteria selected for the study. Details of the patient's relevant history, chief and present complaints, and physical examination findings were recorded. Patients were evaluated carefully, and the particulars of the patients, including history and clinical examination, were taken in the prescribed form noted in the data sheet. Patients who were diagnosed with ovarian cancer and who resided to attend the targeted hospitals during the study period were included in this study. Each patient was verified to make sure that it was counted once in this study regardless of the number of visits to avoid duplication of enrolment as patients may potentially visit more than one hospital. Questionnaire forms, including distribution of demographic and health characteristics, lifestyle factors, current residence, and eating habits, were filled out through an in-person interview.

A random blood sample of 5 ml was collected from each subject. Samples were transported to the Dept. of Biochemistry and Molecular Biology, Priemasia University, where serum was prepared and preserved at -20°C for future analysis. Serum levels of BPA were measured by enzyme-linked immunosorbent assay (ELISA), and another biochemical parameter was measured by an automated analyser.

Human Bisphenol A (BPA) ELISA Kit, Cat No. MBS269957. This product is suitable for the in vitro quantitative detection of human serum, plasma, or cell culture supernatant and organisations in the natural and recombinant AAV concentration. This kit employs the "Double Antibody Sandwich" technique. Samples and biotinylated antibodies are added into ELISA plate wells and washed out with PBS or TBS after their respective additions to the wells. Then avidin-peroxidase conjugates are added to the wells after. TMB substrate is used for colouration after the enzyme conjugate has already been thoroughly washed out of the wells by PBS or TBS. TMB reacts to form a blue product from the peroxidase activity and finally turns yellow after addition of the stop solution (Colour Reagent C). The colour intensity and quantity of target analyte in the sample are positively correlated.

Steps	Summary of the operating procedures
1	Prepared reagents, standards, and samples
2	Add the prepared samples and standard, and then incubate at 37 °C for 90 minutes.
3	Wash 2 times, add biotinylated antibody solution, and incubate at 37°C for 60 minutes.
4	Wash 3 times, add the enzyme solution, and incubate at 37°C for 30 minutes.
5	Wash 5 times, add the substrate reagent solution, and incubate at 37°C for up to 30 minutes.
6	Added the colour reagent C solution
7	Within 10 minutes, measure the sample OD by using the microplate reader machine.
8	Finally, calculate the sample results based on the standard sample OD.

Detection range; 200 ng/mL-3.12 ng/mL
Sensitivity; up to 0.6 ng/mL.
Place of study: This study was conducted at the-Department of Biochemistry and Molecular Biology, Primeasia University, Banani, Dhaka.

3. Statistical Analysis

Values were expressed as the mean with SD or as the median and interquartile range in case of a skewed distribution. For comparison between the groups, students "t" tests (unpaired) were done, and correlation between variables was measured by correlation tests. Further statistical analysis of the results was done by using the software package for social science (SPSS).

4. Results and Discussions

In this study, a total of 55 breast cancer patients who were living in the various parts of Bangladesh were selected as our study population. According to the clinical findings and decision of the physician, all of the study populations were diagnosed with breast cancer. Patient's sociodemographic history and other information were collected through a direct interview with them following a well-structured questionnaire. All of the summarised findings have been illustrated in the following sections. Table 1 shows that the maximum age of 17% of patients was between 30 and 40 years. About 74% of patients were adults in age below 50 years old, whereas only 12% were over 60 years old. In addition, compared to the rural women, two-thirds of urban women (67%) were suffering from breast cancer. Among the total study patients, almost 95% were married, and over 50% were job holders. The privilege rate among students was significantly low, at 3.6%, and that of housemakers was 42%. Therefore, it was clear from Table 1 that young job holders and married urban women were suffering more from breast cancer. The collected medical history from the patients in Table 2 reports that preexisting health problems like diabetes, hypertension, and heart disease had significant influence on the breast cancer. Family history had no alarming effects on the rate of breast cancer. In addition, 76% and 58% of patients with positive results of female hormones, i.e., oestrogen and progesterone, respectively, were suffering from breast cancer. Females in the postmenopausal stage are under less risk of developing breast cancer. Among the many physical complications of patients, tenderness in affected breast was the dominant problem (44%), whereas nipple discharge and pain were only 12.5 and 7%, respectively. Table 3 exhibits the calculated concentration of BPA in serum samples of breast cancer patients following a sandwich ELISA technique. Compared to the average values of BPA (4.0 ng/ml) from control adult females, i.e., noncancerous patients, the average BPA in the serum of cancer patients was 4~7 times higher (17.0~34.0 ng/ml), as shown in Table 3 under different age groups. A maximum of 26 patients have a BPA concentration above 30 ng/ml, whereas only 7 patients showed an average BPA below 20 ng/ml. Therefore, this result reflects that BPA is one of the environmental risk factors for the breast cancer patient. As shown in Table 4, complications of breast cancer are statistically significant (in terms of p value 0.000) with the concentration of BPA in patient blood serum. Higher levels of BPA increase the severity of tenderness in affected breasts and physical weakness. Similar trends

