Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 05, pp.50426-50431, May, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

ASSOCIATION OF URINARY BISPHENOL A CONCENTRATION WITH BREAST CANCER

[1]Sadaf Alipour, [2]Maryam Zare Jeddi, [3]Majorie B.M. van Duursen, [4]Shahrzad Jafari Adli, [5]Mohammad Ali Mansournia, [4]Hadith Rastad, [6]Reza Ahmadkhaniha, [5]Mehrdad Karimi, [1]Azin Saberi, [2,7]Masud Yunesian, [8]Delaram Feizizadeh, [4]Ladan Hosseini and *[2]Noushin Rastkari

[1]Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran
[3]Endocrine Toxicology Research Group, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands
[4]Research Development Center, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[5]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[6] Department of Human Ecology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[7]Department of Environmental Health Engineering, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[8]Department of Food Science and Technology, Sciences and Research Branch, Islamic Azad University, Tehran, Iran

ARTICLE INFO

Article History:
Received 21st February, 2017
Received in revised form
08th March, 2017
Accepted 11th April, 2017
Published online 23rd May, 2017

Key words:
Ambient air quality,
SPM, RSPM, SO_2, NO_X,
Epidermal cell, Stomata.

ABSTRACT

The estrogen-mimic bisphenol A (BPA) is a synthetic phenolic compound which people are exposed to frequently via different exposure routes. In this study association between urinary BPA concentration and breast cancer was investigated. This case-control study included patients with malignant breast mass, benign breast mass and women with normal breast. The effect of urinary concentration of BPA on breast cancer was tested using multinomial logistic regression models. Overall, results have shown a strong positive association between urinary concentration of BPA and both benign and malignant breast masses (OR= 2.14 [CI: 1.04 to 4.42] and OR= 2.27 [CI: 1.09 to 4.72] respectively), although other included covariates were only significantly associated with increased risk of benign breast mass. BPA exposure was associated with breast cancer but, given inconsistencies with previous findings for other study populations, results should be interpreted with caution. Future prospective studies are needed to confirm or disprove this finding.

Citation: Sadaf Alipour, Maryam Zare Jeddi, Majorie B.M. van Duursen, Shahrzad Jafari Adli, Mohammad Ali Mansournia *et al,* 2017. "Association of urinary bisphenol a concentration with breast cancer", *International Journal of Current Research*, 9, (05), 50426-50431.

INTRODUCTION

Bisphenol A (BPA), as an endocrine-disrupting chemical (EDC), is widely used chemical in the manufacture of polycarbonate plastics and epoxy resin and has become ubiquitous environmental contaminant (NTP, 2008).

Corresponding author: Noushin Rastkari
Center for Air Pollution Research (CAPR), Institute for Environmental Research (IER), Tehran University of Medical Sciences, Tehran, Iran

BPA-based materials have a broad range of applications and are found in many commonly used products such as water bottles, epoxy resin linings in food and beverage cans, medical equipment and dental sealants (Nahar *et al*., 2012). Because of the widespread use of BPA, the potential for human exposure is high(Calafat *et al*., 2005). Due to its endocrine disruptor properties, the potential metabolic effects of BPA are also of interest. BPA acts as endocrine-disrupting compounds (EDCs), which capable of causing dysfunction in hormonally regulated body systems The main action attributed to BPA is an estrogen-

like activity. The estrogenic property of EDCs has seen many associations between ongoing exposures and the development of endocrine-related diseases, including breast cancer (Knower *et al*., 2014). BPA acts as an estrogen mimetic, and can interact with the ligand binding domain of ERα (Sengupta *et al*., 2013), increasing cellular proliferation, potentially via reducing the rate of apoptosis (Mlynarcikova *et al*., 2013), and inducing a gene expression profile that clusters with breast cancer poor prognosis (Katchy *et al*., 2013). BPA has a lower binding affinity, interacting with the α and β estrogen receptors (ER) at 10^4 times lower potency compared to estradiol (Welshons *et al*., 2003). However, BPA has been reported to stimulate rapid cellular responses at concentrations much lower than anticipated, potentially due to high binding affinities for G-protein coupled receptor 30 (GPR30) and estrogen related receptor gamma (ERRg) as shown in human studies (Thomas and Dong, 2006, Matsushima *et al*., 2007). Both estrogenic and nonestrogenic effects from exposures to BPA in vivo and in vitro have been linked to changes in gene expression and cell proliferation in a variety of cells, tissues, and organs including the mammary glands and prostate (Richter *et al*., 2007, Wetherill *et al*., 2007). Studies suggest that environmental exposure to BPA is associated with behavioral and reproductive abnormalities, as well as chronic diseases (Nahar *et al*., 2012).

