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Association Between Dietary Phytoestrogen Intake and Xenoestrogen Exposure and Estrogen-Dependent Cancers

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Walden University

College of Health Sciences and Public Policy

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Pisita Bolsue

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Walden University
2023

Abstract

Association Between Dietary Phytoestrogen Intake and Xenoestrogen Exposure and Estrogen-Dependent Cancers

by

Pisita Bolsue

MA, Stevens Institute of Technology, 2005

BS, New York University, 2003

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2023

Abstract

The role of circulating estrogens and the impact of lifetime exposure to multiple sources of exogenous estrogens as factors in carcinogenesis were not well understood. Research showed conflicting results when dietary phytoestrogen (PE) intake and xenoestrogen (XE) exposure occurred independently and when co-exposed. The purpose of this quantitative cross-sectional study was to investigate the association between dietary PE intake and XE exposure and the development of estrogen-dependent cancers in an epidemiological context. The advanced model of the epidemiology triangle was the theoretical framework for the current study in which binary logistic regression was employed on secondary data from the 2003–2006 National Health and Nutrition Examination Survey. Results indicated that dietary PEs and XEs in combination were not statistically significant ($p > 0.05$) predictors of development of estrogen-dependent cancers for any level of soy, bean, or bottled drinking water consumption. Co-exposure to the highest levels of bean consumption ($aOR = 1.012$, 95% CI [0.378, 2.712], $p = 0.981$) and soy consumption ($aOR = 0.621$, 95% CI [0.108, 3.578], $p = 0.594$) with bottled drinking water exposure did not yield statistically significant results. The interaction between low PE urine and low phthalate urine levels ($aOR = 0.544$, 95% CI [0.290, 1.020], $p = 0.058$) was close to being statistically significant. The exposures do not seem to be major risk factors in this population. Findings may increase the understanding of dietary estrogen exposure pathways and raise awareness of modifiable behaviors.

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Dedication

To my dear husband, your unwavering belief in my abilities and your encouragement have been the guiding light throughout this academic pursuit. Your patience, understanding, and countless sacrifices to allow me to focus on my education have been nothing short of exceptional.

To my precious children, you have been the constant source of my inspiration and the reason I strive to be the best version of myself. You are the reasons I persevered through the long nights, the challenges, and the moments of self-doubt. It is with immeasurable love and heartfelt appreciation that I dedicate this dissertation to my family.

Acknowledgments

I extend my heartfelt gratitude to my dissertation committee chair, Dr. Lee Caplan, whose guidance, support, and expertise throughout this challenging academic journey have been unwavering. Your mentorship, insightful feedback, constructive criticism, and encouragement have continually motivated me to strive for excellence.

I am also immensely thankful to my committee member, Dr. Heba Tawfik, for her thoughtful reviews, valuable insights, and expert guidance. Her expertise has been instrumental in enriching the depth and quality of my research.

Finally, Mom and Dad, your support throughout my life has been the cornerstone of my achievements and the bedrock of my resilience. From the beginning, you nurtured my curiosity and instilled the importance of education and the pursuit of knowledge, all of which have been the driving force behind my academic journey. Thank you for all of your sacrifices and for encouraging me to embrace learning as a lifelong journey.

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Chapter 1: Introduction to the Study

The increasing global incidence of estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) and the morbidity and mortality associated with these cancers reflects a need for further exploration of the association between dietary phytoestrogen (PE) intake and xenoestrogen (XE) exposure and the development of estrogen-dependent cancers. This is an important first step in highlighting the significance of the public health problem and understanding the potential impact of diet on the risk of developing estrogen-dependent cancers. In the United States and around the world, cancer is ranked as the second leading cause of death (American Cancer Society, 2022; Centers for Disease Control and Prevention [CDC], 2020a), accounting for approximately 10 million global deaths among men and women in 2020 (World Health Organization, 2022). Worldwide, the economic burden of cancer in 2010 was estimated at $1.16 trillion based on 2010 data (Stewart & Wild, 2014). The economic cost of cancer mortality in the United States for 2020 was projected at $308 billion (Bradley et al., 2008).

Epidemiological and experimental data suggested that estrogen-dependent cancers could result from the accumulation of lifetime environmental exposure to endocrine-disrupting chemicals (EDCs) with estrogenic effects (Bilancio et al., 2017; Chung et al., 2010; Fénichel & Chevalier, 2019; Gray et al., 2017; Jafer et al., 2018; Soto et al., 1997; Watson et al., 2019). Exposure to endogenous (naturally occurring) estrogen in combination with exogenous (external) estrogens, where both PEs and XEs represent two dietary sources of environmental exposure, can activate different biological effects. The

