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Associations of urinary BPA levels and dietary fat intake with prior breast cancer diagnosis among women: Results from the National Health and Nutrition Examination Survey

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Abstract

Introduction: The prevalence of breast cancer, high saturated fat intake and environmental toxicant ingestion continues to be an issue within the United States. The aim of this study was to evaluate the association between urinary Bisphenol A (BPA) levels and dietary fat intake with breast cancer diagnosis in U.S. women 30 years and older using data from the National Health and Nutrition Examination Survey (NHANES).

Methods: This study examined dietary data for 200 women who participated in NHANES study cycles between 2003-2014. Inclusion criteria were women aged 30 years or older with a diagnosis of breast cancer, complete urinary BPA data, and complete dietary data for Healthy Eating Index calculation and ability to normalize BPA for body mass index (BMI). The sample population was matched with a randomly selected group of women of similar age from the same NHANES study cycles but no diagnosis of breast cancer. Non-parametric statistical analyses were performed. After descriptive and correlations were performed for preliminary statistics, the study population was divided into three groups for analyses: 1) never diagnosed with breast cancer (n=100), 2) less than 5 years since diagnosis (n=39), and 3) greater than 5 years since diagnosis (n=61) for regression and ANOVA analyses.

Results: Out of a scale of 100, average HEI scores for each group were found to be 55.96 (13.62) in never diagnosed, 56.58 (12.98) in women diagnosed with breast cancer less than 5 years ago, and 58.81 (13.41) in women more than 5 years from diagnosis. In all groups, urinary BPA was significantly correlated with HEI fatty acid ratio and saturated fat intake ($r= 0.20$, $n=200$ $p= 0.007$, $\alpha=0.05$; $r=-0.16$, $n=200$, $p=0.03$, $\alpha=0.05$). Urinary BPA levels, however, did not correlate with breast cancer diagnosis ($r=0.143$, $n=200$, $p=0.157$, $\alpha=0.05$). There were no statistically significant interactions between saturated fat, added sugars in the diet, a healthy diet overall (HEI score), or urinary BPA levels and a prior diagnosis of breast cancer ($p>0.05$ and $\alpha=0.05$ for all dietary components and urinary BPA). Urinary BPA levels varied with time since diagnosis. Women who had been diagnosed with cancer more than 5 years prior to the survey had significantly lower urinary total BPA levels and lower BPA levels normalized for body mass index (BMI) than the women who had never been diagnosed or women who had been diagnosed within the past five years, ($p<0.05$, $\alpha=0.05$). Women who were more than 5 years from diagnosis also had significantly higher levels of polyunsaturated fat in their diets than women who were never diagnosed or had been recently diagnosed. Although not statistically significant, both groups of women with a prior cancer diagnosis scored higher on the HEI than women who had never had a cancer diagnosis. Cancer survivors of greater than 5 years since diagnosis had higher HEI scores compared to either groups.

Conclusions: The study found evidence that urinary BPA levels are associated with saturated fat intake. The study also showed a trend for a reduction in BPA levels and an increase in dietary polyunsaturated fat intake in cancer survivors more than 5 years post-diagnosis. It could be inferred from these trends that women modify their diet and fat intake levels post-cancer diagnosis. The study did not, however, find links between overall diet quality, saturated fat, or urinary BPA levels and a prior cancer diagnosis. This finding is consistent with previous research that suggests neither BPA levels in the blood nor saturated fat can be statistically linked to the incidence of breast cancer. That does not mean endocrine disruptors have no role in the

development of cancer. Diet, lifestyle, and environmental factors all have the potential to alter DNA methylation, gene expression patterns, and inflammatory responses resulting in adverse health outcomes. Future examinations of the relationships between plastic packaging, canned foods, and processed foods on urinary BPA levels and the prevalence of breast cancer should be taken into consideration.

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1. Literature Review

A. Overview

Breast cancer is on the rise across the world, with a notable increase in aggressive forms of cancer in young women (Teegarden, 2012). The American Cancer Society estimated that approximately 40920 women would lose their lives to breast cancer in the United States during 2018, making it the second leading cause of cancer death in females (American Cancer Society, 2018). Breast cancer occurs when cells within the ductal glands or lobules continuously grow and divide, eventually forming a tumor. The presence of malfunctioning tumor suppressor genes, mutated proto-oncogenes, or specific genomic single nucleotide polymorphisms (SNPs) may allow the tumor to grow and metastasize (American Cancer Society, 2018). The diversity of gene expression profiles found in breast cancers indicates that transcriptional control may determine the outcome of the disease. Since DNA transcription, and therefore gene expression patterns, can be controlled and modified by diet there is a need for studies on nutrients and dietary factors that might affect epigenetic control of transcription and cancer incidence and survivorship (Teegarden, 2012).

Risk Factors of Breast Cancer

Hormones & Age:

Reproductive confounders such as age at menarche, age at first birth, age of last menstrual cycle, and parity must be considered when attempting to understand the effects of hormonal levels on cancers predominantly found in females (Bernstein et al., 1993). These ontogenetic factors produce fluctuations in the endocrine system, particularly in estrogen

production. Estrogens are of particular interest as these hormones and hormone fractions influence the growth of breast epithelium (Bernstein et al., 1993).

Two principal estrogens circulate in the blood: estradiol and estrone. Estradiol is the most active estrogen hormone in breast tissue. These estrogen levels change across the lifespan. Females of reproductive age tend to have significantly higher levels of estradiol and estrone than other age groups. Postmenopausal females tend to have a higher risk of breast cancer as the ovarian production of these estrogens ceases, while their production continues as a byproduct of the metabolism of adrenal androgens (e.g., testosterone and androstenedione). When these androgens are produced, they are subsequently metabolized into estrogens (Bernstein et al., 1993). Studies have shown that postmenopausal females with higher levels of these estrogens have a significantly higher risk of breast cancer as compared to healthy postmenopausal females in the United States (Dorgan et al., 1996; Dorgan et al., 1997; Thomas et al., 1997; Hankinson et al., 1998; Toniolo et al., 1995).

Environmental Toxicants; Bisphenol A (BPA):

Several studies have shown that environmental toxicants, diet, and lifestyle play crucial roles in cancer. Environmental toxicants, in particular, can disrupt physiological homeostatic mechanisms, including those of the endocrine system. BPA is an environmental toxicant and endocrine-disrupting hormone with a wide distribution in every-day household and food/beverage items. When BPA or any other endocrine disruptor is ingested, absorbed and assimilated at the adipose tissue level, they can increase or decrease normal, homeostatic hormonal levels, mimic natural hormones within the body, or alter production of those natural hormones (NIH Endocrine Disruptors, 2019).

BPA is found in the manufacturing of polycarbonate plastics such as beverage containers, plastic dinnerware, toys, and other everday household items. BPA exposure occurs when foods or beverages are packaged in containers made from BPA-containing plastics, or oral contact or hand-to-mouth contact with BPA-containing materials (CDC, 2017). Upon exposure, BPA interacts with estrogen receptors found in a wide range of mammalian cells. Estrogen receptors have a high affinity for BPA due to structural similarities with estradiol; as a result, BPA can cause adverse endocrine changes within the body (Fig. 1; Palacios-Arreola et al., 2017). These changes can occur within reproductive organs, mammary development, adipose tissue, the immune system, and within a fetus during sexual differentiation, subsequently increasing risk to hormonal cancers like breast cancer (Palacios-Arreola et al., 2017).

Numerous animal studies have identified the mechanisms of breast cancer risk due to BPA ingestion. A 2017 study conducted by Xu et al. used both bovine vascular endothelial cells (BVECs) and female mice to assess BPA-induced hypoxia inducible factor 1-alpha (HIF-1alpha) and vascular endothelial growth factor (VEGF) gene expression in order to have a better understanding of the molecular mechanism of tumor progression in vascular endothelial and breast cancer cells of mice (Xu et al., 2017). Xu et al. (2017) suggested cellular exposure to BPA under low-oxygen conditions, or a hypoxic environment, such as that found in breast cancer cells or vascular endothelial cells, increases susceptibility to induction of HIF-1alpha expression. This gene expression, in turn increases tumor cell proliferation and migration (Xu et al., 2017).

Another study conducted in 2017 sought to perform genome-wide methyl-binding domain sequencings (MBDCap-Seq) on mammary glands of ten 100-day-old per lactating dam of rats that were prepubertally exposed to BPA and phytoestrogen genistein (GEN) alone or together in order to explore the epigenetic factors to breast cancer throughout life (Jadhav et al.,

2017). The network analysis identified differentially methylated genes in human female breast care patients compared to the rats; bioinformatic techniques were then used to evaluate genetic predictors of long-term survival (Jadhav et al., 2017). The network analysis found that there were 4 (BPA), 119 (GEN), 134 (BPA+GEN), and 305 (control) genes with differentially methylated loci in the rats (Jadhav et al., 2017). The top differentially connected networks related to BPA exposure involved cellular assembly/organization, organismal injury/abnormalities, cancer, cell death/survival, reproductive system disease, cellular movement, cell cycle, and cell morphology similar to those genes of human breast cancer patients (Jadhav et al., 2017).

The results from this study show that postnatal exposure to BPA may result in long-term epigenetic modifications within breast tissue; these modifications remain stable for long periods because of the changes to the genome (Jadhav et al., 2017). There may, however, be potential to reverse BPA's effects on breast cancer progression through the consumption of phytoestrogen genistein (Jadhav et al., 2017). If these findings are extrapolated to humans, the possibility that BPA exposure may epigenetically modify genes involved in breast cancer progression should be considered. The dietary consumption of phytoestrogenic plants, however, could potentially reverse those epigenetic modifications.

Not only have researchers studied the effects of BPA on breast cancer in real-time, but they have also looked at the tumor microenvironment over time and throughout adulthood in mice (Palacios-Arreola et al., 2017). Mice share 99% of the same genes with humans. A study conducted by Palacios-Arreola et al. (2017) proposed that endocrine disruption by BPA may permanently alter the immune system. These changes would likely affect the anti-tumoral response during the neonatal stage, as the endocrine system and the immune system interact with one another (Palacios-Arreola et al., 2017).

Through exposing female neonate mice to BPA, assessing endocrine parameters, cell cultures, 4T1 tumor induction within the mammary tissue at the time of sexual maturity, flow cytometry, immunofluorescence, and RT-PCR, it was found that there was a significant increase in large tumor development with an 88% increase in tumor weight (Palacios-Arreola et al., 2017). Regulatory T lymphocytes within the tumors of the BPA exposed mice were significantly greater in number than that of the control mice (Palacios-Arreola et al., 2017). There was a decrease in TNFa, INFy, and a decrease in the M2 macrophage biomarker, Fizz-1 within the BPA treated mice (Palacios-Arreola et al., 2017). Finally, there were significant differences in estrogen receptor alpha expression through T lymphocytes, macrophages, and natural killer cells associated with BPA exposure as well as tumor development, supporting the researchers' hypothesis (Palacios-Arreola et al., 2017). The results from this study suggest that environmental exposure, such as BPA ingestion, may significantly alter the genome, affecting specific gene expression not only involved in tumor progression but also involved in the effectiveness of the immune system.