EDCs have been suspected as potential risks of increasing cancers in reproductive systems and mammary gland, such as prostate cancer, breast cancer, etc. For example, chronic exposure to specific organochlorine pesticides and polychlorinated biphenyls in the general population is suggested to have increased the risk of prostate cancer (Ritchie *et al*., 2003). In the case of breast cancer, organochlorine pesticides and bisphenol A (BPA) have been suspected of increasing risks (Yang *et al*., 2009). Breast cancer is the most frequent cancer and the most common cause of death from cancer among women worldwide. Most recently, a case-control study of women in USA found that serum BPA was positively associated with mammographic breast density after adjusting for age, body mass index, and other potentially confounding factors (Sprague *et al*., 2013). These findings raise important questions regarding the potential impacts of BPA on breast tissue and because animal studies found that BPA contributes to development of breast cancer, but human data are scarce we hypothesized that urinary levels of BPA may be positively associated with inducing neoplastic processes in the breast.

MATERIALS AND METHODS

Chemicals and standards preparation: Bisphenol A (99%), BPA-d16 and N,O-bis-(trimethylsilyl)trifluoroacetamide (BSTFA) were obtained from Aldrich (St. Louis, MO, USA). Sep-Pak C18 cartridge (Vac 200 mg, 3 mL) was purchased from Waters Co. (Milford, MA, USA). BPA-d16 was converted to BPA-d14 by dissolving in aqueous sodium hydroxide and re-precipitation by acidifying with dilute sulfuric acid as described by Goodson *et al*. (2002). This BPA-d14 was used as internal standard. Artificial urine was obtained from Ward's Natural Science (Rochester, NY, USA). All other chemicals and solvents were of analytical reagent grade or better. Stock solutions of BPA and internal standard were prepared in acetonitrile (100 µg/ mL) and stored at 4 ◦C in teflon-capped amber glass bottles until use. The working standards were prepared in 1:9 acetonitrile: water by serial dilutions of the stock solutions and stored at 4 ◦C until use.

Stock solution was prepared for standard substance at 100 µg/ml in acetonitrile. For the preparation of the calibration curves and development of the assay, different amounts of the phenol standard were added to 50 ml of artificial urine (blank matrix) to make the final concentration range from 0.2 to 20 ng/ml . The method was optimized by using blank urine sample spiked with the BPA at 10 ng/ml concentration as quality control sample (QC).

Subjects and urine specimens

Extraction procedure

50 ml of a urine sample was placed in a conical flask equipped with a ground stopper, and 100 µl of β-glucuronidase solution and 100 µl of BPA-d14 as internal standard were added to the flask. The mixture was subjected to an enzymolysis at 37 °C for 90 minutes. To the resultant mixture, 1 ml of 7.5 M phosphoric acid was added in order to adjust pH to 3 or lower. The mixture thus obtained was loaded onto a C_{18} cartridge that had been preconditioned with 5 ml of methanol and 10 ml of purified water, to extract BPA. The cartridge was then washed with 10 ml of 10 % methanol to eliminate most of the watersoluble urinary constituents, which were not adsorbed on the solid support. After the cartridge washing, 3 ml of methanol was added to elute BPA. The entire effluent was evaporated to dryness under a nitrogen stream at 45 ◦C. To derivatize the hydroxyl groups, 100 µl of BSTFA was added to the dried residue. The reaction vial was mixed thoroughly using vortex mixer followed by heating at 65 ◦C for 30 min. After cooling, the derivatized solution was evaporated to dryness and the residue was redissolved in 100 µL chloroform. The resulting solution was analyzed by GC-MS.