effects of these sources of estrogen can be anti-estrogenic by blocking receptors and inhibiting or suppressing estrogen production, thereby preventing carcinogenesis (Basu & Maier, 2018; Y.-J. Chang et al., 2017). Conversely, PEs and XEs can also activate estrogenic properties that mimic human estrogen and contribute to carcinogenesis (Jafer et al., 2018). PEs containing high levels of isoflavones are a potential candidate responsible for the observed regional variation and decreased risk of estrogen-dependent cancers attributed to Asian and Mediterranean diets that are high in soy foods and lignans (Y.-J. Chang et al., 2017; Godos et al., 2017; Maskarinec et al., 2017; T. T. Zhao et al., 2019). XEs represent a potential culprit responsible for the observed presence of phthalates and other plasticizers leached from packaging materials and food contaminants (Aneck-Hahn et al., 2018; H. Li et al., 2019). However, the identification and quantification of these dietary sources of environmental risk factors, and their influence on estrogen-dependent cancers, remain elusive (California Breast Cancer Research Program, n.d.; National Institute of Environmental Health Sciences, 2023; Safe, 1997; Soto et al., 1997). Furthermore, the interaction between PEs and XEs and their relationship to estrogen-dependent cancer incidence has not been thoroughly recognized and is understudied, particularly epidemiologically.

The limited epidemiological, preclinical, and clinical studies have been inconsistent and inconclusive regarding the association between dietary intake of PEs and dietary XE exposure, and incidence of estrogen-dependent cancers. Diet is an essential route of lifetime EDC exposure and may play a role in the prevention of estrogen-dependent cancers. Currently, it is unclear which components of a diet are causative

agents for these effects. More research on this topic is needed to clarify this potential relationship between dietary intake of PEs and dietary exposure of XEs, and estrogen-dependent cancer risk. Results from such research could be used by public health practitioners to develop interventions aimed at reducing the risk of estrogen-dependent cancers, which would yield positive implications for social change.

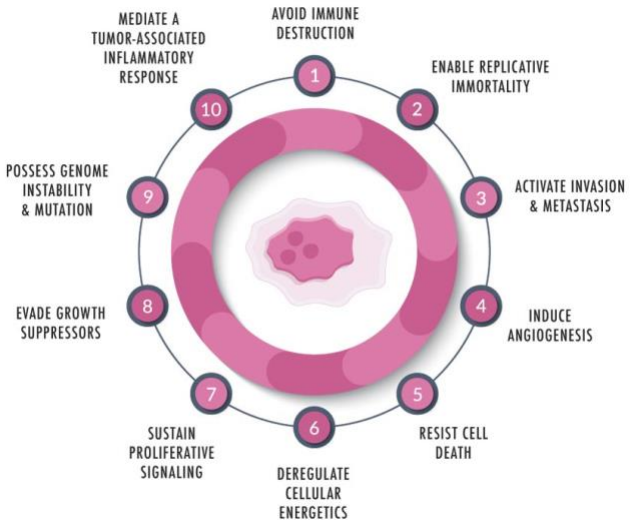
This chapter includes an overview of the key components of this study. The chapter provides the background, research problem, study purpose, and research questions and hypotheses. Additional aspects of the study design are presented in this chapter, which include the theoretical framework, nature of the study, definitions, underlying assumptions, scope and delimitations, limitations, and significance.

Background

Cancer is a disease characterized by abnormal disruption in the cell cycle that results in an uncontrolled growth of cells that divide without stopping and spread into nearby tissue (American Cancer Society, 2023; National Cancer Institute, 2021). Normally, cell cycle regulators signal cells to grow (proliferate) and divide (replicate) as needed by the body, with new cells replacing old or damaged cells that are programmed for cell death (apoptosis). In cancer, there is a loss of the mechanisms that maintain the balance of cells in one or more ways resulting in the promotion of cancer development through two key activities: (a) overactivation of positive regulators (oncogenes) or (b) inactivation of negative regulators (tumor suppressors; NCI, 2021.). These two activities trigger additional responses or nonresponses that result in the characteristic features of cancer cells. Typical features of cancer are presented in Figure 1.

Figure 1

10 Hallmarks of Cancer



Note. Adapted from Lansdowne (2018).

Estrogen plays a critical role in regulation of cell proliferation and apoptosis among hormone-dependent cancers, including breast, cervical, colorectal, endometrial, ovarian, and prostate cancers. Research indicated that either hyper or hypo levels of estrogen in the body, whether from endogenous or exogenous sources, are known to result in carcinogenicity, teratogenicity, and immunotoxicity due to the modulating effects of estrogen (Choi et al., 2004; Roy et al., 2007). Estrogen also plays a contributing role in the development of estrogen-dependent cancers.

The current study addressed PEs present in soy and bean products. For XEs, the study focused on phthalate plasticizers that leach from bottled drinking water. Estrogen exerts its effects via estrogen receptors α and β (ERα and ERβ, respectively), and ; research suggested that PEs are selective estrogen receptor modulators. Genistein is an isoflavone class of PEs that is commonly found in soy-based foods. Genistein structurally

mimics 17β-estradiol (E_2) and completes with E_2 for binding to estrogen receptors (Bronowicka-Kłys et al., 2016; Hwang et al., 2012). Because genistein has a greater binding affinity for ERβ than ERα, genistein is shown to have anti-estrogenic properties that modulate hormone receptors and metabolic pathways, thereby promoting cell death and playing a preventive role in cancer development (Mukund et al., 2017; Spagnuolo et al., 2015). Although the proposed underlying mechanisms for phthalates are not completely known, the literature suggested phthalates increase ERα activity stimulating cell proliferation and mutations leading to replication errors, which promote carcinogenic activity (Bronowicka-Kłys et al., 2016; H. H. Chen et al., 2018; Henderson et al., 1988; Yue et al., 2013).