Further support for the link between BPA ingestion and breast cancer comes from a study by Hussain et al. (2015) on the HOX6 gene, a homeobox-containing gene associated with mammary gland development and often overexpressed in breast cancer patients. Hussain et al. (2015) cultured cells from 12 adult female rats with and without BPA treatment to observe the behavior of ER+ breast cancer cells (Hussain et al., 2015). They used RT-PCR and immunohistochemical localizations to observe the flag-HOX6 expression. They found that HOX6 was overexpressed in breast cancer tissues as compared to the controls, with expression higher in ER+ breast cancer cells than in ER- cells, and that transcription was BPA concentration-dependent manner (Hussain et al., 2015). Overall, this study showed that breast

cancer tissues with estrogen receptors can be upregulated through the increased expression of the HOX6 gene. When BPA is added in a dose-dependent manner, both HOX6 gene expression and tumor progression increase (Hussain et al., 2015). The link between BPA dosage and tumor progression highlights the importance of understanding the dosage of BPA that will increase tumor progression through the binding of the estrogen receptors in breast cancer tissue relative to an individual's body weight or body fat percentage.

Although results from animal studies do not always reliably apply to human systems, there is some justification for using animal models to test BPA exposure. There have been several studies comparing results from in-vitro human breast cancer cell lines and animal models that have come to similar conclusions (Fillon, 2012). There is no ethical way scientists can study BPA exposure and its internal dose-response or routes of exposure in humans (Fillon, 2012). Without animal studies, scientists must rely on uncontrolled post-exposure observational studies on humans. As such, the majority of breast cancer research concerning the ingestion of environmental toxicants has primarily focused on animal models that are genetically similar to humans (Fillon, 2012), such as mice. There are, however, studies that bridge the link between animal and human models at the cellular level.

A study published in 2014 looked at the antisense transcript, HOTAIR, a gene silencer, and BPA and diethylstilbestrol (DES) exposure in both human breast cancer cells and rat mammary tissue (Bhan et al., 2014). Cell cultures were treated with estradiol, BPA, and DES, and RNA extraction. RT-PCR, qPCR, were used to quantify expression patterns (Bhan et al., 2014). HOTAIR expression was induced by both BPA and DES in the human breast cancer cells as well as the rat in-vivo model in a dose-dependent manner (Bhan et al., 2014); 100nM of BPA and 10nM of DES caused a 6-fold increase in expression whereas 0.1nM of estradiol caused an

increase of 5-fold. When estradiol was present with BPA and DES, however, there was a slight reduction in HOTAIR expression (Bhan et al., 2014). Similar results were found in the in-vivo rat model; expression was upregulated in the mammary glands (4.1-fold BPA; 3.3-fold estradiol) (Bhan et al., 2014). These results suggest that when estrogen molecules are present along with endocrine disruptors (e.g., BPA), there is competition for the estrogen receptors. Estrogen receptors have a higher affinity for estradiol than BPA; its presence potentially reverses the risk of BPA on breast cancer due to decreased binding (Bhan et al., 2014).

A study conducted by Song et al. (2017) explored the mechanism by which BPA induces inflammatory pathways in both human pulmonary epithelial cells as well as human breast cancer cells. The study focused on the relationship between urinary BPA levels and inflammatory markers in elderly populations aged 60 or older (Song et al., 2017). Using in-vitro human breast cancer cells, the researchers performed several molecular biological assays to determine COX-2 expression and found that BPA treatments induced COX-2 expression through the NF-kB pathway and the MAPK pathway, both known inflammatory pathways (Song et al., 2017).

Inflammatory pathways are known to influence the immune system, with the primary response being an increase in blood circulation to the point of infection or abnormalities (Nelms et al., 2010). Increased blood flow increases the number of circulating white blood cells and helps re-establish homeostasis (Nelms et al., 2010); it may also promote apoptosis or an increase in helper T lymphocyte cells. This response can prolong activation of the pathways involved in chronic inflammation (Nelms et al., 2010). This is the case in cancers like breast cancer (Nelms et al., 2010). Chronic inflammation is a potential cause of cancers that develop through cellular positive feedback mechanisms. Unhealthy dietary patterns (e.g., increased saturated fat intake), obesity, diabetes, and insulin resistance often promote chronic inflammation (Nelms et al.,

2010). One of the major inflammatory markers controlling chronic inflammation is the nuclear factor kappa-beta (NF-kB) molecule. NF-kB inflammatory pathways can be down-regulated through a high dietary intake of polyunsaturated fatty acids and natural antioxidants/flavonoids and a low intake of refined grains. Alternatively, dietary components that stimulate increased insulin release, such as high intakes of sugar, saturated fat, and trans-fat, or increased intake of endocrine-disrupting environmental toxicants will increase inflammation (Nelms et al., 2010).

COX-2 pathways are known to play a role in inflammation, along with tumorigenesis (Song et al., 2017). NF-kB belongs to a known family of transcription factors, complexes, and dimers controlling the expression of several genes that are known to be involved in cellular processes like cell proliferation/differentiation and apoptosis (Park et al., 2016). Components of NF-kB involved in the expression of COX2 are the p50/p65 dimer and a complex of kinases (Park et al., 2016). Figure 2 illustrates the NF-kB pathway with which increases COX2 expression. Song et al. ’s work suggested that BPA treatment induces an increase in ROS production, potentially increasing the activation of NF-kB, hence increasing COX-2 expression (Fig. 2; Song et al., 2017). These results suggest that BPA levels within elderly, post-menopausal populations increase inflammatory markers as well as COX-2 expression, thus increasing overall inflammation and inflammation and potentially causing an increase in tumorigenesis in breast tissue (Song et al., 2017).

Evidence from both animal and in vitro human studies demonstrates a correlation between BPA and increased risk of breast cancer. BPA also appears to promote tumorigenesis with diet potentially modifying the risk (i.e., either increasing or decreasing tumorgenesis depending on dietary components). Additional factors, however, such as diet and physical activity levels, must also be considered as modifiers for the risk of breast cancer.

Dietary Fat Intake:

Like other cancers and diseases, diet plays an important role in both the risk and prevention of breast cancer. A 2017 multi-case-control study conducted by Castelló et al. explored the effects that three dietary patterns, designated as Western, Prudent, and Mediterranean, might have on breast cancer risk (Castelló et al., 2017). The Western diet was defined as a diet with high intakes of fat, added sugars, and red, processed meats whereas a Prudent diet was defined as a diet with high intake of low-fat foods, vegetables, fruits, whole grains, and juices (Casetlló et al., 2017). The Mediterranean diet was defined as a diet with high intakes of fish, vegetables, legumes, potatoes, fruits, olives, vegetable oil, a low intake of juices (Castelló et al., 2017). This study found that the Western diet increased breast cancer risk in both pre and post-menopausal women, whereas the Prudent diet did not show any effect on breast cancer at all (Castelló et al., 2017).

The Mediterranean dietary pattern, however, was found to be protective against breast cancer (Castelló et al., 2017). These findings are significant because although some individuals and healthcare professions consider low fat intake to be healthy overall, it does not have any beneficial effects when considering breast cancer. In contrast, a diet that is high in unsaturated fats due to fish consumption and olive and vegetable oils (poly and monounsaturated fatty acids), is protective. These three classes of fatty acids (saturated, monounsaturated, and polyunsaturated) differ in molecular structure.. A monounsaturated fatty acid, such as oleic acid, has only one double bond in its chain, allowing for different chemical properties than that of a saturated fatty acid with no double bonds in its chain (Lada, 2003). Polyunsaturated fatty acids, such as omega-3 and omega-6 fatty acids seen in seafood and vegetable oils, have two or more double bonds in its structure; this allows for more fluidity than is seen in saturated fatty acids

(Lada, 2003). Research has shown that both of these unsaturated fatty acids have beneficial effects on both coronary-artery disease (Lada, 2003). Both mono- and polyunsaturated fatty acids aid in reducing total LDL-cholesterol compared to saturated fatty acids (Lada, 2003). This leads to the question of whether it is the fat intake that is the problem, or the ratio of unsaturated fat to saturated or trans-fat intake. Fish, a common food component of the Mediterranean Diet, as well as other kinds of seafood and plant oils, have a fatty acid ratio higher in unsaturated fats.

Researchers conducted a randomized control trial to examine the effects of the Mediterranean diet on breast cancer through the analysis of this diet supplemented with extra virgin olive oil or nuts in the PREDIMED trial (Toledo et al., 2015). Using 4282 women from the PREDIMED trial from 2003-2009, the researchers randomly assigned subjects to treatment groups in a 1:1:1 ratio (Toledo et al., 2015). These treatment groups were: Mediterranean diet supplemented with extra virgin olive oil, Mediterranean diet supplemented with nuts, and a control group with no supplemental foods and a decrease in overall fat intake (Toledo et al., 2015). The researchers ran group sessions at both baseline and quarterly during the 6-year intervention where participants completed a dietary questionnaire for the Mediterranean diet groups and a dietary questionnaire for the control (Toledo et al., 2015).

With breast cancer as a secondary outcome and controlling for covariates including energy intake with nutrients, smoking, sociodemographic variables, weight, height, and waist circumference, the researchers found that after a follow up of 4.8 years, there were 35 confirmed incident cases of breast cancer (Toledo et al., 2015). The observed rates for each group were as follows: 1.1 for Mediterranean diet with extra virgin olive oil, 1.8 for Mediterranean diet with nuts, and 2.9 for control, suggesting that there are potential beneficial effects of the Mediterranean diet with extra virgin olive oil (Toledo et al., 2015). These incident rates could

potentially be explained by the enhanced absorption of nutrients aiding in a decrease of breast cancer risk through the aid of extra virgin olive oil whereas a Mediterranean diet supplemented with other fats such as nuts, had no benefits (Toledo et al., 2015). Although research has already suggested that the Mediterranean diet is beneficial for the reduction of breast cancer risks, supplementing this diet with extra virgin olive oil enhances these effects. The results from the Toledo et al. (2015) study suggest that the contents of the oil (monounsaturated fats, oleic acid, polyphenols/flavenoids) have antiproliferative effects through changing the expression of oncogenes at an epigenetic level, potentially the NF-kB inflammatory response (Toledo et al., 2015).

The Mediterranean dietary pattern has also been shown to be beneficial in reducing cancer recurrence and increasing cancer survival rate post-diagnosis. One prospective study was designed to assess the relationship between post-breast cancer diagnosis dietary factors and all-cause mortality in women with invasive breast cancer history (Beasley et al., 2011). The researchers used a 126-item food frequency questionnaire (FFQ) to assess dietary intake, and hazard ratios (HR) and confidence intervals (CI) to calculate estimated macronutrient and micronutrient intake in relation to breast cancer diagnosis (Beasley et al., 2011). Women in the highest quintile of saturated and trans-fat intake had a significantly higher risk of death, suggesting that a lower intake of dietary saturated fats post-diagnosis is associated with an improved survival rate for breast cancer patients (Beasley et al., 2011). The results from this study suggest that dietary patterns low in saturated and trans-fat intake, post-cancer diagnosis, have a beneficial effect on breast cancer recurrence in these individuals, making diet quality and habits important for both reducing the risk of diagnosis as well as reducing cancer recurrence or cancer death.

The Healthy Eating Index (HEI):

The Healthy Eating Index (HEI) is widely used in epidemiological and intervention research. It permits a measure of diet quality, independent of quantity, that can assess alignment with the dietary patterns suggested by the Dietary Guidelines for Americans (Kirkpatrick et al., 2018). As a scoring metric, the HEI reflects adequacy (dietary components to increase) and moderation (dietary components to decrease) in food choice recommendations. Components of the HEI are expressed and scored on a density basis in relation to energy intake (Kirkpatrick et al., 2018). Calculation of an HEI score requires dietary data, such that is generalized by 24-hour recall records (Kirkpatrick et al., 2018).