Instrumental and analytical conditions

The instrument used for GC-MS analysis was an Agilent (Agilent Technologies, Palo Alto, CA, USA) 6890 plus gas chromatograph equipped with a 5973 mass selective detector quadrupole mass spectrometer. A 1µL aliquot of the final derivatized extract was injected into the system operated in the split-less mode. The injector temperature was set at 250 ◦C. The column was DB-5MS, 30m×0.25mm i.d., film thickness 0.25µm (Agilent Technologies, Palo Alto, CA, USA). The GC oven temperature was initially set at 70 ◦C (2 min) and then programmed to 150 ◦C at a rate of 20 ◦Cmin−1 then to 300 ◦C at 10◦Cmin−1 and maintained for 2min. The temperature of the transfer line was maintained at 270 ◦C. Helium (99.999%) was used as carrier gas at 1mLmin−1. The source and quadrupole temperatures were kept at 230 and 150 ◦C, respectively. The electronic beam energy of the mass spectrometer was set at 70 eV. The mass selective detector was operated in electron impact (EI) mode using selected ion monitoring (SIM). The dwell time of each ion was set at 100 ms. Confirmation of the identities of BPA and its derivatives was performed in selected ion monitoring mode (SIM), after selection of characteristic masses (ions (m/z) 357,372).

Quantitative analysis

The calibration curve parameters listed in Table 1 were obtained under optimized condition. Linearity of the calibration curve was determined in the range of 0.2 –20 ng mL−1. Coefficient of correlation was 0.992. The LOD was defined as three times the standard deviation of baseline noise (n = 6) and

determined by spiking serially diluted analyte standard into a blank urine sample. According to the ICH (International Conference on Harmonization of Technical Requirements for Bioanalytical Methods) guideline for analytical method validation, limit of quantification (LOQ) for analyte was determined as the lowest concentration on the calibration curve with a precision of less than 20% coefficient of variation (CV%) and an accuracy of 80–120% [42]. The results showed that the LOD and LOQ for the target analyte was 0.1 and 0.2 ng /ml, respectively.

ultrasonographic scan, as well as in mammography if above 40 years, were picked as controls (Group 3). Since it has been reported in the literature that a single urinary level in one sample is sufficiently sensitive to demonstrate long-term exposure to BPA (Mahalingaiah *et al*., 2008), one random spot urine sample was collected from each participant before any treatment. All samples were collected between 9:00 to 12:00 in the morning in polyethylene containers and frozen immediately in - 20 ºC. A data collection form containing information about age, age at menarche, menstrual cycles, menopause status,

Table 1. Common characteristics of the participants

Continuous variable	Mean	Min	Max	95% CI
Age (year)*				
Control	48.73	29	59	44.35-53.12
Benign	35.80	19	50	30.03-41.57
Malignant	48.40	31	71	42.15-54.65
Urinary BPA(µg/L)*				
Control	0.60	0.15	1.45	0.41-0.80
Benign	1.01	0.15	2.63	0.66-1.35
Malignant	0.95	0.41	1.65	0.70-1.20
Duration of Breastfeeding (month)*				
Control	47.33	13	96	32.23-62.43
Benign	17.87	0	65	5.00-30.74
Malignant	47.23	0	144	21.14-73.53
Age at Menarche(year)				
Control	13.60	10	16	12.48-14.72
Benign	13.33	11	16	12.53-14.13
Malignant	13.20	9	18	12.05-14.35
Categorical variable	Control N(%)	Benign mass N(%)		Malignant mass N (%)
Menopause condition				
Premenopausal				
regular	2(13.3)	10(66.7)		5(33.3
Irregular	4(26.7)	4(26;7)		3(20.0)
total	6(40.0)	14(93.3)		8(53.3)
Menopausal	9(60.0)	1(6.7)		7(46.7)
OCP consumption(last 5 years)				
No	12(80.0)	8(53.3)		10(66.7)
Yes	3(20.0)	7(46.7)		5(33.3)
Eating preheated canned food				
1-5 times a year	10(41.7%)	6(25.0%)		8(33.3%)
6-10 times a year	2(28.6%)	2(28.6%)		3(42.9%)
10-15 times a year	0.0	3(60.0%)		2(40.0%)
More than 15 times a year	2(25.0%)	4(50.0%)		2(25.0%)