Although cancer is a complex genetic disease, an overwhelming 90%–95% of cancer cases are due to genetic mutations that result from environmental and lifestyle factors, with only 5%–10% being due to inherited genetics (Anand et al., 2008). Furthermore, dietary factors accounted for 30%–50% of all cancers (Anand et al., 2008). To date, researchers focused on either the dietary PE intake or dietary XE exposure independently to assess their potential association with estrogen-dependent cancer risk. Limited research has been conducted that examined co-exposure to both dietary PEs and XEs in combination and the potential association with cancer (Hwang et al., 2012; Katchy et al., 2014; Yakimchuk et al., 2018). However, the findings from these in vitro and in vivo animal studies showed an inconsistent association between PE and XE exposure and the development of cancer (Bronowicka-Kłys et al., 2016; Hwang et al.,

2012; Jadhav et al., 2017; Katchy et al., 2014; Lee et al., 2018; Patisaul et al., 2012; J. Wang et al., 2014; Yakimchuk et al., 2018).

Conversely, no studies have addressed co-exposure with both dietary PEs and XEs in combination in human populations. In further consideration of the argument that dietary factors are a significant contributor to the development of cancers, it was reasonable to assume that findings from an epidemiological study, such as the current study, may elucidate the association between dietary PE intake and dietary XE exposure and estrogen-dependent cancer in humans. Hwang et al. (2012) reported on the association between genistein and ovarian cancer by showing that genistein was able to inhibit cell proliferation when exposed to E_2 or Bisphenol A (BPA). However, the findings of a study by Katchy et al. (2014) did not support this association; instead, Katchy et al. found a different effect, as genistein and BPA acted in an additive manner to exert magnified estrogenic effects and increase breast cancer risk. Therefore, it was important to further investigate within an epidemiological context whether diet was a significant route of exposure for exogenous estrogens, such as with soy and bean products intake and bottled drinking water consumption, and implications of whether dietary modifications can reduce estrogen-dependent cancer risk.

Problem Statement

Estrogen-dependent cancers, specifically breast, cervical, colorectal, endometrial, ovarian, and prostate cancers, make up a major portion of the world's cancer burden. Breast cancer is the most common cancer among women and comprises 18% of all female cancers, with one million new cases identified worldwide each year (American

Cancer Society, 2022; Cleveland Clinic, 2013; McPherson et al., 2000; Momenimovahed & Salehiniya, 2019). Prostate cancer is one of the leading causes of cancer death among men of all races and ethnicities (CDC, 2019b). Colorectal cancer is the third leading cause of cancer-related deaths in the United States, and the third most common cancer among both men and women (CDC, 2019a). Cancer can be a preventable disease that requires significant lifestyle and dietary habit changes (Anand et al., 2008; Harris et al., 2015; McKale & Aishwarya, 2019). To reduce the global burden of these estrogen-dependent cancers, it was necessary to analyze the potential factors that affect circulating estrogen levels to provide insight into modifiable lifestyle factors that can be used to reduce the risk of cancer.

According to Patel et al. (2018), there are a number of lifestyle factors that increase inflammation and elevate levels of aromatase, which increases estrogen production in the body. Research indicated that reduced blood levels of circulating estrogen can decrease the risk of cancer, particularly for hormone-receptor positive tumors (Basree et al., 2019; Giudice et al., 2019; Sorenmo et al., 2019; Yue et al., 2013). Dietary consumption of soy and bean products represents the primary route of PE exposure. Likewise, people are exposed to environmental XEs during food ingestion as a result of environmental contaminants or leaching of food packaging (Park et al., 2017; Safe, 1997; Schettler, 2006). This made diet the most common route of exposure to both PEs and XEs and a significant topic worthy of further investigation. However, the results of the in vivo and in vitro studies on the impact of PEs and XEs on cancer risk were inconsistent and inconclusive (Hwang et al., 2012; Katchy et al., 2014; J. Wang et al.,

2014; Yakimchuk et al., 2018). At the time of the current study, there were no epidemiological studies on the association between dietary PE intake and dietary XE exposure, and estrogen-dependent cancer among adults that could identify lifestyle and dietary habit changes to reduce cancer risk.

Given the abundance of bottled drinking water consumed in the United States and globally, the long-term impact of the accumulation of dietary XE exposure is alarming and may warrant a change in bottled water drinking habits. Similarly, aside from Asian and Mediterranean diets that contain high levels of isoflavones from soy foods and lignans from citrus fruit, Western diets lack substantial PE intake and the beneficial protective effects of PEs in reducing cancer risk. An epidemiological study that assessed the association between dietary PE intake and dietary XE exposure, and estrogen-dependent cancer was needed to fill this gap and better quantify the degree to which dietary PEs and XEs are factors in cancer risk.