The current HEI-2015 scoring algorithm is based on 13 components (9 adequacy, 4 moderation; Kirkpatrick et al., 2018; Reedy et al., 2018). Adequacy components include total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acid ratio of mono and polyunsaturated fatty acids to saturated fatty acids (Reedy et al., 2018). Although the HEI-2015 includes seafood consumption, it does not differentiate between types of seafood (Kirkpatrick et al., 2018). The moderation components of the HEI-2015 scoring include refined grains, sodium, added sugars, saturated fats, and empty calories (Reedy et al., 2018).

Numerical scoring for the HEI is based on the sum of scores of each component, including both adequacy and moderation components; the maximum total HEI score is 100, and the minimum is zero (Kirkpatrick et al., 2018). Each of the HEI components has a maximum score of 10 points; however, if components include subcomponents, the subcomponents have a maximum score of 5 points (Table 1.) (Kirkpatrick et al., 2018). After the addition of each component HEI score, the total score indicates the overall diet quality of that individual, with a

better overall diet scoring closer to 100 and a poor overall diet scoring closer to zero (Kirkpatrick et al., 2018; Reedy et al., 2018). Researchers can estimate amounts of particular nutrients consumed, such as folate, from the score of leafy green vegetables.

The HEI has been used previously for a prospective cohort study that examined post-cancer diagnosis mortality in post-menopausal women with breast cancer (George et al., 2014). Participants were given food frequency questionnaires in order to determine the statistical significance of dietary patterns according to the HEI-2005 (George et al., 2014). From this, it was found that a better post-cancer diagnosis diet was associated with a reduction in cancer death (George et al., 2014). The findings from this study support previous findings that diet quality post-cancer diagnosis is extremely important when attempting to reduce breast cancer relapse. The study also demonstrated use of the HEI for preventative measures within the healthcare field.

Combined Effects of BPA and Dietary Fat on Breast Cancer Risk and Recurrence:

There are significant interactions between epigenetics, nutrition, and the development of cancers (Bishop et al., 2015). The pathophysiology of all types of cancers is synergistic with risk factors such as the environment, an individual's lifestyle, genetic predisposition, and the epigenome (i.e., the cellular environment above the level of the gene) (Bishop et al., 2015). The mechanisms that control these epigenetic modifications are known to involve both dietary factors (e.g., saturated fat intake) (Table 2.) and environmental exposures (e.g., BPA). Epigenetic modifications can occur in utero or throughout life, making diet, lifestyle, and environment crucial components to health (Bishop et al., 2015). The most common epigenetic modification with respect to all cancers, including breast cancer, is the genomic methylation pattern (Bishop et

al., 2015). Portions of DNA sequences that are subject to either hyper or hypo-methylation are more commonly seen in the intergenic and promoter regions (Bishop et al., 2015). Hypermethylated regions of a DNA sequence can serve as a protective barrier to the gene expression and thus effectively silencing specific genes (Bishop et al., 2015). In breast cancer however, these areas of the DNA sequence are hypomethylated and readily available to be transcribed and expressed, thus promoting tumor progression (Bishop et al., 2015). High concentrations of dietary BPA, saturated fat, as well as added sugars are thought to increase the hypomethylation of specific genes. Thus, these factors are potential promoters of tumorgenesis. Research has shown that a good overall diet quality includes the consumption of dark green vegetables and high folate concentrations (Chen et al., 2014; CDC 2020). The consumption of folate decreases cancer risk, including breast cancer, because it plays a role in hypermethylating the same regions of DNA that promote tumorgenesis (Chen et al., 2014; CDC, 2020).

The European Prospective Investigation into Cancer and Nutrition (EPIC) was a prospective cohort study to determine the relationship between dietary folate/folic acid and breast cancer risk (Batlle et al., 2015). The study found a significant inverse association between dietary folate and breast cancer ($p = 0.037$) in a cohort of 11575 women within postmenopausal range (35 to 70 years) diagnosed with breast cancer (Battle et al., 2015). The conclusion was that dietary folate decreased breast cancer risk through the hypermethylation of DNA.

The current study is specifically focused on the presence of BPA and saturated fat intake in the diets of breast cancer survivors. It is common for diets in the United States (western diet) to contain high levels of processed and fast foods (e.g., fast-foot hamburgers and soda) and therefore have a lower HEI-2015 score. These foods typically contain high levels of BPA from exposure to packaging, as well as containing a high saturated fat content (Almeida et al. 2018,

Castello & NIH, 2018). High intakes of BPA (a fat soluble molecule) and saturated fat are associated with altered fat metabolism and an increase in adipose tissue; subsequently increasing the storage of BPA in the adipose tissue (Do et al., 2017). In women, this gain in adipose tissue often occurs within the mammary tissue, predisposing them to an increase in the genomic mechanisms leading to tumor progression.

Even if individuals attempt to consume healthier fats and less processed foods (e.g., the Mediterranean Diet), there is still a likelihood of ingesting BPA due to bioaccumulation through the food chain, specifically in marine foods. High concentrations of healthy fats, such as omega-3 polyunsaturated fatty acids, are associated with a decrease in breast cancer risk. Unfortunately, recent research has shown that there are also high concentrations of BPA within these foods due to pollution from plastics (Bishop et al. 2015, Environmental Health Perspectives 2015). Canned fish, such as tuna, have been shown to contain particularly high levels of BPA (e.g., 106 ng/g; Almeida et al., 2018). Trace quantities of BPA have been found in all bodies of water across the globe (Environmental Health Perspectives, 2015). BPA contamination potentially increases in severity from the high rate of pollution from environmental micro-plastics. Micro-plastics are absorbed and metabolized by sea life, undergoing increasing concentration up through the food chain. Eventually, the accumulated micro-plastic concentration ends up in the human diet through the consumption of fish and other kinds of seafood (Zhou et al., 2018; Environmental Health Perspectives, 2015).

Socioeconomic and Related Risk Factors:

Many cancers are diagnosed more often in one particular race or ethnicity than others. Breast cancer conforms to this pattern. The CDC states that as of 2016, per 100,000 women

worldwide, breast cancer was more commonly found in white and black women than other demographics (CDC, 2020). This difference between groups is due to differences in genetics, environmental exposures due to the locations in which these particular demographics are predominantly found, and other factors that lead to increase risk in this cancer (CDC, 2020).

Studies have shown that BPA is present in measurable concentrations in the tap water of several different areas in the United States. Although tap water tends to have a lower in BPA concentration than that of fish and seafood, it is important to include tap water consumption as a potential confounding variable in the analysis of associations between BPA and cancer (Arnold et al., 2013).

Alcohol consumption is also a well-known risk factor for many cancers. Several studies have shown that the more alcohol consumed, the higher the risk of breast cancer (CDC, 2020). This is due to 1) alcohol's interface in folate absorption across the intestinal enterocytes and 2) renal conservation of folate in the individual consuming the alcohol (Wani et al., 2013). Alcohol ingestion also appears to counteract the effect of folate on DNA methylation patterns. Alcohol causes hypomethylation patterns allowing for tumor expression genes to be transcribed, increasing tumorgenesis in the breast tissue (Wani et al., 2013).

Finally, education level also plays a part in increasing or decreasing the risk of disease. Research has shown that there is a direct dose-response association between women's education level and post-menopausal breast cancer risk (Heck, 1997). Similar to education level, family income poverty ratio may also affect breast cancer risk and recurrence. The reason for this not only stems from reduced access to breast cancer education but also reduced availability to make doctors visits or take rehabilitative action in decreasing risk or recurrence (Schootman et al., 2008).

Using NHANES Data to Examine the Relationships between BPA, HEI, Dietary Fat, and Breast Cancer Survivorship:

Prior analysis of HEI scores derived from NHANES data has shown that in general, post-cancer diagnosis diets higher in saturated fat and low in unsaturated fat are associated with increased cancer mortality (Deskmukh et al., 2018). An independent analysis of HEI scores showed an inverse relationship with the risk of breast cancer death, specifically (George et al., 2014). The current study seeks to elaborate on earlier studies by including a BPA biomarker in the analysis. This study used data from postmenopausal women from the years of 2003-2014, who have had a previous diagnosis of cancer to explore links between the HEI scores, current levels of inflammatory biomarkers, and levels of urinary BPA excretion. We compared these trends to dietary patterns and urinary BPA levels found in age-matched women who have never had a diagnosis of cancer. We expected to see significant differences in HEI scores between cancer survivors and women who have never had a cancer diagnosis. We also predicted that cancer survivorship, as estimated by time elapsed following a cancer diagnosis, will correlate with higher HEI scores and lower levels of BPA excretion and inflammatory biomarkers. Our analysis used data from the National Health and Nutrition Examination Survey (NHANES).

2. Manuscript

A. Introduction

Previous research has shown that some dietary patterns increase the risk of breast cancer whereas others, such s dietary patterns similar to the Mediterranean Diet, tend to decrease cancer risk. Specifically, high dietary saturated fat intake has been shown to have a significant increase to the risk of death both before and following breast cancer diagnosis and increase the risk to the

onset of breast cancer and cancer recurrence (Beasley et al. 2011, Jochems et al. 2018). The aim of this study was to use NHANES data from survey cycles between 2003-2014 to examine associations between urinary BPA levels, saturated fat intake, and dietary quality in women with either a diagnosis of breast cancer or women with a post-cancer diagnosis. The study population included women in the United States who have never been diagnosed with breast cancer, those diagnosed less than five years since the completion of the NHANES survey, and those diagnosed more than five years from the completion of the NHANES survey.

B. METHODS

Study Design and Participants

The NHANES survey program is a widely used program for the National Center for Health Statistics (NCHS), which is a part of the CDC and provides health statistics for the U.S. (NCHS, 2018). NHANES data permit a measure of both the exposure to dietary factors and a given biomarker outcome at one point in time, showing a potential correlation. Using the interview and examination components of this survey, health professionals can study a representative sample of the U.S. (NCHS, 2018). Each year, a sample of about 5000 participants in counties across the country are used for this survey (NCHS, 2018). The interview component of this survey includes questions regarding demographics, socioeconomic status, dietary habits, and health-related issues whereas the examination component includes laboratory tests, medical, dental, and physiological measurements conducted by medical professionals (NCHS, 2018).

Dietary and biomarker data from the United States NHANES data cycles between 2003-2014 were used to test two hypotheses: 1) that current urinary BPA levels and a past breast cancer diagnosis are correlated, and 2) that dietary patterns (e.g., higher polyunsaturated &

monounsaturated fat intake, higher HEI score) and breast cancer survivorship are correlated. The study is retrospective in design, although the data were cross-sectional. The NHANES 2003-2014 cycles were explicitly chosen because they include all variables required for testing the proposed hypotheses and can be scored using the HEI. The dependent/outcome variable for both hypotheses were breast cancer diagnosis and the independent/exposure variables included urinary BPA, dietary fat intake, and HEI scores.

Subjects Selection and Inclusion Criteria:

Screening of 10 years of available NHANES data resulted in the identification of 100 cases of breast cancer in women over the age of 30 years old. The survey asked when breast cancer was diagnosed in terms of the age of the individual. Because of the way in which the survey question was formatted, several of these cases had a breast cancer diagnosis of a missing value (.) (NHANES, 2019). For this study, those cases were classified as a component of the control/never diagnosed with breast cancer study group. Using the total pool of women over 30 who had never been diagnosed with breast cancer, including those with a missing value, between 2003 and 2014, a subsample of 100 control cases were selected using a random number generator (https://www.randomizer.org). These groups were used for initial comparisons between women diagnosed with cancer and those never diagnosed (the control group) and to identify confounding variables through correlation analysis. Additional analyses examined dietary differences between women diagnosed less than five years before the time of the survey (n=39) and more than five years prior to the survey (n=61).