were found in the case of possible treatments for breast cancer patients, as shown in Table 5. With increasing the concentration of BPA, the treatment for the patients was also complicated. The preexisting health condition (comorbidity) significantly influences the overall condition of breast cancer patients. Compared to the patient with no comorbidity problem, patients with preexisting health problems show a higher amount of BPA concentration in their blood serum. Especially heart disease with high blood pressure and diabetes had a positive correlation with the level of BPA of patients (Table 6).

Table 1. Summary of sociodemographic characters of the patients (N=55)

		Count	Column N %
Age group	15-30 years	9	16.4%
	31-40 years	17	31.0%
	41-50 years	14	25.5%
	51-60 years	8	14.5%
	60+ years	7	12.7%
Residencial area	Urban	37	67.0%
	Rural	18	33.0%
Marital Status	Unmarried	3	4.5%
	Married	52	94.5%
Occupation	Student	2	3.6%
	Job holder	30	54.5%
	Housemaker	23	41.8%

Table 2. Summary of medical history of the patients (N=55)

		Count	Column N %
Co-morbidity	Diabetes mellitus	11	20.0%
	Hypertension	18	33.3%
	Ischemic heart diseases	8	14.5%
	Bronchial asthma	3	5.5%
	No problem	8	14.5
Progesterone receptor	Positive	32	58.2%
	Negative	6	41.8%
Menstrual history	Regular	36	65.8%
	Post menopausal stage	19	35.2%
Family history	Positive	6	11.0%
	Negative	49	89.0%
Chiefcomplications	Weakness	20	36.3%
	Tenderness in affected breast	24	43.6%
	Nipple discharge	7	12.5%
	Nipple pain	4	7.3%
Estrogen receptor	Positive	42	76.3%
	Negative	13	23.7%

Table 3. Correlation between BPA concentration and age of patients (N=55)

BPA vs Ages Crosstabulation							
			Age of the Patients (Years)				
			15-30	31-40	41-50	51-60	60+
BPA result (ng/ml)	**17.00**	Count (%)	1 (12%)	2 (12%)	1 (7%)	2 (22%)	1 (14%)
	24.00	Count (%)	1 (12%)	2 (12%)	2 (14%)	1 (11%)	1 (14%)
	28.00	Count (%)	2(25%)	5 (29%)	4(28%)	2 (22%)	2 (14%)
	32.00	Count (%)	0 (0%)	2 (12%)	2 (14%)	1 (11%)	0 (0%)
	33.00	Count (%)	0 (0%)	3 (18%)	3 (21%)	0 (0%)	1 (14%)
	34.00	Count (%)	4 (50%)	3 (18%)	2 (14%)	3 (33%)	2 (29%)
Total (N=55)		Count (%)	8 (100%)	17(100%)	14(100%)	9(60%)	7(70%)
		P-Value	0.000*				

Table 4.Correlation between BPA concentration and major complications of breast cancer patients

BPA Conc. Vs major complications						
			Weakness	Tenderness in affected breast	Nipple Discharge	Nipple Pain
BPA result (ng/ml)	17.00	Count (%)	2(10%)	2 (8%)	1(14%)	0(0%)
	24.00	Count (%)	4(20%)	5(21%)	0(0%)	1(25%)
	28.00	Count (%)	4(20%)	7(29%)	2(29%)	0(00%)
	31.00	Count (%)	2(10%)	3 (13%)	1(14%)	0(0%)
	32.00	Count (%)	1(5%)	2 (8%)	1(14%)	1(25%)
	33.00	Count (%)	2(10%)	0 (0%)	2(29%)	0(10%)
	34.00	Count (%)	5 (25%)	5(21%)	0(0%)	2(50%)
Total (N=55)		Count (%)	20 (100%)	24 (100%)	7 (100%)	4(100%)
		P-Value	0.000*			