*p-value <0.20

Study Design and Participants

In this study, we compared urinary BPA levels in patients with malignant breast mass, benign breast mass and, women with normal breast. The study was approved by the Institutional Review Board of Tehran University of Medical Sciences and was carried out from March 2013 through October 2013 at the department of Surgery of Arash Women's Hospital and the Institute for Environmental Research, Tehran University of Medical Sciences, Tehran, Iran. Among women attending the breast clinic of Arash women's hospital, 45 were enrolled in this study. Exclusion criteria consisted of any previous history of breast cancer, a positive family history of breast cancer in first or second degree relatives, consumption of warm food in plastic containers or canned food in the last week prior to entering the study, and residence in the neighborhood of industrial factories. After completing the written informed consent, 15 cases of newly diagnosed, non-metastatic breast cancer were selected as the cancer group (Group 1). Fifteen other cases were selected among patients with a newly palpable or non-palpable mass which had been diagnosed as simple fibroadenoma via histological assessment; these composed the benign group (Group 2). Thereafter, 15 women whose breasts had been confirmed as normal in physical examination and duration of lactation and history of hormone consumption was filled by a trained interviewer for women in the 3 groups. In addition, the yearly habits of consumption of canned foods or warm foods in disposable containers were asked and recorded. Tumor characteristics of breast malignancies, including histology and nuclear grade, disease stage and hormone receptor status of the tumors were recorded.

Assessment of BPA concentrations

All the case and control participants supplied urine samples that were then analyzed for total BPA concentration. BPA was analyzed using solid-phase extraction coupled with gas chromatography-mass spectrometry after derivatization with BSTFA 14. The limit of detection (LOD) and limit of quantification (LOQ) under the chromatographic conditions were determined at signal-to-noise ratios (S/N) of 3 and 6, respectively. The LOD was 0.1 ng/mL and the LOQ was 0.2 ng/mL. Individuals whose urinary concentrations fell below the LOD were assigned a value of LOD/2. A comprehensive quality control system, including reagent blanks, was used to ensure that samples were not contaminated during handling, storage, and analysis.

Table 2. Tumor characteristics of breast cancers

Characteristics		Number	Percent
Nuclear grade*	1	3	20
	2	6	40
	3	6	40
Tumor stage**	1	3	20
	2	7	46.7
	3	5	33.3
	4	0	0
Estrogen receptor	+	12	80
	-	3	20
Progesterone receptor	+	11	73.3
	-	4	26.7
Her2***	+	3	20
	-	12	80

* Based on Bloom-Richardson grading system, **Based on American Joint Committee on Cancer (AJCC) TNM system, ***Human Epidermal Growth Factor Receptor 2

Data analysis

Urinary BPA was compared among the three target groups of study using Kruskal-Wallis nonparametric test. Continuous variables are presented as mean (95% confidence interval), and categorical variables are shown as proportions (percentages). Association between urinary BPA with benign and malignant breast masses was tested using multinomial logistic regression models (unadjusted and adjusted adjusted for potential confounding variables models).

Type of the breast mass regarding its benign or malignant nature was considered as the dependent variable. We used two models, Model 1: unadjusted model and Model 2: adjusted for age, age at menarche, duration of breastfeeding, use of oral contraceptives (OCP) during the last 5 years and eating preheated canned food during the last year. The odds ratio (OR) [95% confidence interval (CI)] of breast with benign and malignant masses for BPA and adjusting variables were calculated by considering the control group as reference. Urinary BPA levels were divided into four equal size groups (quartiles) and the effects of both BPA quartiles and linear trend of BPA were tested in models.