Measures

Breast Cancer Diagnosis:

The CDC collected breast cancer diagnosis through the NHANES survey from 2003 to 2014 and reported this as a variable label code MCQ240E, within the medical conditions section (CDC, 2018). This section provides self-reported personal data that was provided through an interview process including a broad range of medical conditions (CDC, 2018). Breast cancer diagnosis was given at the age in which the individual was first diagnosed (CDC, 2018), allowing for more straightforward data collection for the use of individuals aged 30 years or older. The data were recorded under codes with value descriptions along with the number of participants who answered with specific responses.

Urinary BPA Levels:

Urinary BPA levels (URXBPH) were reported in ng/mL in the NHANES database (CDC, 2018). Urinary levels of any substance are usually indicative of spillover, meaning the individual has consumed large quantities of this substance so the body excretes the excess. Thus, having large quantities of BPA within the urine would be indicative of excessive quantities of BPA within the body.

The CDC uses urinary levels of environmental toxicants to determine its occurrence in humans (CDC, 2018). BPA levels within the urine are measured by using biological matrixes within gas chromatography or high-performance liquid chromatography (CDC, 2018). Urine samples were processed, stored, and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) to ensure high-quality. At the center, the samples were stored at -20 degrees Celsius (CDC).

Dietary Assessment:

Values for average energy intake, saturated fat intake, and polyunsaturated fat intake were determined for each subject from two day-dietary recalls; these then became the basis for the HEI calculation. The USDA's MyPyramid Equivalents Database for USDA survey foods allows researchers to locate foods and food groups that are in equal amounts and patterns to determine diet quality through the HEI scores (USDA, 2017, National Cancer Institute HEI, 2015). The HEI accounts for the following food groups: total vegetables, green beans, total fruit, whole fruit, whole grains, dairy, total protein foods, seafood and plant proteins, the ratio of fatty acids (saturated and poly/mono unsaturated), sodium, refined grains, saturated fats, added sugars (NIH, 2019). These are then expressed as numbers of cups, ounces, teaspoons, and/or grams following the interview component of the dietary recall within the NHANES survey (Table 1.).

Data files of the HEI individual food groups and nutrients for each subsequent year of NHANES were downloaded using the SAS/STAT® version 9.4 software program. SAS codes were used to calculate HEI-205 scores (NIH, NCI, 2019) for each individual. The main food groups of focus for this study were seafood and plant proteins, fatty acids, saturated fats, and alcohol. Seafood and plant proteins were chosen as a focus due to similarity to the large quantity of poly and monounsaturated fats found in a Mediterranean diet. However, it was also of focus due to the potential for increased BPA contamination from bioaccumulation and pollution (Zhou et al. 2018, Environmental Health Perspectives, 2015). The fatty acid component of the HEI-2015 was of relevance and interest because it allowed for a better understanding of how the fatty acid ratio between saturated and unsaturated fats, affects breast cancer and BPA levels (National Cancer Institute HEI, 2015). The HEI-2015 score was matched to the sequence number assigned to the subject through NHANES to further statistical analysis (SAS, 2016).

Statistical Analysis:

Descriptive statistics of demographic variables were used to determine frequencies and averages for each study group. All variables were tested for normality before further analysis. Data that were not normally distributed according to the Kolmogorov-Smirnov test of normality were log-transformed as appropriate or were analyzed using non-parametric analyses. This included measurements of urinary BPA for both the control group, $D(100) = 0.324$, $p = 0.00$ and those diagnosed with breast cancer $D(100) = 0.408$, $p = 0.00$. Correlation matrixes generated through SPSS were used to determine pairs of variables with the highest correlations within the study (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corp.). Logistic and multiple linear regression models, ANOVA, and ANCOVA were used to examine the association of breast cancer diagnosis as a function of urinary BPA levels, dietary components, total HEI scores, and HEI dietary components within three diagnosis groups of never diagnosed, diagnosed less than five years since survey, and diagnosed more than five years since the survey.

Urinary BPA levels were normalized by each subject's BMI to account for body size/fat. Research has shown that adipose tissue has a high affinity for BPA hence, high storage capacity (NIH Endocrine Disruptors, 2019). In conjunction with this, the presence of BPA in the urine is indicative of BPA spillover when adipose storage, including mammary tissue, has reached its limit (NIH Endocrine Disruptors, 2019). Normalizing BPA levels with respect to BMI accounts for the fact that BPA levels are likely higher in people with more body fat, thereby removing the effect of body size as a variable. Although BPA normalized by adiposity would have been more appropriate for this analysis, the NHANES data do not include information on body composition; BMI was therefore used as a surrogate measure for adiposity.

Potential confounding variables were identified from a review of the literature, including race/ethnicity (Mexican American, Other Hispanic, non-Hispanic white, non-Hispanic black), educational level (<9th grade, 9-11, high school/GED, bachelors/associates, > college), family income poverty ratio, BMI (continuous in kg/m^2), fish consumption, tap water consumption, alcohol use, refined grains, and added sugars. Several of these variables were excluded from the final analysis after verifying that no significant interaction or correlation existed.

C. RESULTS

Demographics:

Women over the age of 30 who had never been diagnosed with breast cancer (n=100) were used as a control group to be compoared to women over the age of 30 who had been diagnosed with breast cancer (n=100). To examine the effects of dietary BPA on post-cancer diagnosis survivorship, breast cancer survivors were further divided into two groups: one of less than five years since diagnosis (n=39) and one of more than five years since diagnosis (n=61).

The mean (±SD) age in years for each analysis groupings was 54 (15) for the control group, 65 (11) <5 years post-diagnosis, and 70 (11) >5 years post-diagnosis. The dominant race for all groups was non-Hispanic White (55%). The highest education level completed for each group was high school diploma (26%) for the control group, high school diploma and associates degree (33.3%, 33.3%) for <5 years post-diagnosis, and associates degree for >5 years post-diagnosis (24.7%). For the study group including subjects with less than five years since diagnosis, the average (±SD) number of years since diagnosis was 3 (1.52). The average number of years since diagnosis for subjects greater than five years since diagnosis was found to be 14 (7.48) years (Tables 3, 4, and 5.). Average BMI for the control group was found to be 31 (8.40). The average

BMI for <5 years post-diagnosis was found to be 30 (6.0) whereas it was 28.8 (5.90) for the >5 years post-diagnosis group.

Correlations:

All variables were initially tested for potential correlations using Pearson's rho. Many of the potential confounding demographic variables had no significant relationship with urinary BPA levels or breast cancer diagnosis. The exception was BMI, which was negatively correlated with age at which breast cancer was first diagnosed ($r = -0.27$, $p = 0.01$); therefore, as the number of years since diagnosis increased, BMI tended to decrease. Insignificant variables were excluded from further analysis, including those of race/ethnicity, education level, family income poverty ratio, fish and tap water consumption, and alcohol use.

Several components of the HEI-2015 were significantly and positively correlated with one another (Table 6). The HEI fatty acid ratios of saturated to unsaturated, and saturated fat intake of the subjects were positively correlated with urinary BPA ($r = 0.20$, $p = 0.01$; $r = -0.16$, $p = 0.03$ respectively) (Table 6.). Added sugars were not significantly correlated with urinary BPA ($r = 0.05$, $p= 0.52$), but were significantly correlated with saturated fat intake ($p < 0.05$) (Table 6.).

Can Breast Cancer Presence/Absence be Predicted from HEI-2015 Components and Urinary BPA:

Logistic regression analysis was used to test whether cancer presence or absence could be predicted from dietary components of fatty acid ratios, refined grains, percent calories of added sugars, and the presence of urinary BPA based on the correlations matrix results and background

research. The full model containing all predictors was not statistically significant, X^2 (4, N=179) = 0.32, p<0.05. Cancer presence/absence could not be predicted from these factors; the model only explained 2% of the variance observed in breast cancer presence/absence along with no significant odds ratios (Table 8.).

Are There Differences In Urinary BPA/BMI, PUFAs, and HEI-2015 Among the Three Study Groups:

One-way ANOVA's and post-hoc means separation tests were used to detect differences in urinary BPA normalized by BMI levels (BPA/BMI), PUFAs, and HEI-2015 among the three diagnostic groups. Mean BPA/BMI levels were 3.69 (7.77) ng/ml in the never diagnosed group, 4.95 (13.77) ng/ml in women diagnosed with breast cancer less than 5 years ago, and 3.44 (10.152) ng/ml in women more than 5 years from diagnosis. Mean dietary PUFA levels were 16.24 (8.95) g in the never diagnosed group, 14.01 (8.45) g in women diagnosed with breast cancer less than 5 years ago, and 13.98 (9.23) ng/ml in women more than 5 years from diagnosis. Out of a scale of 100, average HEI scores for each group were found to be 55.96 (13.62) in never diagnosed, 56.58 (12.98) in women diagnosed with breast cancer less than 5 years ago, and 58.81 (13.41) in women more than 5 years from diagnosis.

There were no statistically significant differences between the less than five years since diagnosis groups and the control group for any variable (BPA/BMI F(2,94)=2.78, p=0.06; PUFA F(2,96)=2.937, p=0.058; and HEI-2015 F(2,197)=1.881, p=0.155). Urinary BPA/BMI and PUFAs differed between the more than five years since diagnosis group and the control group (post-hoc LSD, p = 0.02 and p = 0.02, respectively; Table 9A-10B.). HEI-2015 scores among the

three groups within the greater than five years since diagnosis were not statistically significant (p= 0.06; Table 9C).

D. DISCUSSION

BMI, Saturated Fat Intake, and Breast Cancer Survival:

Researchers have found that the amount of fat consumed and type of fat consumed post-cancer diagnosis influences cancer recurrence and survivorship (Jochems et al., 2018; Toledo et al., 2015, Castello et al., 2017); this could explain the trends observed in the current study. Subjects who survived more than five years after initial cancer diagnosis tended to have a lower BMI than those with a more recent cancer diagnosis (less than 5 years). Women who were more than five years past the point of diagnosis also had significantly lower saturated fat intake and compared to the control group or those with a more recent diagnosis. The observation that BMI and dietary saturated fat decrease with time from initial cancer diagnosis conforms to a pattern of healthier lifestyle choices, in keeping with research that has shown that a healthier quality of life can decrease breast cancer occurrence and recurrence (Karimi et al., 2014).

Fatty Acid Ratio, Urinary BPA, Inflammatory Response, & Breast Cancer Survival:

Xu et al. (2010) used methods similar to this study to analyze NHANES survey cycles from 1999-2004 for associations between serum concentrations of organochloride pesticides. Organochloride pesticide exposure may have a significant effect on cancer risk as they function as endocrine disruptors (Xu et al., 2010) in a manner similar to BPA. We had, therefore, anticipated results similar to that of Xu et al. (2010). Our study, however, was inconclusive. This is not without precedent. In 2009, Yang et al. found borderline significant associations between BPA and breast cancer risk. The sample size of that study, however, was too small (N=167) to

detect a significant relationship (Yang et al., 2009). Yang et al. 's (2009) findings highlight the necessity of obtaining a sufficiently large sample size for adequate statistical power. Although the current study analyzed data that cover a 10 year period, we were only able to identify 100 breast cancer survivors of an appropriate age to meet the analysis criteria. Our results are very similar to Yang's 2009 work, suggesting that small sample size likely contributed to many of the borderline significant observations we report here.