Table 5. Correlation between BPA concentration and treatment of breast cancer patients (N=55)

BPA vs Management Protocol Crosstabulation							
			Medication with Advice	Surgery, Chemotherapy and Medication	Surgery and Medication with advice	Surgery, Chemotherapy, Radiotherapy and Medication	
BPA result (ng/ml)	17.00	Count (%)	2 (11.1%)	1 (7.1%)	0 (0%)	1 (20%)	1 (7.1%)
	24.00	Count (%)	3 (17%)	2 (14.3%)	1 (25%)	1 (20%)	2 (14.3%)
	26.00	Count (%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	1 (7.1%)
	28.00	Count (%)	5 (28%)	3 (21.9%)	1 (25%)	1 (20%)	3 (21.9%)
	30.00	Count (%)	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	1 (7.1%)
	31.00	Count (%)	2 (11%)	1 (7.1%)	0 (0%)	0 (0%)	1 (7.1%)
	32.00	Count (%)	2 (11%)	1 (7.1%)	0 (0%)	0 (0%)	1 (7.1%)
	33.00	Count (%)	1 (6%)	2 (14.3%)	0 (0%)	0 (0%)	2 (14.3%)
	34.00	Count (%)	3 (17%)	2 (14.3%)	2 (50%)	2 (20%)	2 (14.3%)
Total (N=55)		Count (%)	18 (100%)	14 (100%)	4 (100%)	5 (100%)	14 (100%)
		P-Value	0.000*				

Table 6. Relations of comorbidity and BPA concentration of patients

	BPA vs Comorbidity Crosstabulation						
			No problem	Bronchial Asthma	Diabetes Mellitus	Hypertension	Ischemic Heart diseases
BPA result (ng/ml)	17.00	Count (%)	3 (37.5%)	0 (0%)	1 (8.0%)	3 (13%)	0 (0%)
	24.00	Count (%)	2 (25%)	0(0%)	1 (8%)	2 (18.2%)	1 (12.1%)
	26.00	Count (%)	1 (13%)	0 (0%)	1 (8%)	4 (17%)	0 (0%)
	28.00	Count (%)	2 (25%)	1 (33%)	2 (16%)	2 (8%)	1 (13%)
	31.00	Count (%)	0 (0%)	0 (0%)	1 (8%)	4 (17%)	2 (25%)
	32.00	Count (%)	0 (0%)	0 (0%)	2 (16.2%)	3 (13%)	0 (0%)
	33.00	Count (%)	0 (0%)	1 (33%)	3 (24%)	2 (8%)	2 (25%)
	34.00	Count (%)	0 (0%)	1 (33%)	2 (16%)	4 (17%)	2 (25%)
Total (N=55)		Count (%)	8 (100%)	3(100%)	11 (100%)	18 (100%)	8(100%)
		P-Value	0.000*				

5. Conclusions

We found that BPA was significantly elevated in breast cancer patients 4` times higher compared to normal females with no breast cancer in consideration of Bangladesh environmental and lifestyle perspectives. Our findings were able to give a preventive message to Bangladeshi women's that BPA is a major environmental risk factor for causing breast cancer. So, we should be concerned about using BPA-containing plastic materials to reduce the risk of breast cancer. As BPA is also responsible for chemoresistant breast cancer drugs like doxorubicin, cyclophosphamide, paclitaxel or docetaxel, and trastuzumab at very small doses, our study is one of the good messages to our oncologist society to explain some case studies in which those patients are chemoresistant. In most of the cases, women are feeling hesitant to discuss their problem with their family members as well as what to expect. Therefore, it becomes late to treat their breast cancer problem at the early stage. It is highly recommended to work for social awareness, especially among the female population in our country, about the treatment and lethal suffering of breast cancer. Government and health policymakers should ensure easily obtainable treatment facilities and expert physicians, especially female physicians, on breast cancer. Health revelations about the marinating proper female hygiene, a healthy lifestyle, and breastfeeding for mothers are highly recommended to reduce this problem.

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Ethical permission: This study was approved by the ethics committee, Primeasia University, Dhaka, Bangladesh. Reference no.: PAU/IEAC/22/13. The results of this research were used only for scientific purposes and not for any other aims, and strict confidentiality was strictly maintained.

Conflict of interest: None declared.

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