Purpose of the Study

The purpose of this quantitative cross-sectional study was to assess the association between dietary PE intake and dietary XE exposure, and the development of estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adults age 18 years and older in the United States. The secondary data from the National Health and Nutrition Examination Survey (NHANES) were used to measure dietary PE intake, dietary XE exposure, and cancer status. The current study extended existing knowledge of potential nutritional benefits of PEs and dietary exposure risk of XEs for estrogen-dependent cancers. I aimed to fill gaps in the literature by

assessing the frequency of soy and bean product consumption and PE urine levels as measures of dietary PE intake. In addition, the frequency of bottled drinking water consumption and phthalate urine levels were used as measures of dietary XE exposure. Phthalates are not chemically bound to a polymer matrix (Jeddi et al., 2016; C. Lin et al., 2017). This characteristic of phthalates makes them easily released into food, water, or the surrounding environment directly and/or indirectly. Therefore, individuals who consume bottled drinking water are potentially exposed to small amounts of leaching plastics and phthalates with each drink. The current study assessed whether there was an association between dietary PE intake and dietary XE exposure and cancer using dietary intake data and laboratory analysis of urine samples from all participants in the 2003–2006 NHANES survey (see NHANES, n.d.). PE and phthalate urine levels were suitable proxies for assessing dietary PE intake and dietary XE exposure among participants in the study (see Rowland et al., 2003).

Research Questions

RQ1: Is there an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

> $H_0$1: There is no association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$1: There is an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ2: Is there an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$2: There is no association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$2: There is an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ3: Is there an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$3: There is no association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among

adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$3: There is an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ4: Is there an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$4: There is no association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$4: There is an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ5: Is there an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$5: There is no association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$5: There is an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

RQ6: Is there an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$6: There is no association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$6: There is an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

Theoretical Framework

The advanced model of the epidemiology triangle was the theoretical base for this study. The advanced model of the epidemiology triangle is an extension of the traditional epidemiologic triangle for infectious diseases (Merrill, 2013). The traditional triangle explains the cause of infectious disease by the factors (the agent, the host, and the environment) that contribute to outbreak (Machado & Bicalho, 2015). Similarly, the advanced model of the epidemiology triangle asserts that three factors work synergistically to influence the occurrence of disease over time, causative factors, environmental/behavioral factors, and the group or population and their characteristics, all of which are contributors over time to cancer diagnosis (Merrill, 2013). Causative factors are the known etiology of estrogen-dependent cancers, such as biological pathways. An individual's food choices and dietary behavior represented the components of environment/behavior. Finally, prior research (Basu & Maier, 2018; Darbre & Charles, 2010) indicated that the population and its characteristics, specifically race, gender, age, education, and socioeconomic status, influence dietary behavior. The research questions and associated variables of the current study aligned with the advanced model of the epidemiology triangle to facilitate this study's exploration of a potential association between dietary PE intake and dietary XE exposure, and estrogen-dependent cancer.

Nature of the Study

The nature of the current study was quantitative with cross-sectional data from the 2003-2006 NHANES data set used to identify individual factors from secondary data that may influence differences in dietary PEs and XEs in adults with and without estrogen-

dependent cancer diagnosis. A key objective of epidemiological research is identifying risk factors for disease and quantifying their significance (Ressing et al., 2010). For this reason, a quantitative research method was suitable for assessing differences in frequency of PE intake and XE exposure with the prevalence of estrogen-dependent cancer outcomes among groups. Furthermore, through the research questions asked, observational epidemiological data analysis could quantify effect measures, such as odds ratio (OR), from a population at a defined point in time (Center for Innovation in Research and Teaching, n.d.; Etikan et al., 2017; Ressing et al., 2010). Cross-sectional designs are often used for population-based surveys, especially for epidemiological studies (Setia, 2016). The quantitative cross-sectional design and analysis of nationally representative retrospective data from publicly available data sets was suitable for determining whether an association exists between an exposure and outcome, such as dietary PEs and XEs and cancer. This quantitative analysis helped me determine whether dietary PE intake in conjunction with dietary XE exposure played a role in the development of estrogen-dependent cancer.

Methodology

I used the NHANES data set to measure the effects of dietary PE intake and XE exposure on estrogen-dependent cancers among U.S. adults. To control for confounders, I assessed the associations between consumption of soy and bean products, bottled drinking water, and estrogen-dependent cancer risk. The NHANES data set used was a secondary data set that contained comprehensive data on the health and nutritional status of U.S. adults collected through interviews and physical examinations (CDC, 2020b). In

the current study, the independent variables were daily PE intake and daily XE exposure, phytoestrogen urine levels, phthalate urine levels, and interaction effect between the two independent variables, PEs and XEs; the dependent variable was estrogen-dependent cancer diagnosis or lack of diagnosis. Confounders that were controlled for included age, gender, race, education level, and marital status.