The current study normalized BPA levels by BMI to further explore the data set and account for adiposity. This uncovered subtle statistical significant differences amongst the three diagnostic groups, with breast cancer survivors of more than five years showing slightly lower urinary BPA levels. The normalization of urinary BPA levels by BMI is supported by prior research on the environmental toxicant and its effects on BMI and obesity (Wang et al., 2012, CDC, NIH). Normalization by body mass or composition accounts for the fact that BPA levels are likely to be higher in people with more body fat; thus removing a confounding variable in the analysis. The fact that the group diagnosed with breast cancer more than five years prior had lower urinary BPA levels seems to align with prior research showing dietary modifications reduce cancer relapse, potentially through diet-induced epigenetic mechanisms (Jahhav et al., 207; Song et al., 2017; Beasley et al., 2011; Bishop et al., 2015). Individuals who have been diagnosed with cancer appeared to conform to healthier dietary patterns, possibly in the hope of decreasing the chances of cancer recurrence. In contrast, individuals who have never been diagnosed with cancer tended to have higher normalized urinary BPA levels. The lower HEI scores and higher BPA levels suggest that in the absence of cancer diagnosis, these individuals had less motivation to alter their dietary habits.

Despite the small sample size of our study, we were still able to detect a significant positive correlation between the ratio of saturated to unsaturated fats and urinary BPA. The HEI saturated fat component score showed an inverse relationship with urinary BPA. This component score is on an inverse scale, with a lower score reflecting a higher consumption of saturated fat. Thus, it supports the conclusion that increased saturated fat in the diet correlates with increases in urinary BPA excretion. This is a potentially meaningful result in that prior research using animal models has shown links between high-fat diets, BPA exposure and risk of cancer (Facina et al., 2017).

High-fat diets and BPA are both risk factors for breast cancer (Zota et al. 2016, Toledo et al. 2015). Both factors operate by altering homeostatic mechanisms at a genomic level, potentially in utero, creating a genetic blueprint for a child's adult life. However, it is also possible that these altered homeostatic mechanisms could be synergistic with each other, potentially enhancing their individual activity levels. For example, a 2017 study sought to determine whether maternal exposure to BPA and a high-fat diet intake during pregnancy can further influence breast cancer risk in the offspring of female rats (Leung et al., 2017). DNA methylation and gene expression of several genes, one being in the same gene family as the previously mentioned ALDH1A3 (ALDH1B1) gene, has been shown to enhance tumor survival in mice with breast cancer more than BPA or fat alone (Leung et al., 2017).

Similar genomic mechanisms could also explain the way in which dietary saturated fat increases estrogen production in older women, leading to an increase in adipocyte formation and an increased number of estrogen receptors (Nagata et al., 2005). Free-floating BPA in the system would then have a higher likelihood of binding to the increased number of receptors due to

structural similarities with estrogen, thus contributing to increased breast cancer risk in post- or perimenopausal females.

Although saturated fat intake was significantly correlated with an increase in urinary BPA in this study, individual linear regressions showed no significant result within the three study groups. When added sugars, a common synergist for cancer diagnosis, were added to the multiple regression model, the model moved to borderline significance; this suggests that fatty acid ratios are only one component of the relationship between BPA and breast cancer. There is some precedent for this result; prior research suggests that BPA and added dietary sugars interact with one another to cause regulatory problems at a molecular, cellular, and inflammatory level, potentially leading to cancers (Branco et al., 2014). These interactions may be part of a complex interaction between added sugars, BPA, saturated fats, and other unhealthy dietary factors that give rise to breast cancer through an increased risk of chronic inflammation through the NF-kB pathway. Inflammation can be linked to the hypomethylation of DNA regions that control the increase in transcription and expression of tumor progressive genes (Nelms et al., 2010). The overall increase in the PUFAs and HEI score seen in the greater than five years from diagnosis group potentially increased the concentration of dietary micronutrients such as folate. The increase in micronutrients might inhibit the NF-kB inflammatory response and aid in the hypermethylation of specific regions of DNA (Nelms et al., 2010).

High BPA concentrations are also often associated with high levels of salt and added sugar in the diet (Almeida et al., 2018). This can also be due to the high salt and sugar content in processed foods, which would increase exposure to BPA contamination through processing and packaging. The current analysis would, therefore, have been stronger if the proportion of the diet obtained from canned, bottled, and processed foods had been considered as opposed to just the

macro and micronutrient ratios. For example, a 2016 study conducted with NHANES data found a positive correlation between fast food and processed food intakes and urinary BPA levels (Zota et al., 2016).

If the current study had also considered sources of foods in the diet, such as the amount of macronutrients consumed from canned foods and bottled drinks, it might have revealed additional relationships through regression analysis. Because BPA is one of the most common industrial chemicals used in canned linings, bottles, and even conveyor belts used to process and package foods, we assume that the levels would be substantially higher in individuals who consume a significant quantity of these foods. A 2016 study supports this supposition. Tzatzarakis et al. (2016) used liquid chromatography-mass spectrometry to quantify the BPA in canned food and bottled soft drinks. Mean BPA levels in the canned foods and soft drinks were 33.4 ± 4.4 ng/g and 2.30 ± 0.18 ng/ml, respectively (Tzatzarakis et al., 2016). If we had been able to identify foods consumed from canned and bottled foods, we may have observed stronger and more statistically significant relationships in this study.

Other factors that may have limited the results of this analysis include the relatively small sample population and the way that the CDC collected dietary intake for the NHANES survey. Quantitative dietary intake measurements such as food-frequency questionnaires can return imprecise measurements, which is problematic when trying looking for relationships between fat intake and cancer prevalence (Bingham et al., 2003).

Although the results presented here are inconclusive, previous studies suggest that registered dietitians working with or making dietary recommendations for cancer patients and/or patients in remission should still consider the effects of dietary BPA. The presence of BPA in conjunction with a high-fat diet seems to amplify the pathophysiological mechanisms of cancer.

A decrease in the consumption of canned/bottled foods potentially containing BPA should, therefore, be recommended to reduce the risk of breast cancer. In addition, a decrease in saturated fat intake and an increase in polyunsaturated fat intake may be helpful in decreasing cancer occurrence in breast cancer patients. In conclusion, a diet more similar to the Mediterranean diet should be considered to extend post-cancer diagnosis survivorship and reduce cancer risk, including increased consumption of more whole, fresh foods and vegetables, oils, and fish (Beasley et al., 2011).

Future Directions:

The results from this study highlight the importance of specific dietary components in reducing the risk of breast cancer. This work could be expanded by looking at whether increased polyunsaturated fatty acid intake can suppress the effect of ingested BPA. Clarifying that interaction might provide a better understanding of one of the epigenetic mechanisms behind breast cancer. Also, adding the proportion of diet obtained from canned, bottled, processed foods, fast foods and different methodologies to measure fat intake and BPA levels could significantly aid in a better understanding of this topic (Zota et al., 2016). Rather than normalizing BPA with BMI, a better measurement would be to account for each subject's fat mass versus lean mass. This would allow for a more accurate analysis of the amount of adipose tissue within the body, potentially correlating with increased BPA assimilation by adipose linked estrogen receptors. Finally, a better statistical analysis of added sugars in the diet would allow for a greater understanding of how the insulin and inflammatory response increases specific inflammatory pathways leading to the expression of genes that increase tumor progression.

Strengths and Limitations:

Although there were limited statistically significant results in this study, it was still beneficial for determining indicators of BPA in the human diet. Use of the NHANES database allowed for access to ample amounts of data obtained through a rigorous and validated survey. The study, however, would have benefitted from the inclusion of more dietary components from prepackaged convenience, fast foods, and types of seafood.

Other limitations to this study include the study design and its time constraint. Although this was a cross-sectional study, it was analyzed as a retrospective study for statistical purposes. Using secondary data that were not collected for the specific study aims was a limitation. If it were possible to obtain a larger sample size, greater than 200 subjects in total, there might have been greater statistical significance, specifically in the comparison of HEI scores between the control and two diagnosis groups. Lastly, this study design forced the assumption of previous exposures to good/bad diet and BPA in all subjects.

E. CONCLUSIONS

This study found evidence that urinary BPA levels are associated with saturated fat intake. The study also showed a trend for lower BPA levels and higher dietary polyunsaturated fat intake in cancer survivors more than 5 years post-cancer diagnosis. It could be inferred from these trends that women modify their diet and fat intake levels post-cancer diagnosis. The study did not, however, find links between overall diet quality, saturated fat, or urinary BPA levels and a prior cancer diagnosis. That does not mean endocrine disruptors have no role in the development of cancer. Diet, lifestyle, and environmental factors all have potential to alter DNA methylation and gene expression patterns, resulting in negative health outcomes. The next step in

this research should be an examination into the relationships between plastic packaging, canned foods, and processed foods on urinary BPA levels and the prevalence of breast cancer.

3. Illustrative Materials

Tables:

Table 1. HEI-205 Component & Scoring Standards (Table adapted from the USDA HEI-2015 Scoring Standard, 2020).

Component	Maximum Points	Standard for Maximum Score	Standard for Minimum Score of Zero
Adequacy:			
Total Fruits[1]	5	≥0.8 cup equivalent per 1,000 kcal	No Fruit
Whole Fruits[2]	5	≥0.4 cup equivalent per 1,000 kcal	No Whole Fruit
Total Vegetables[3]	5	≥1.1 cup equivalent per 1,000 kcal	No Vegetables
Greens and Beans[3]	5	≥0.2 cup equivalent per 1,000 kcal	No Dark-Green Vegetables or Legumes
Whole Grains	10	≥1.5 ounce equivalent per 1,000 kcal	No Whole Grains
Dairy[4]	10	≥1.3 cup equivalent per 1,000 kcal	No Dairy
Total Protein Foods[3]	5	≥2.5 ounce equivalent per 1,000 kcal	No Protein Foods
Seafood and Plant Proteins[3,5]	5	≥0.8 ounce equivalent per 1,000 kcal	No Seafood or Plant Proteins
Fatty Acids[6]	10	(PUFAs + MUFAs) / SFAs ≥2.5	(PUFAs + MUFAs) / SFAs ≤1.2
Moderation:			
Refined Grains	10	≤1.8 ounce equivalent per 1,000 kcal	≥4.3 ounce equivalent per 1,000 kcal
Sodium	10	≤1.1 grams per 1,000 kcal	≥2.0 grams per 1,000 kcal
Added Sugars	10	≤6.5% of energy	≥26% of energy
Saturated Fats	10	≤8% of energy	≥16% of energy

[1] Includes 100% fruit juices.
[2] Includes all forms EXCEPT juices.
[3] Includes legumes (beans and peas)
[4] Includes milk products, such as fluid milk, yogurt, cheese, and fortified soy beverages
[5] Includes seafood; nuts, seeds, soy products (other than beverages), and legumes (beans and peas).
[6] Ratio of poly- and mono-unsaturated fatty acids (PUFAs and MUFAs) to saturated fatty acids (SFAs).