RESULTS

In this study, we compared urinary BPA levels in patients with malignant breast mass, benign breast mass and healthy women with normal breasts. In addition, The probale confounding effect of some none risk factors such as age and reproductive factors were investigated on breast mass. Mean age of the 45 participants was 44.3±11.5 years, with a range of 19 to 71 years. General characteristics of patients with regard to common risk factors of breast cancer (other than previous history and family history, which were negative in all due to our exclusion criteria) are demonstrated in Table 1. None of the participants had received hormone replacement therapy in the recent 2 years.

Table 3. Multinomial logistic regression models (unadjusted and adjusted models) results for testing association between BPA and breast mass

Model: unadjusted models					
Cancer type[a]	variable		OR	95% Confidence Interval for OR	*P* value
Benign	BPA	Trend	2.14	1.038-4.426	0.039
		1	.	.	.
		2	1.167	0.133 - 4.221	0.889
		3	3.667	0.673 - 7.4	0.119
		4	5.333	0.711 - 12.6	0.089
		Trend	2.270	1.092 - 4.721	0.028
Malignant	BPA	1	.	.	.
		2	2.345	0.216 - 8.245	0.486
		3	4.423	0.564 - 11.94	0.158
		4	8.178	1.504 - 19.253	0.024
Model 2: Adjusted models					
Benign	BPA		2.685	1.012-7.225	0.048
Malignant	BPA		2.937	1.182-7.302	0.020

a. The reference category is: control group.

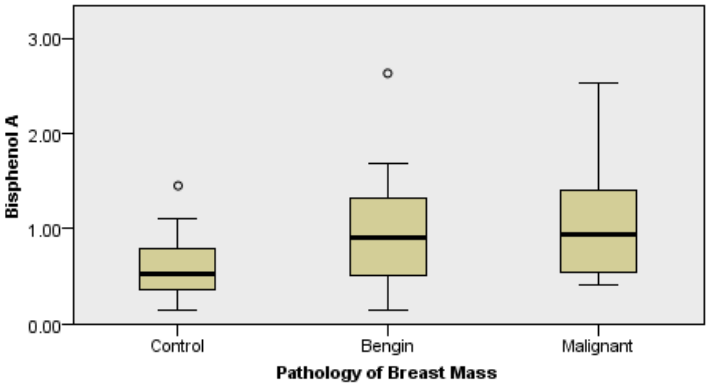

Figure 1. Box plot of BPA in different groups

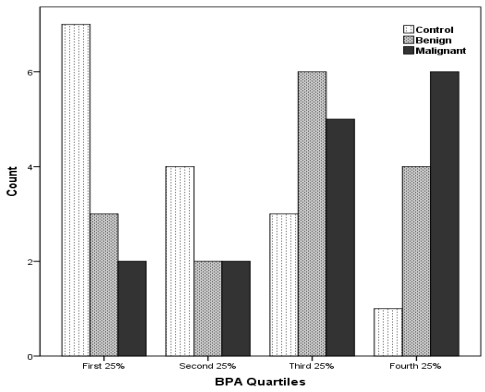

Figure 2. Frequency distribution of different groups in BPA quartiles

Features of malignant tumors are shown in Table 2. Concentration of BPA had significant differences among target groups (P<0.05). Pairwise comparisons displayed a significant difference between malignant and control group. When we compared BPA levels among patients with benign or malignant mass and control, the median value of BPA levels was higher in the patients with breast masses than the control(malignant mass> benign mass > control) (Figure. 1); this trend was statistically significant. Frequency distribution of target groups in BPA quartiles is showed in figure 2. With increasing urinary concentration of BPA in quartile, the number of patients with breast mass increased (Figure. 2). In the multinomial logistic regression models, we observed a positive association (P<0.05) between increasing urinary BPA levels with both malignant and benign breast mass in unadjusted and the multivariable-adjusted models (for age, age of menarche, breastfeeding duration, use of OCP during the last 5 years and eating perheated canned food during the last year). Based on model 1, we saw a trend in breast masses odds (OR=2.14 for patient with malignant breast mass *vs* control group and OR= 2.27 for patient with benign breast mass *vs* control group). According to the statistical resulrs, the adjusted model odds ratio (OR= 2.68 for patient with benign breast mass vs control group and OR= 2.94 for patient with malignant breast mass vs control group) is increased more than10 % compared to unadjasted model. Table 3 displays estimated Odds Ratio and 95% CI for the effect of each variable on breast cancer.