Statistical Procedures

Descriptive statistics of NHANES 2003-2006, including measures of central tendency (mean) and dispersion (minimum, maximum, and standard deviation), were provided for the continuous variable, age (see Marshall & Jonker, 2010). Frequency distribution tables reporting the number and percentage of occurrence were provided for all categorical variables to summarize demographic information, including gender, race, education level, marital status, income, and cancer type in the logistic regression (see Marshall & Jonker, 2010). I examined the continuous variables to determine whether they met assumptions for statistical analysis of normality, skewness, and kurtosis. I used logistic regression for inferential statistics to answer the research questions (Walden University**,** 2016). The statistical procedures used in the current study also included a power analysis for logistic regression using G*Power for sample size computation.

Definitions

Antagonistic effect: The effect produced by two (or more) chemical groups in combination that have contrasting actions (Chisamore et al., 2009). For example, the opposing actions of a drug that blocks or inhibits the stimulating effect of estrogen on a tumor cell would represent an antagonistic effect of the drug (NCI, 2021).

Bean products consumption: Consumption of dried beans such as baked beans, black-eyed peas, lentils, and lima, kidney, pinto, and refried beans or soybeans, excluding bean soups or chili (NHANES, n.d.). The measurement of the frequency of bean products consumed during the past 12 months by participants in the 2003-2006 NHANES was defined by frequency in times per day, per week, per month, and per year. The responses were obtained from two 24-hour dietary recalls. An average of the values obtained from each 24-hour dietary recall was used to provide an estimate of bean product consumption for participants in this study.

Bottled drinking water consumption: The measurement of dietary intake of bottled drinking water consumed during the 24-hour period prior to the interview (midnight to midnight) by participants in the 2003-2006 NHANES in grams (NHANES, n.d.). The responses were obtained from two 24-hour dietary recalls. An average of the values obtained from each 24-hour dietary recall was used to indicate typical bottled drinking water consumption for participants in this study.

Breast cancer: Cancer that develops in breast tissue. Ductal carcinoma, breast cancer that starts in the lining of the milk ducts, is the most common form of breast cancer (NCI, 2021).

Cancer: A complex disease defined by an abnormal division of cells that proliferate out of control that can invade adjacent and distant tissue and organs (NCI, 2021).

Cervical cancer: Cancer that develops in the cells lining the cervix, the lower part of the uterus. The cervix is made of two parts and is covered with two different types of

cells. The place where these two cell types meet in the cervix is called the transformation zone, which is where most cervical cancers begin (American Cancer Society, 2023).

Colorectal cancer: Cancer that develops in the cells of the colon or rectum. This type of cancer can also be referred to as colon or rectal cancer, depending on where the cancer starts (NCI, 2021). In the literature and as part of clinical diagnoses, colon and rectal cancers are commonly grouped together based on their many common features (NCI, 2021).

Endometrial cancer: Cancer that develops in the cells of the endometrium, the tissue lining of the uterus (Ulm et al., 2019).

Estrogen-dependent cancer: A cancer that develops as a result of the cancer's dependence on the hormone estrogen, which is essential for the cancer's continued growth (Ulm et al., 2019). Estrogen receptors, including ERα and ERβ, play a pivotal role in hormone-dependent cancer development because these receptors mediate estrogen activities (Berger et al., 2013). In the current study, estrogen-dependent cancers were defined as breast, cervical, colorectal, endometrial, ovarian, and prostate.

Ovarian cancer: Cancer that develops in the cells of the ovaries, the female reproductive glands, that form the ova or eggs (NCI, 2021).

Phytoestrogen urine level: The level of PE measured in a person's urine. Values for PE urine levels came from a laboratory analysis of urine samples from participants in the 2003-2006 NHANES (NHANES, n.d.). High performance liquid chromatography was used to quantitatively detect various urinary isoflavones (daidzein, genistein, equol, O-desmethylangolensin) and lignans (enterodiol, enterolactone) in the urine. An average

of the various urinary isoflavones values obtained from urine samples was used to indicate PE intake. These PE urine values were suitable for assessing PE intake among participants in the study.

Phytoestrogens (PE): A diverse group of biologically active phenolic compounds found primarily in plant-based foods that structurally mimic endogenous mammalian estrogen, 17β-estradiol (Mense et al., 2008). Due to their structural similarities, PEs are capable of estrogen-receptor binding, thereby influencing biologic pathways. There are four major classes of PEs: isoflavones, lignans, stilbenes, and coumestans. The primary sources of dietary PEs are fruits, legumes, vegetables, and beverages such as tea (Corcoran et al., 2012).

Phthalate urine level: The level of XE metabolites measured in a person's urine. Values for XE metabolite urine levels came from a laboratory analysis of urine samples from participants in the 2003-2006 NHANES (NHANES, n.d.). High performance liquid chromatography was used to quantitatively detect various phthalate metabolites in the urine. The following phthalate metabolites were included in the analysis: monoethyl phthalate, monobutyl phthalate, mono-isobutyl phthalate, mono (2-ethylhexyl) phthalate, monobenzyl phthalate, mono (2-ethyl-5-oxohexyl) phthalate, and mono (2-ethyl-5-hydroxyhexyl) phthalate. An average of the various urinary phthalate metabolites values obtained from urine samples was used to indicate XE exposure. These XE urine values were suitable for assessing XE exposure among participants in the study.