Table 2. Epigenetic & Anti-Breast Cancer Effects of Nutrients (Table adapted from Bishop et al., 2015)

Nutrient/Food Component	Source	Epigenetic Effect	Anti-Breast Cancer Effect
Omega 3-EPA & DHA	Fish Oil	Methylation of COX2 in breast cancer cell lines linked to gene silencing; maternal intake of polyunsaturated fatty acids influences epigenetic regulation of FADS in offspring	Fish oil increases apoptosis during tumor initiation acting through COX2 pathway; lower levels of COX2
Trans Fat/Saturated Fat	Processed foods	DNA hypomethylation in brains of offspring; histone modifications; hypomethylation at SacII in ER gene	Associated with risk of invasive breast cancer

Table 3. Demographics of the Never Diagnosed with Breast Cancer Group

Demographic	N (%)
Age:	
30-39	20 (20)
40-49	19 (19)
50-59	22 (22)
60-69	23 (23)
70-79	11 (11)
>80	5 (5)
Race/Ethnicity:	
Mexican American	12 (12)
Other Hispanic	5 (5)
Non-Hispanic White	55 (55)
Non-Hispanic Black	23 (23)
Other (Including Multi-Racial)	5 (5)
Education:	
Less Than 9th Grade	8 (8)
9-11th/No Diploma	16 (16)
High School/GED	26 (26)
Associated	25 (25)
Bachelor's & Above	25 (25)

Table 4. Demographics of the Less Than Five Years Since Diagnosis Breast Cancer Group

Demographic	N (%)
Age:	
30-39	0 (0)
40-49	5 (13)
50-59	6 (15)
60-69	13 (33)
70-79	10 (26)
>80	5 (13)
Race/Ethnicity:	
Mexican American	7 (18)
Other Hispanic	1 (3)
Non-Hispanic White	21 (54)
Non-Hispanic Black	9 (23)
Other (Including Multi-Racial)	1 (3)
Education:	
Less Than 9th Grade	3 (7)
9-11th/No Diploma	3 (7)
High School/GED	13 (33)
Associated	13 (33)
Bachelor's & Above	7 (18)

Table 5. Demographics of the Greater Than Five Years Since Diagnosis Group

Demographic	N (%)
Age:	
30-39	0 (0)
40-49	1 (2)
50-59	9 (15)
60-69	19 (31)
70-79	16 (26)
>80	16 (26)
Race/Ethnicity:	
Mexican American	3 (5)
Other Hispanic	6 (10)
Non-Hispanic White	41 (67)
Non-Hispanic Black	9 (15)
Other (Including Multi-Racial)	2 (3)
Education:	
Less Than 9th Grade	11 (18)
9-11th/No Diploma	11 (18)
High School/GED	12 (20)
Associated	15 (25)
Bachelor's & Above	12 (20)

Table 6. Correlations matrix for urinary BPA & HEI Scores. Significant values in bold; n=200

Correlations

		KCAL	Urinary Bisphenol A (ng/mL)	Sodium	Saturated Fat	MUFA	Refined Grains	Added Sugars	Fatty Acid Ratio	Sodium per 1000 g	HEI Sodium Score	Refined Grains per 1000g	HEI Refined Grains Score	HEI SFA Score	HEI Score for Empty Calories, Including Alcohol	Percent calories added sugar	HEI Sugar Score	Total HEI	Age when breast cancer first diagnosed	Body Mass Index (kg/m**2)
KCAL	Pearson Correlation	1	-0.045	.780**	.795**	.886**	.580**	.454**	0.129	-0.057	0.089	-0.056	0.057	.147*	-0.126	0.041	-0.026	0.037	0.092	0.024
	Sig. (2-tailed)		0.526	0.000	0.000	0.000	0.000	0.000	0.064	0.419	0.209	0.424	0.050	0.075	0.586	0.730	0.601	0.360	0.737
Urinary Bisphenol A (ng/mL)	Pearson Correlation		1	-0.058	-0.120	-0.039	-0.047	-0.053	.200**	-0.080	0.064	-0.004	0.040	-.158*	0.072	-0.042	0.048	0.110	0.143	-0.048
	Sig. (2-tailed)			0.444	0.110	0.608	0.533	0.482	0.007	0.288	0.370	0.963	0.578	0.034	0.313	0.578	0.520	0.120	0.157	0.504
Sodium	Pearson Correlation			1	.612**	.678**	.526**	.190*	0.129	.545**	-.472**	0.007	-0.036	0.105	-0.085	-0.135	0.145	-0.071	0.054	0.024
	Sig. (2-tailed)				0.000	0.000	0.000	0.011	0.065	0.000	0.000	0.925	0.631	0.162	0.258	0.072	0.052	0.345	0.609	0.755
Saturated Fat	Pearson Correlation				1	.740**	.482**	.351**	-.262**	-0.058	0.057	-0.045	0.009	.688**	-.660**	0.015	-0.015	-.293**	0.052	0.123
	Sig. (2-tailed)					0.000	0.000	0.000	0.000	0.440	0.372	0.554	0.904	0.000	0.000	0.846	0.843	0.000	0.624	0.102
MUFA	Pearson Correlation					1	.453**	.259**	.386**	-0.028	0.011	-0.089	0.088	.219**	-.191*	-0.109	0.117	0.057	0.023	0.055
	Sig. (2-tailed)						0.000	0.000	0.000	0.713	0.879	0.235	0.240	0.003	0.011	0.147	0.119	0.446	0.826	0.469
Refined Grains	Pearson Correlation						1	0.129	-0.006	0.045	-0.037	.710**	-.705**	0.086	-0.067	-0.125	0.114	-.273**	0.146	0.043
	Sig. (2-tailed)							0.084	0.934	0.548	0.624	0.000	0.000	0.251	0.370	0.084	0.127	0.000	0.165	0.565
Added Sugars	Pearson Correlation							1	-0.143	-.273**	.294**	-.172*	.172*	0.044	-0.018	.878**	-.850**	-.334**	0.031	0.137
	Sig. (2-tailed)								0.057	0.000	0.000	0.021	0.022	0.558	0.816	0.000	0.000	0.000	0.769	0.068
Fatty Acid Ratio	Pearson Correlation								1	0.055	-0.086	-0.053	0.092	-.594**	.590**	-.226**	.227**	.481**	-0.048	-0.084
	Sig. (2-tailed)									0.461	0.258	0.480	0.219	0.000	0.000	0.002	0.002	0.000	0.648	0.264
Sodium per 1000 grams food	Pearson Correlation									1	-.911**	0.042	-0.124	-0.024	0.012	-.266**	.255**	-.169*	-0.097	0.021
	Sig. (2-tailed)										0.000	0.577	0.099	0.748	0.876	0.000	0.001	0.024	0.360	0.761
HEI Sodium Score	Pearson Correlation										1	-0.024	.143*	0.008	-0.022	.273**	-.275**	.209**	0.152	-0.092
	Sig. (2-tailed)											0.749	0.043	0.917	0.759	0.000	0.000	0.003	0.132	0.198
Refined Grains per 1000 grams Food	Pearson Correlation											1	-.888**	-0.078	0.070	-.187*	.152*	-.300**	0.025	0.047
	Sig. (2-tailed)												0.000	0.302	0.352	0.012	0.042	0.000	0.811	0.530
HEI Refined Grains Score	Pearson Correlation												1	-0.003	-0.059	.156*	-0.134	.404**	-0.063	-0.078
	Sig. (2-tailed)													0.965	0.406	0.037	0.075	0.000	0.532	0.276
HEI SFA Score	Pearson Correlation													1	-.969**	-0.011	0.009	-.517**	-0.036	0.132
	Sig. (2-tailed)														0.000	0.881	0.907	0.000	0.734	0.078
HEI Score for total Empty Calories Including Alcohol	Pearson Correlation														1	0.035	-0.025	.413**	0.018	-0.014
	Sig. (2-tailed)															0.642	0.742	0.000	0.860	0.839
Percent of calories that were added sugar	Pearson Correlation															1	-.971**	-.409**	-0.038	0.132
	Sig. (2-tailed)																0.000	0.000	0.717	0.078
HEI Sugar Score	Pearson Correlation																1	.429**	0.038	-0.127
	Sig. (2-tailed)																	0.000	0.722	0.092
Total HEI Score	Pearson Correlation																	1	0.028	.203**
	Sig. (2-tailed)																		0.782	0.004
Age when breast cancer first diagnosed	Pearson Correlation																		1	.260**
	Sig. (2-tailed)																			0.009
Body Mass Index (kg/m**2)	Pearson Correlation																			1
	Sig. (2-tailed)																			

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
c. Cannot be computed because at least one of the variables is constant.

Table 7. Multiple Linear Regression to test whether urinary BPA and components from the HEI-2015 fatty acid ratio explain breast cancer prevalence in non-white and white women.

	Sum of Squares	df	Mean Square	F	p-value
Non-White Women	3.7	4	0.92	1.18	0.33
Non-Hispanic White Women	0.43	4	0.11	0.23	0.98

Table 8. Logistic regression to test whether breast cancer presence/absence could be predicted from dietary components of fatty acid ratios, refined grains, percent calories from added sugars and the presence of urinary BPA (N=179).

	B	S.E.	Wald	df	p-value	X^2
Fatty Acid Ratios	-0.02	0.27	0.01	1	0.94	
Refined Grains	0.06	0.12	0.28	1	0.59	
% Calories Sugars	0.00	0.02	0.04	1	0.84	
Urinary BPA	0.00	0.02	0.00	1	0.97	0.32

Table 9. One-way ANOVA with LSD method of means separation to determine the differences among the study groups (never diagnosed/control, <5 years, and >5 years).

9A. ANOVA & LSD Urinary BPA normalized by BMI (BPA/BMI)

ANOVA

BPA/BMI

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.606	2	.303	2.786	.067
Within Groups	10.231	94	.109		
Total	10.837	96			

	Mean Difference	Std. Error	p-value	95% Confidence Interval (CI)
<5 Years	0.04	0.82	0.60	-0.12 to 0.21
>5 Years	0.18	0.82	0.02*	0.02 to 0.34

9B. Polyunsaturated Fatty Acids (PUFAs)

ANOVA

PUFA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	468.141	2	234.071	2.937	.058
Within Groups	7650.606	96	79.694		
Total	8118.747	98			

	Mean Difference	Std. Error	p-value	95% Confidence Interval (CI)
<5 Years	-4.0	2.20	0.07	-8.33 to 0.39
>5 Years	-5.1	2.20	0.02*	-9.42 to -0.70

* Represents statistically significant finding

9C. HEI-2015.

ANOVA

HEI

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	672.560	2	336.280	1.881	.155
Within Groups	35219.496	197	178.779		
Total	35892.056	199			

	Mean Difference	Std. Error	p-value	95% Confidence Interval (CI)
<5 Years	1.61	2.39	0.50	-3.10 to 6.32
>5 Years	5.49	2.87	0.057	-0.16 to 11.15

Figures:

Figure 1. Structures of Estradiol vs. Bisphenol A

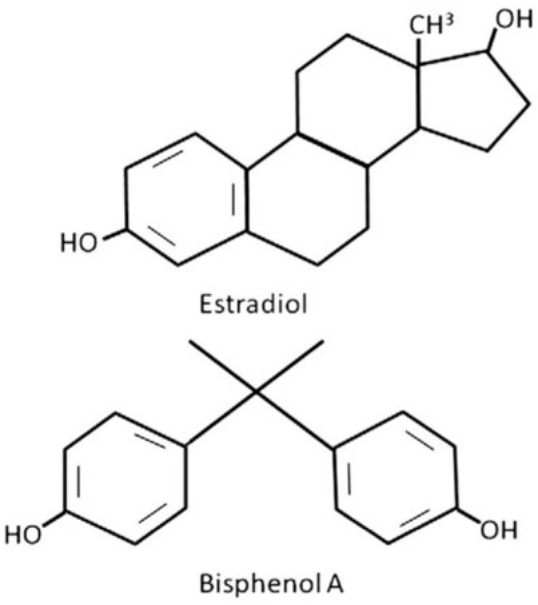


Figure 2. NF-kB Canonical Pathway (Figure adapted from Park et al., 2016)