DISCUSSION

Each year, over a million women worldwide are diagnosed with breast cancer, accounting for 25% of all female cancers (LaPensee and Ben-Jonathan, 2010). The significant capacity of environmental and exogenous components, such as EDCs, to alter endocrine processes such as female hormonal pathways, has resulted in greater awareness towards their probable effects on breast cancer risk. Animal studies have suggested that BPA is an endocrine disruptor which might have various side effects on human health and may contribute to the development of neoplasia (Knower *et al*., 2014). On the other hand, there is ample evidence from rodents (Durando *et al*., 2007, Markey *et al*., 2001, Vandenberg *et al*., 2007, Markey *et al*., 2002, Jenkins *et al*., 2009) and primate (Tharp *et al*., 2012) studies that prenatal exposure to BPA causes disruption of the mammary tissue and increases susceptibility of the tissue to chemical carcinogens.

Data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) showed that 93% of individuals sampled among the American general population had detectable levels of BPA in their urine (Calafat *et al*., 2008). Results from many other researchers have shown the same level of BPA exposure in different population groups (Lee *et al*., 2008, Braun *et al*., 2009, He *et al*., 2009, HealthCanada, 2010). Measuring urinary BPA is a suitable approach for estimating BPA intake levels in individuals and/or estimating the average exposure level of populations. Therefore, urine analyses will be increasingly important in human health risk assessment of BPA (Arakawa *et al*., 2004). Our results showed that the urinary BPA levels in the Iranian subjects were comparable to those reported from other countries (Mahalingaiah *et al*., 2008, Itoh *et al*., 2007). Recently, Sprague *et al*. (2013), demonstrated that serum levels of BPA were cross-sectionally associated with higher mammographic breast density in postmenopausal women independent of BMI and other covariates (Sprague *et al*., 2013). Up to now, to the best of our knowledge, there is only one report about the association of BPA and breast cancer in human. In this study, Yang *et al*. investigated the association between BPA exposure and breast cancer in Korean women. They analyzed total serum BPA in women with and without breast cancer. They results showed no difference in mean serum BPA concentrations between cases and controls. However, median serum BPA concentrations (1.7 µg/l) were non-significantly higher among breast cancer cases compared with controls. In this study no information was provided about the type, stage or grade of the tumours (Yang *et al*., 2009).

In this study, we investigated the potential associations between BPA exposure and type of breast neoplasm (benign and malignant) in Iranian women by performing biomonitoring of BPA in urine samples among target groups. BPA was detected in all samples. Our results have shown a strong positive association between urinary concentrations of BPA and both benign and malignant breast masses. However this study has some limitations. First limitation is the low precision of the study estimates of the odds ratios for breast mass per unit increase in BPA concentration, even though they are statistically significant at 5% level. For example, 95% confidence limits of 1.04 and 4.43 for the odds ratio between BPA concentration and breast mass indicate that data are compatible with a very small to a large association between BPA and breast carcinoma. Second, the current study is case–control in nature, hence, making it impossible to draw a cause and effect in the observed associations. Large cohort studies are needed to precisely estimate the causal effect of high serum BPA levels on the breast cancer. Additionally, because this study only examined BPA exposure among adults, it was impossible to investigate any effect of BPA exposure during critical growth periods, such as prenatally. Future independent replication and follow up studies are needed to confirm or disprove these findings. If the results of this research would be confirmed in future prospective studies, reducing BPA exposure may play a role in the prevention and reduce of breast cancer incidence.