Prostate cancer: Cancer that develops in the prostate gland (Ulm et al., 2019).

Soy consumption: Consumption of soy such as soy burgers, soy meat substitutes, or tofu (NHANES, n.d.). The measurement of the frequency of soy consumed during the past 12 months by participants in the 2003-2006 NHANES was defined in times of per day, per week, per month, and per year. The responses were obtained from two 24-hour dietary recall interviews. An average of the values obtained from each 24-hour dietary recall was used to provide an estimate of soy consumption for participants in this study.

Xenoestrogens (XE): A diverse group of EDCs that exerts estrogenic effects by mimicking or blocking endogenous mammalian estrogen, 17β-estradiol, and interferes with normal endocrine function (Z.-X. Xu et al., 2017). Due to their structural similarities, XEs are capable of estrogen-receptor binding, thereby influencing biologic pathways. XEs can have different estrogenic or anti-estrogenic properties. The major classes of environmental XEs include, estrone, estriol, 17α-ethynylestradiol, nonylphenol, 4-tert-octylphenol, bisphenol A (BPA), dibutyl phthalate, and phthalate esters (PAEs; Z.-X. Xu et al., 2017).

Assumptions

There were several assumptions in the current study that were primarily related to use of secondary data. In using secondary data from the NHANES, I needed to assume that the data came from a sample of adults that was representative of the U.S. population. I also assumed that in the initial collection of data, such as by dietary recall interviews and urine analyses, the instruments used to collect the data were valid and reliable, and the data were accurate. Furthermore, I assumed that in using the average of the two 24-hour dietary recall interviews, the measurement was reflective of the study participant's

typical dietary intake. However, when using secondary data, I was unable to rule out the possibility that study participants may have modified their dietary habits in recent years or were not truthful about their dietary habits. Nonetheless, research showed the use of multiple 24-hour dietary recalls was an acceptable method to determine average dietary patterns (Carroll et al., 2012; Freedman et al., 2011; Schatzkin et al., 2003).

Finally, a critical assumption necessary to the meaningfulness of the study was that reported differences in the frequency of soy and bean product and bottled water consumption reflected any corresponding differences in levels of dietary PE consumption and XE exposure. This assumption was necessary in the context of the study because there was limited research on measuring these differences in epidemiological studies. Correspondingly, I assumed that the measurements of PE urine levels and phthalate urine levels were accurate proxies for diet as the principle routes of exposure PE and XE, respectively, with minimal influence from other nondiet sources of XE exposure. Conversely, phthalate metabolites were considered accurate proxy indicators for overall XE exposure based on previous validation (Blount et al., 2000; Hashemipour et al., 2018; Koch et al., 2013; LaKind & Naiman, 2015; C. Lin et al., 2017). Even so, Koch et al. (2013) found urinary levels of high molecular weight phthalates to be reflective of dietary intake, but low molecular weight phthalates were a result of contributions from nondietary routes such as personal care products and other ubiquitous sources.

In addition, levels of phthalates in bottled drinking water were highly varied based on a number of factors such as water source, time in storage, and storage temperature (Aneck-Hahn et al., 2018; H. Li et al., 2019; Mazzaglia et al., 2016;

Nawrocki et al., 2002), and these factors were not collected in the NHANES questionnaire. Therefore, I needed to assume that people who reported drinking bottled water had significantly higher lifetime phthalate exposure from bottled drinking water than people who reporting drinking water from other sources.

Scope and Delimitations

In this study, the purpose was to investigate the association between dietary soy and bean product intake and dietary XE consumption and estrogen-dependent cancers among a representative sample of U.S. adults age 18 and older. Frequencies of soy and bean product consumption in combination with consumption of bottled drinking water were the dietary exogenous estrogen exposures of interest. This scope was chosen due to the limited number of epidemiological studies conducted on co-exposure of dietary PEs and XEs in combination associated with estrogen-dependent cancer incidence. Estrogen-dependent cancers were limited to breast, cervical, colorectal, endometrial, ovarian, and prostate cancers based on the literature available dealing with associations between dietary PE intake and dietary XE exposure and cancer. In addition, these six cancers share several similarities, most commonly their dependence on hormones for continued growth (Ulm et al., 2019). Secondary data from the 2003–2006 NHANES were used to examine potential associations between dietary PE intake and dietary XE exposure, and estrogen-dependent cancer diagnosis. Potential confounders included race, age, gender, education level, and marital status (Hilz & Wagner, 2018; House et al., 1990; Kahlert et al., 2017; Kato et al., 1989; Sakharkar & Kahaleh, 2017). Participants with missing responses for dietary PE intake or dietary XE exposure or whose self-reported responses

for cancer diagnosis were “unknown” or “refused to answer” were excluded. To determine this study’s sample size, I performed a power calculation.