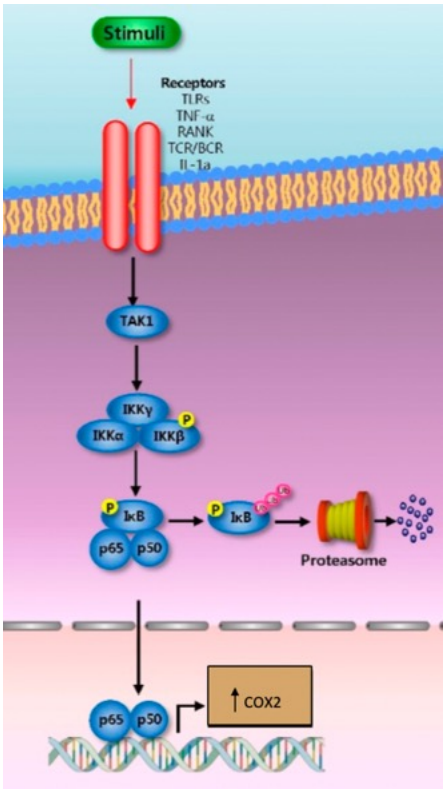
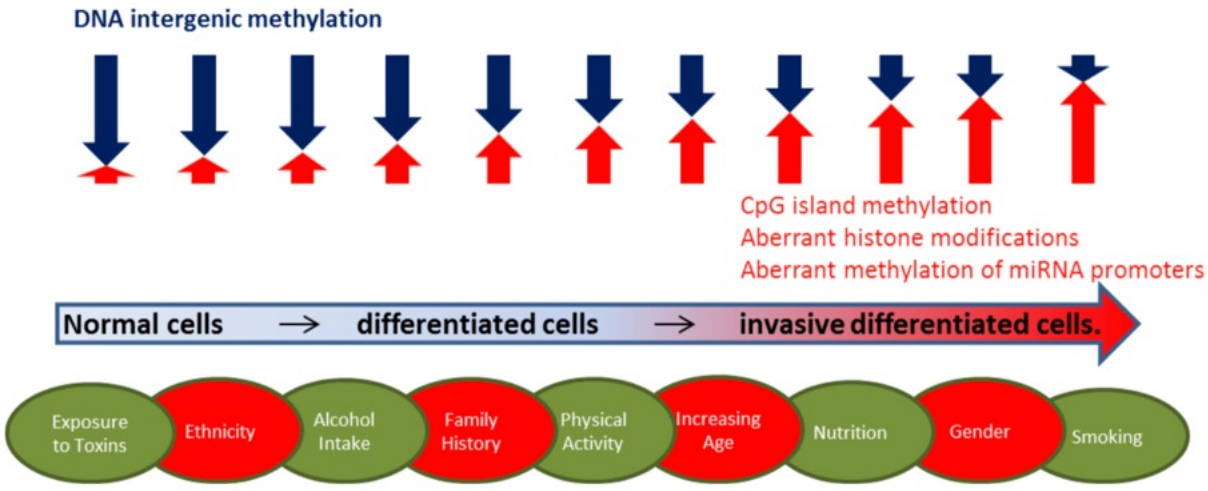


Figure 3. Epigenetic Modifications Causing an Increase to Cancer Risk (Figure adapted from Bishop et al., 2015).



4. Appendices

Logistic Regression on Cancer Presence Based on Dietary Components

Notes

Resources	Processor Time	00:00:00.05
	Elapsed Time	00:00:00.09

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	179	89.5
	Missing Cases	21	10.5
	Total	200	100.0
Unselected Cases		0	.0
Total		200	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
.00	0
1.00	1

Block 0: Beginning Block

Classification Table[a,b]

			Predicted		
			Y_N_CANCER		Percentage Correct
	Observed		.00	1.00	
Step 0	Y_N_CANCER	.00	0	87	.0
		1.00	0	92	100.0
	Overall Percentage				51.4

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	.056	.150	.140	1	.709	1.057

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	UR_BPA	.000	1	.991
		FATTYACID_RATIO	.022	1	.882
		REFINED_GRAINS1000	.263	1	.608
		PERCENT_CALORIES_ADDED_SUGAR	.015	1	.904
	Overall Statistics		.318	4	.989

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	.319	4	.989
	Block	.319	4	.989
	Model	.319	4	.989

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	247.688[a]	.002	.002

a. Estimation terminated at iteration number 3 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			Y_N_CANCER		Percentage Correct
	Observed		.00	1.00	
Step 1	Y_N_CANCER	.00	23	64	26.4
		1.00	21	71	77.2
	Overall Percentage				52.5

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.
Step 1[a]	UR_BPA	.001	.015	.001	1	.971
	FATTYACID_RATIO	-.020	.267	.006	1	.939
	REFINED_GRAINS1000	.064	.120	.284	1	.594
	PERCENT_CALORIES_ADDED_SUGAR	.004	.021	.039	1	.844
	Constant	-.128	.757	.028	1	.866

Variables in the Equation

		Exp(B)
Step 1[a]	UR_BPA	1.001
	FATTYACID_RATIO	.980
	REFINED_GRAINS1000	1.066
	PERCENT_CALORIES_ADDED_SUGAR	1.004
	Constant	.880

a. Variable(s) entered on step 1: UR_BPA, FATTYACID_RATIO, REFINED_GRAINS1000, PERCENT_CALORIES_ADDED_SUGAR.

T-Test Looking at Cancer Prevalence Between Ethnic Groups (White & Non-White)

Group Statistics

	Y_N_CANCER	N	Mean	Std. Deviation	Std. Error Mean
UR_BPA	.00	100	3.74	7.772	.777
	1.00	100	4.06	12.135	1.214
Race/Ethnicity - Recode	.00	100	3.04	.984	.098
	1.00	100	2.97	.881	.088

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of .
		F	Sig.	t
UR_BPA	Equal variances assumed	.217	.642	-.222
	Equal variances not assumed			-.222
Race/Ethnicity - Recode	Equal variances assumed	1.106	.294	.530
	Equal variances not assumed			.530

Independent Samples Test

		t-test for Equality of Means		
		df	Sig. (2-tailed)	Mean Difference
UR_BPA	Equal variances assumed	198	.824	-.320
	Equal variances not assumed	168.511	.825	-.320
Race/Ethnicity - Recode	Equal variances assumed	198	.597	.070
	Equal variances not assumed	195.651	.597	.070

Independent Samples Test

		t-test for Equality of Means		
		Std. Error Difference	95% Confidence Interval of the Difference	
			Lower	Upper
UR_BPA	Equal variances assumed	1.441	-3.162	2.522
	Equal variances not assumed	1.441	-3.165	2.525
Race/Ethnicity - Recode	Equal variances assumed	.132	-.190	.330
	Equal variances not assumed	.132	-.191	.331

One-Way ANOVA Looking at Difference in BPA, Fatty Acid, or Cancer Prevalence Between Ethnic Groups

ANOVA

		Sum of Squares	df	Mean Square	F
UR_BPA	Between Groups	148.664	4	37.166	.355
	Within Groups	20415.336	195	104.694	
	Total	20564.000	199		
FATTYACID_RATIO	Between Groups	.290	4	.073	.204
	Within Groups	61.844	174	.355	
	Total	62.134	178		
Y_N_CANCER	Between Groups	.511	4	.128	.503
	Within Groups	49.489	195	.254	
	Total	50.000	199		

ANOVA

		Sig.
UR_BPA	Between Groups	.840
	Within Groups	
	Total	
FATTYACID_RATIO	Between Groups	.936
	Within Groups	
	Total	
Y_N_CANCER	Between Groups	.733
	Within Groups	
	Total	

ANOVA

		Sum of Squares	df	Mean Square	F
UR_BPA	Between Groups	.002	1	.002	.000
	Within Groups	20563.998	198	103.859	
	Total	20564.000	199		
FATTYACID_RATIO	Between Groups	.192	1	.192	.550
	Within Groups	61.942	177	.350	
	Total	62.134	178		
Y_N_CANCER	Between Groups	.252	1	.252	1.004
	Within Groups	49.748	198	.251	
	Total	50.000	199		

ANOVA

		Sig.
UR_BPA	Between Groups	.997
	Within Groups	
	Total	
FATTYACID_RATIO	Between Groups	.459
	Within Groups	
	Total	
Y_N_CANCER	Between Groups	.318
	Within Groups	
	Total	

Multiple Regression Looking at BPA and Dietary Components to Explain Prevalence of Cancer in Non-White Women

Variables Entered/Removed[a,b]

Model	Variables Entered	Variables Removed	Method
1	UR_BPA, ADD_SUGARS, FATTYACID_RATIO, REFINED_GRAINS1000[c]	.	Enter

a. Dependent Variable: CANCER

b. Models are based only on cases for which WHITEOTHER = 1.00

c. All requested variables entered.

Model Summary

Model	R WHITEOTHER = 1.00 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.253[a]	.064	.010	.882

a. Predictors: (Constant), UR_BPA, ADD_SUGARS, FATTYACID_RATIO, REFINED_GRAINS1000

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	3.670	4	.917	1.179	.328[c]
	Residual	53.682	69	.778		
	Total	57.351	73			

a. Dependent Variable: CANCER

b. Selecting only cases for which WHITEOTHER = 1.00

c. Predictors: (Constant), UR_BPA, ADD_SUGARS, FATTYACID_RATIO, REFINED_GRAINS1000

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	2.263	.551		4.104	.000
	FATTYACID_RATIO	-.130	.194	-.081	-.673	.503
	ADD_SUGARS	-.011	.006	-.221	-1.750	.085
	REFINED_GRAINS1000	.031	.074	.052	.416	.679
	UR_BPA	-.005	.011	-.060	-.511	.611

a. Dependent Variable: CANCER

b. Selecting only cases for which WHITEOTHER = 1.00

Variables Entered/Removed[a,b]

Model	Variables Entered	Variables Removed	Method
1	UR_BPA, ADD_SUGARS, REFINED_GRAINS1000, FATTYACID_RATIO[c]	.	Enter

a. Dependent Variable: CANCER

b. Models are based only on cases for which WHITEOTHER = 2.00

c. All requested variables entered.