Competing Financial Interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgments

This research has been supported by the Deputy of Research of the Tehran University of Medical Sciences (project no. 91-03-46-19110). Dr Batool H. Rashidi and Mrs. Fedyeh Haghollahi from Vali-e-Asr Reproductive Health Research Center, Tehran University of Medical Sciences are gratefully acknowledged for their contribution in the coordination of clinical and basic science study groups.

REFERENCE

Arakawa, C., Fujimaki, K., Yoshinaga, J., Imai, H., Serizawa, S. and Shiraishi, H. 2004. Daily urinary excretion of bisphenol A. *Environmental health and preventive medicine,* 9, 22-26.

Braun, J. M., Yolton, K., Dietrich, K. N., Hornung, R., YE, X., Calafat, A. M. and Lanphear, B. P. 2009. Prenatal bisphenol A exposure and early childhood behavior. *Environmental Health Perspectives,* 117, 1945.

Calafat, A. M., Kuklenyik, Z., Reidy, J. A., Caudill, S. P., Ekong, J. and Needham, L. L. 2005. Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environmental Health Perspectives*, 113, 391.

Calafat, A. M., YE, X., Wong, L.-Y., Reidy, J. A. and Needham, L. L. 2008. Exposure of the US population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. *Environmental Health Perspectives,* 116, 39.

Durando, M., Kass, L., Piva, J., Sonnenschein, C., Soto, A. M., Luque, E. H. and Muñoz-De-Toro, M. 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. *Environmental Health Perspectives,* 80-86.

He, Y., Miao, M., Herrinton, L. J., Wu, C., Yuan, W., Zhou, Z. and Li, D.-K. 2009. Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels. *Environmental research,* 109, 629-633.

Healthcanada, 2010. Environmental and Workplace Health.Report on Human Bi omoni tori ng of Envi ronmental Chemicals in Canada. Results of the Canadian HealthMeasures Survey Cycle 1 (2007-2009). Available: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/ chmsecms/index-eng.php [accessed 16 August 2010].

Itoh, H., Iwasaki, M., Hanaoka, T., Sasaki, H., Tanaka, T. and Tsugane, S. 2007. Urinary bisphenol-A concentration in infertile Japanese women and its association with endometriosis: a cross-sectional study. *Environmental health and preventive medicine,* 12, 258-264.

Jenkins, S., Raghuraman, N., Eltoum, I., Carpenter, M., Russo, J. and Lamartiniere, C. A. 2009. Oral exposure to bisphenol A increases dimethylbenzanthracene-induced mammary cancer in rats. *Environ Health Perspect*, 117, 910-915.

Katchy, A., Pinto, C., Jonsson, P., Nguyen-Vu, T., Pandelova, M., Riu, A., Schramm, K.-W., Samarov, D., Gustafsson, J.-Å. and Bondesson, M. 2013. Co-exposure to Phytoestrogens and Bisphenol A mimic estrogenic effects in an additive manner. *Toxicological Sciences*, kft271.

Knower, K., TO, S. Q. G., Leung, Y.-K., Ho, S.-M. and Clyne, C. 2014. Endocrine disruption of the epigenome: a breast cancer link. *Endocrine-Related Cancer*.

Lapensee, E. W. and Ben-Jonathan, N. 2010. Novel roles of prolactin and estrogens in breast cancer: resistance to chemotherapy. *Endocrine-Related Cancer*, 17, R91-R107.

Lee, Y. J., Ryu, H.-Y., Kim, H.-K., Min, C. S., Lee, J. H., Kim, E., Nam, B. H., Park, J. H., Jung, J. Y. and Jang, D. D. 2008. Maternal and fetal exposure to bisphenol A in Korea. *Reproductive Toxicology,* 25, 413-419.

Mahalingaiah, S., Meeker, J. D., Pearson, K. R., Calafat, A. M., Ye, X., Petrozza, J. and Hauser, R. 2008. Temporal variability and predictors of urinary bisphenol A concentrations in men and women. *Environmental Health Perspectives,* 116, 173.

Markey, C. M., Luque, E. H., De Toro, M. M., Sonnenschein, C. and Soto, A. M. 2001. In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. *Biology of reproduction*, 65, 1215-1223.