The current study was limited to the population of the United States in which NHANES studies are conducted. Given the study design and the large population of the United States, the results were expected to be generalizable to other countries or populations in which similar Westernized lifestyles or dietary consumption habits were found. The results may not be generalized to populations whose diet contains high levels of isoflavones from soy foods and lignans, such as Asians or Europeans.

Limitations

The use of secondary data was planned, which posed the greatest potential limitations to the study. However, the limitations related to secondary analysis were not expected to be outside the norm of concerns associated with use of an existing data set. Examples of expected concerns related to the secondary analysis of existing data included that the data were not collected to address the present study’s particular research questions, the data were not collected during the years desired, the variables were not categorized the same, and the data were not valid (Cheng & Phillips, 2014; Doolan & Froelicher, 2009; Doolan et al., 2017; Ross & Bibler Zaidi, 2019; Trinh, 2018).

The first limitation was the possibility of both recall and interviewer bias associated with the use of dietary recall data. Another limitation was the lack of long-term dietary information other than 24-hour dietary recall information. Similarly, the cross-sectional design of the study limited the establishment of any cause-effect relationship between the dependent and independent variables. Finally, the lack of

availability of the dependent and independent variables required for the current study was a key potential limitation to note. For this reason, the current study was restricted to the use of archival data from the 2003–2006 iterations of NHANES. I selected the 2003–2006 iterations of NHANES for the current study because 2003–2006 were the only years in which the current study's defined variables used to measure dietary PE consumption and dietary XE exposure were collected. NHANES did not collect measures of dietary PE consumption and dietary XE exposure within the survey before or after the 2003–2006 years. Given the age of the data, it was necessary to consider the potential limitations of interpretation of secondary analysis. When the data were not current, such as the 2003–2006 NHANES, it was vital to assess whether the study's findings would be relevant today.

At the time this current study was conducted, a search of the literature did not identify any new research on the dependent and independent variables under study to warrant further concerns regarding this limitation or to challenge the applicability of the previously collected NHANES data. Since the time of the 2003–2006 NHANES data collection, there had not been any new research or a substantial shift in the understanding of dietary PEs or XEs or the relationship between them to suggest that the results of the current study would not be relevant. Furthermore, this was supported by the fact that both soy and bean product and bottled drinking water consumption among U.S. adults have remained constant since 2006, which makes these data as relevant today as when they were collected (Shan et al., 2019; Vieux et al., 2020). For these reasons, the date of the data was not expected to impact the study's findings. Furthermore, the archival data may

provide greater insight into foundational work that influences the understanding of cancer exposure pathways associated with dietary PEs and XEs today. Review of epidemiologic studies in humans indicated that there were no more current data on dietary PE intake, dietary XE exposure, and cancer. Additionally, results from in vivo and in vitro studies to date on dietary PEs and XEs remained inconclusive (Katchy et al., 2014; Z.-X. Xu et al., 2017). Because the association between dietary PEs and XEs and cancer was not completely understood, more epidemiological studies were needed to understand the mechanisms.

Significance

Researchers had not conducted studies to assess the potential relationship between dietary PE intake and dietary XE exposure and estrogen-dependent cancers in the U.S. population using a nationally representative sample. The current study provided a broader perspective to substantiate dietary estrogen's role as the primary route of PE intake and XE exposure in the human population. In addition, I sought to fill the gap that existed in epidemiological studies that targeted health outcomes related to dietary PE intake and dietary XE exposure in adults with cancer. Results from the current study provided evidence whether an association was found between dietary PEs and XEs and estrogen-dependent cancers and added to the current literature on this topic. Examining the association between soy and bean product consumption, bottled drinking water consumption, PE and XE urine levels, and cancer status may enhance current knowledge of dietary risk factors for estrogen-dependent cancer. The current study has the potential to provide additional information to reinforce recommendations for a healthy diet high in

PE-rich foods and low in consumption of bottled drinking water to decrease XE exposure.

By filling the gap in the literature, the current study may be able to create positive social change by providing cancer researchers with a better understanding of dietary estrogens as exposure pathways and assessing their carcinogenesis risk. Measuring the association of dietary PEs and XEs with estrogen-dependent cancer outcomes may help provide a more thorough picture of the magnitude and long-term implications of exposure to daily, dietary exogenous estrogens, creating greater awareness for change in dietary habits to improve health. Identification of the risks of co-exposure to dietary PEs and XEs in combination in daily life constitutes a critical first step for developing interventions. Quantification of the association between dietary PEs and XEs and cancer outcomes may provide evidence of the need for appropriate control and prevention measures. Further implications for positive social change may come from utilization of knowledge of this topic to inform public health policies and develop interventions aimed to reduce estrogen-dependent cancer incidence, morbidity, and mortality.