Model Summary

Model	R WHITEOTHER = 2.00 (Selected)	R Square	Adjusted R Square	Std. Error of the Estimate
1	.069[a]	.005	-.035	.948

a. Predictors: (Constant), UR_BPA, ADD_SUGARS, REFINED_GRAINS1000, FATTYACID_RATIO

ANOVA[a,b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.426	4	.106	.119	.976[c]
	Residual	89.803	100	.898		
	Total	90.229	104			

a. Dependent Variable: CANCER

b. Selecting only cases for which WHITEOTHER = 2.00

c. Predictors: (Constant), UR_BPA, ADD_SUGARS, REFINED_GRAINS1000, FATTYACID_RATIO

Coefficients[a,b]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	1.766	.418		4.227	.000
	FATTYACID_RATIO	.074	.157	.049	.470	.639
	ADD_SUGARS	.002	.005	.047	.469	.640
	REFINED_GRAINS1000	-.021	.088	-.024	-.242	.809
	UR_BPA	-.001	.009	-.007	-.067	.947

a. Dependent Variable: CANCER

b. Selecting only cases for which WHITEOTHER = 2.00

T-Test with Post Hoc Means of Separation (1=Nonwhite 2=White)

Group Statistics

	WHITEOTHER	N	Mean	Std. Deviation	Std. Error Mean
Y_N_CANCER	1.00	83	.4578	.50125	.05502
	2.00	117	.5299	.50125	.04634
UR_BPA	1.00	83	3.90	9.316	1.023
	2.00	117	3.90	10.767	.995
FATTYACID_RATIO	1.00	74	1.98	.551	.064
	2.00	105	1.91	.618	.060

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means	
		F	Sig.	t	df
Y_N_CANCER	Equal variances assumed	.120	.730	-1.002	198
	Equal variances not assumed			-1.002	176.736
UR_BPA	Equal variances assumed	.130	.719	.004	198
	Equal variances not assumed			.004	190.260
FATTYACID_RATIO	Equal variances assumed	1.157	.284	.741	177
	Equal variances not assumed			.756	167.491

Independent Samples Test

		t-test for Equality of Means		
		Sig. (2-tailed)	Mean Difference	Std. Error Difference
Y_N_CANCER	Equal variances assumed	.318	-.07208	.07193
	Equal variances not assumed	.318	-.07208	.07193
UR_BPA	Equal variances assumed	.997	.006	1.463
	Equal variances not assumed	.997	.006	1.427
FATTYACID_RATIO	Equal variances assumed	.459	.067	.090
	Equal variances not assumed	.450	.067	.088

Independent Samples Test

		t-test for Equality of Means	
		95% Confidence Interval of the Difference	
		Lower	Upper
Y_N_CANCER	Equal variances assumed	-.21394	.06977
	Equal variances not assumed	-.21404	.06988
UR_BPA	Equal variances assumed	-2.878	2.890
	Equal variances not assumed	-2.809	2.821
FATTYACID_RATIO	Equal variances assumed	-.111	.244
	Equal variances not assumed	-.107	.240

Means & Standard Deviations For Variables & Dietary Components (1=Nonwhite; 2=White)

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
UR_BPA * WHITEOTHER	200	100.0%	0	0.0%	200	100.0%
AGE_SINCE_DIA * WHITEOTHER	200	100.0%	0	0.0%	200	100.0%
G_REFINED * WHITEOTHER	179	89.5%	21	10.5%	200	100.0%
SFAT * WHITEOTHER	179	89.5%	21	10.5%	200	100.0%
FATTYACID_RATIO * WHITEOTHER	179	89.5%	21	10.5%	200	100.0%
PERCENT_CALORIES_ADDED_SUGAR * WHITEOTHER	179	89.5%	21	10.5%	200	100.0%

Report

WHITEOTHER		UR_BPA	AGE_SINCE_DIA	G_REFINED	SFAT	FATTYACID_RATIO
1.00	Mean	3.90	3.96	9.26	38.36	1.98
	N	83	83	74	74	74
	Std. Deviation	9.316	6.581	4.735	18.303	.551
2.00	Mean	3.90	5.33	8.70	42.46	1.91
	N	117	117	105	105	105
	Std. Deviation	10.767	7.904	4.732	17.088	.618
Total	Mean	3.90	4.77	8.93	40.77	1.94
	N	200	200	179	179	179
	Std. Deviation	10.165	7.397	4.728	17.666	.591

Report

WHITEOTHER		PERCENT_CALORIES_ADDED_SUGAR
1.00	Mean	11.77
	N	74
	Std. Deviation	7.437
2.00	Mean	11.80
	N	105
	Std. Deviation	7.640
Total	Mean	11.78
	N	179
	Std. Deviation	7.536

ANOVA

BPA/BMI

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.606	2	.303	2.786	.067
Within Groups	10.231	94	.109		
Total	10.837	96			

Contrast Coefficients

1=N,2=under 5, 3=over 5

Contrast	1.00	2.00	3.00
1	1	.5	.5
2	1	.5	.5

Contrast Tests

		Contrast	Value of Contrast	Std. Error	t	df
BPA/BMI	Assume equal variances	1	.1510[a]	.07071	2.135	94
		2	.1510[a]	.07071	2.135	94
	Does not assume equal variances	1	.1510[a]	.04933	3.060	33.173
		2	.1510[a]	.04933	3.060	33.173

Contrast Tests

		Contrast	Sig. (2-tailed)
BPA/BMI	Assume equal variances	1	.035
		2	.035
	Does not assume equal variances	1	.004
		2	.004

a. The sum of the contrast coefficients is not zero.

Multiple Comparisons

Dependent Variable: BPA/BMI

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	Mean Difference (I-J)	Std. Error
Tukey HSD	1.00	2.00	-.04315	.08252
		3.00	-.18365	.08122
	2.00	1.00	.04315	.08252
		3.00	-.14050	.08252
	3.00	1.00	.18365	.08122
		2.00	.14050	.08252
LSD	1.00	2.00	-.04315	.08252
		3.00	-.18365*	.08122
	2.00	1.00	.04315	.08252
		3.00	-.14050	.08252
	3.00	1.00	.18365*	.08122
		2.00	.14050	.08252

Multiple Comparisons

Dependent Variable: BPA/BMI

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	Sig.	95% ... Lower Bound
Tukey HSD	1.00	2.00	.860	-.2397
		3.00	.066	-.3771
	2.00	1.00	.860	-.1534
		3.00	.210	-.3370
	3.00	1.00	.066	-.0098
		2.00	.210	-.0560
LSD	1.00	2.00	.602	-.2070
		3.00	.026	-.3449
	2.00	1.00	.602	-.1207
		3.00	.092	-.3043
	3.00	1.00	.026	.0224
		2.00	.092	-.0233

Multiple Comparisons

Dependent Variable: BPA/BMI

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	95% Confidence . Upper Bound
Tukey HSD	1.00	2.00	.1534
		3.00	.0098
	2.00	1.00	.2397
		3.00	.0560
	3.00	1.00	.3771
		2.00	.3370
LSD	1.00	2.00	.1207
		3.00	-.0224
	2.00	1.00	.2070
		3.00	.0233
	3.00	1.00	.3449
		2.00	.3043

*. The mean difference is significant at the 0.05 level.

Homogeneous Subsets

BPA/BMI

	1=N,2=under 5, 3=over 5	N	Subset for alpha = 0.05 1
Tukey HSD[a,b]	1.00	33	.0188
	2.00	31	.0619
	3.00	33	.2024
	Sig.		.070

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 32.305.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

ANOVA

PUFA

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	468.141	2	234.071	2.937	.058
Within Groups	7650.606	96	79.694		
Total	8118.747	98			

Contrast Coefficients

1=N,2=under 5, 3=over 5

Contrast	1.00	2.00	3.00
1	1	.5	.5
2	1	.5	.5

Contrast Tests

		Contrast	Value of Contrast	Std. Error	t	df
PUFA	Assume equal variances	1	31.6061[a]	1.90327	16.606	96
		2	31.6061[a]	1.90327	16.606	96
	Does not assume equal variances	1	31.6061[a]	2.03870	15.503	53.517
		2	31.6061[a]	2.03870	15.503	53.517

Contrast Tests

		Contrast	Sig. (2-tailed)
PUFA	Assume equal variances	1	.000
		2	.000
	Does not assume equal variances	1	.000
		2	.000

a. The sum of the contrast coefficients is not zero.

Multiple Comparisons

Dependent Variable: PUFA

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	Mean Difference (I-J)	Std. Error
Tukey HSD	1.00	2.00	3.96970	2.19771
		3.00	5.06061	2.19771
	2.00	1.00	-3.96970	2.19771
		3.00	1.09091	2.19771
	3.00	1.00	-5.06061	2.19771
		2.00	-1.09091	2.19771
LSD	1.00	2.00	3.96970	2.19771
		3.00	5.06061*	2.19771
	2.00	1.00	-3.96970	2.19771
		3.00	1.09091	2.19771
	3.00	1.00	-5.06061*	2.19771
		2.00	-1.09091	2.19771

Multiple Comparisons

Dependent Variable: PUFA

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	Sig.	95% ... Lower Bound
Tukey HSD	1.00	2.00	.173	-1.2622
		3.00	.060	-.1713
	2.00	1.00	.173	-9.2016
		3.00	.873	-4.1410
	3.00	1.00	.060	-10.2925
		2.00	.873	-6.3228
LSD	1.00	2.00	.074	-.3927
		3.00	.023	.6982
	2.00	1.00	.074	-8.3321
		3.00	.621	-3.2715
	3.00	1.00	.023	-9.4230
		2.00	.621	-5.4533

Multiple Comparisons

Dependent Variable: PUFA

	(I) 1=N,2=under 5, 3=over 5	(J) 1=N,2=under 5, 3=over 5	95% Confidence . Upper Bound
Tukey HSD	1.00	2.00	9.2016
		3.00	10.2925
	2.00	1.00	1.2622
		3.00	6.3228
	3.00	1.00	.1713
		2.00	4.1410
LSD	1.00	2.00	8.3321
		3.00	9.4230
	2.00	1.00	.3927
		3.00	5.4533
	3.00	1.00	-.6982
		2.00	3.2715

*. The mean difference is significant at the 0.05 level.

Homogeneous Subsets

PUFA

	1=N,2=under 5, 3=over 5	N	Subset for alpha = 0.05 1
Tukey HSD[a]	3.00	33	13.0000
	2.00	33	14.0909
	1.00	33	18.0606
	Sig.		.060

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 33.000.

ANOVA

HEI

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	672.560	2	336.280	1.881	.155
Within Groups	35219.496	197	178.779		
Total	35892.056	199			

Contrast Coefficients

N=1, under5=2, >5=3

Contrast	1.00	2.00	3.00
1	1	.5	.5

Contrast Tests

		Contrast	Value of Contrast	Std. Error	t	df
HEI	Assume equal variances	1	115.25[a]	2.038	56.553	197
	Does not assume equal variances	1	115.25[a]	1.965	58.660	127.855

Contrast Tests

		Contrast	Sig. (2-tailed)
HEI	Assume equal variances	1	.000
	Does not assume equal variances	1	.000

a. The sum of the contrast coefficients is not zero.

Multiple Comparisons

Dependent Variable: HEI

	(I) N=1, under5=2, >5=3	(J) N=1, under5=2, >5=3	Mean Difference (I-J)	Std. Error	Sig.
Tukey HSD	1.00	2.00	-5.492	2.867	.137
		3.00	-1.611	2.388	.779
	2.00	1.00	5.492	2.867	.137
		3.00	3.881	3.352	.480
	3.00	1.00	1.611	2.388	.779
		2.00	-3.881	3.352	.480
LSD	1.00	2.00	-5.492	2.867	.057
		3.00	-1.611	2.388	.501
	2.00	1.00	5.492	2.867	.057
		3.00	3.881	3.352	.248
	3.00	1.00	1.611	2.388	.501
		2.00	-3.881	3.352	.248

Multiple Comparisons

Dependent Variable: HEI

			95% Confidence Interval	
	(I) N=1, under5=2, >5=3	(J) N=1, under5=2, >5=3	Lower Bound	Upper Bound
Tukey HSD	1.00	2.00	-12.26	1.28
		3.00	-7.25	4.03
	2.00	1.00	-1.28	12.26
		3.00	-4.04	11.80
	3.00	1.00	-4.03	7.25
		2.00	-11.80	4.04
LSD	1.00	2.00	-11.15	.16
		3.00	-6.32	3.10
	2.00	1.00	-.16	11.15
		3.00	-2.73	10.49
	3.00	1.00	-3.10	6.32
		2.00	-10.49	2.73

HEI

	N=1, under5=2, >5=3	N	Subset for alpha = 0.05 1
Tukey HSD[a,b]	1.00	133	55.85
	3.00	41	57.46
	2.00	26	61.34
	Sig.		.142

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 42.631.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
HEI * N=1, under5=2, >5=3	200	100.0%	0	0.0%	200	100.0%

Report

HEI

N=1, under5=2, >5=3	Mean	N	Std. Deviation
1.00	55.85	133	13.441
2.00	61.34	26	11.506
3.00	57.46	41	14.197
Total	56.90	200	13.430

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