Markey, C. M., Rubin, B. S., Soto, A. M. and Sonnenschein, C. 2002. Endocrine disruptors: from Wingspread to environmental developmental biology. *The Journal of steroid biochemistry and molecular biology*, 83, 235-244.

Matsushima, A., Kakuta, Y., Teramoto, T., Koshiba, T., LIU, X., Okada, H., Tokunaga, T., Kawabata, S.-I., Kimura, M. and Shimohigashi, Y. 2007. Structural evidence for endocrine disruptor bisphenol A binding to human nuclear receptor ERRγ. *Journal of biochemistry,* 142, 517-524.

Mlynarcikova, A., Macho, L. and Fickova, M. 2013. Bisphenol A alone or in combination with estradiol modulates cell cycle-and apoptosis-related proteins and genes in MCF7 cells. *Endocrine regulations,* 47, 189-199.

Nahar, M. S., Soliman, A. S., Colacino, J. A., Calafat, A. M., Battige, K., Hablas, A., Seifeldin, I. A., Dolinoy, D. C. and Rozek, L. S. 2012. Urinary bisphenol A concentrations in girls from rural and urban Egypt: a pilot study. *Environ Health,* 11, 20.

NTP 2008. NTP Brief on Bisphenol A [CAS NO. 80- 5-07]. http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf. Accessed 30 Mar 2012.

Richter, C. A., Birnbaum, L. S., Farabollini, F., Newbold, R. R., Rubin, B. S., Talsness, C. E., Vandenbergh, J. G., Walser-Kuntz, D. R. and Vom SAAL, F. S. 2007. < i> In vivo</i> effects of bisphenol A in laboratory rodent studies. Reproductive Toxicology, 24, 199-224.

Ritchie, J. M., Vial, S. L., Fuortes, L. J., Guo, H., Reedy, V. E. and Smith, E. M. 2003. Organochlorines and risk of prostate cancer. *Journal of occupational and environmental medicine*, 45, 692-702.

Sengupta, S., Obiorah, I., Maximov, P., Curpan, R. and Jordan, V. 2013. Molecular mechanism of action of bisphenol and bisphenol A mediated by oestrogen receptor alpha in growth and apoptosis of breast cancer cells. *British journal of pharmacology,* 169, 167-178.

Sprague, B. L., Trentham-Dietz, A., Hedman, C. J., Wang, J., Hemming, J. D., Hampton, J. M., Buist, D. S., Bowles, E. J. A., Sisney, G. S. and Burnside, E. S. 2013. Circulating serum xenoestrogens and mammographic breast density. Health, 4, 6.

Tharp, A. P., Maffini, M. V., Hunt, P. A., Vandevoort, C. A., Sonnenschein, C. and Soto, A. M. 2012. Bisphenol A alters the development of the rhesus monkey mammary gland. Proceedings of the National Academy of Sciences, 109, 8190-8195.

Thomas, P. and Dong, J. 2006. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. *The Journal of steroid biochemistry and molecular biology*, 102, 175-179.

Vandenberg, L. N., Maffini, M. V., Wadia, P. R., Sonnenschein, C., Rubin, B. S. and Soto, A. M. 2007. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. Endocrinology, 148, 116-127.

Welshons, W. V., Thayer, K. A., Judy, B. M., Taylor, J. A., CURRAN, E. M. and VOM SAAL, F. S. 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environmental Health Perspectives, 111, 994.

Wetherill, Y. B., Akingbemi, B. T., Kanno, J., Mclachlan, J. A., Nadal, A., Sonnenschein, C., Watson, C. S., Zoeller, R. T. and Belcher, S. M. 2007. < i> In vitro</i> molecular mechanisms of bisphenol A action. Reproductive Toxicology, 24, 178-198.

Yang, M., Ryu, J.-H., Jeon, R., Kang, D. and Yoo, K.-Y. 2009. Effects of bisphenol A on breast cancer and its risk factors. Archives of toxicology, 83, 281-285.

****