Summary

In 2018, over 400,000 men and women were diagnosed with hormonal cancers, leading to 100,000 deaths (Ulm et al., 2019). Estrogen-dependent cancers represent a major public health concern due to their significant disease burden among men and women. The multiple sources of exogenous estrogen increase lifetime exposure to circulating estrogens, which are a contributing factor in carcinogenesis among estrogen-dependent cancers (Assi et al., 2013; Basree et al., 2019; Bronowicka-Kłys et al., 2016;

Fucic et al., 2012; LaKind & Naiman, 2011). Although the exact causes of estrogen-dependent cancers are not completely known, research indicated that most of these cancers are a result of environmental exposures that lead to genetic mutations; therefore, lifestyle and dietary factors are important opportunities for prevention of this public health issue (McKale & Aishwarya, S2019; Park et al., 2017; Z.-X. Xu et al., 2017).

The literature suggested that overall diet, the intake of specific foods, and exposure to estrogen in the diet can affect the onset and progression of estrogen-dependent cancers. However, there were a number of inconsistent and inconclusive findings in the literature on the combined impact of the various sources of dietary estrogen exposure (Y.-J. Chang et al., 2017; Russo et al., 2018). The effect of co-exposure to dietary PEs and XEs in combination and how these interact to contribute to increased risk of estrogen-dependent cancers, particularly in human or epidemiological studies, was uncertain. Research suggested that there may be an association between high soy and soy-based product intake, phthalate exposure from bottled drinking water consumption, and estrogen-dependent cancer outcomes. Therefore, this quantitative study was conducted to assess the association between dietary intake of soy and bean products, bottled drinking water consumption, and estrogen-dependent cancers among U.S. adults using a large representative sample.

Chapter 2: Literature Review

Globally, an increase in the incidence of estrogen-dependent cancers (breast, cervical, colorectal, ovarian, and prostate) was reported (Bray et al., 2018; Kato et al., 1989). Estrogen-dependent cancers are main contributors to the world's cancer burden. In 2020, there were approximately 18.1 million newly diagnosed cancer cases, with breast, colorectal, and prostate cancers accounting for 2.26 million, 1.93 million, and 1.41 million cancer cases, respectively (WHO, 2022). Accumulating research on studies of migrants indicated a strong nonhereditary component of estrogen-dependent cancers, such as the diet/dietary patterns, lifestyle factors, and obesity, in explaining the regional variation often associated with a more Westernized lifestyle (Bray et al., 2018). A substantial body of research revealed that Western countries have a higher incidence of estrogen-dependent cancer compared to Asian countries, which was believed to be associated with lower consumption of soy foods in Western countries (H. H. Chen et al., 2018; Franke et al., 2014; Maskarinec et al., 2017; Russo et al., 2018; F. Zhang et al., 2017; H. Y. Zhang et al., 2016; Q. Zhang et al., 2017; T. T. Zhao et al., 2019).

In both men and women, an association exists between excess estrogen levels and an increase in hormone-dependent cancers. Among estrogen-dependent cancers, such as breast and ovarian, research suggested that parity and breastfeeding reduced cancer risk through the reduction in lifetime exposure to circulating estrogens (Ambrosone et al., 2014; Fortner et al., 2019). Similarly, a number of studies have shown that consumption of some dietary PEs decreased the risk of prostate and colorectal cancers via estrogen receptor-mediated activities that regulate cell proliferation, cell cycle, and apoptosis

(Alipour et al., 2015; H. Li et al., 2019; Russo et al., 2018; Viggiani et al., 2019; F. Zhang et al., 2017). Expanding on this idea, Patel et al. (2018) contended that there are a number of lifestyle factors that increase inflammation and elevated levels of aromatase, leading to increases in estrogen production. In all instances, lower blood levels of estrogen decreased the risk of cancer, particularly for hormone-receptor positive tumors (Giudice et al., 2019; Sorenmo et al., 2019; Yue et al., 2013).

In addition to endogenous estrogen sources, dietary or environmental sources of estrogen that people are exposed to in daily life can contribute to elevated estrogen levels. PEs, plant-based compounds that mimic mammalian estrogen hormone (17β-estradiol, E_2), have been shown to exert estrogenic or anti-estrogenic effects by playing a role in estrogen synthesis and metabolism (Basu & Maier, 2018). The estrogenic or anti-estrogenic effects are induced as a result of PEs' weak binding affinities to estrogen receptors. Studies have shown that the determinant for whether PEs exert estrogenic or anti-estrogenic effects is concentration of genistein (Basu & Maier, 2018). In addition, recruitment of coactivators was also responsible for determining the tissue-specific estrogen response and was often a pre-requisite for estrogen receptor action (An et al., 2001). Furthermore, as expected for an anti-estrogenic effect, genistein recruited coactivators more potently to ERβ than to ERα. Based on the findings by Basu and Maier (2018), it was reasonable to postulate that the protective properties of PEs resulted from increased activation of ERβ that generated antiproliferative processes and promotion of apoptosis, thereby leading to reduced risk of estrogen-dependent cancers. Conversely,

estrogenic properties of XEs that initiated ERα activities exacerbated cellular growth and proliferation (C. Z. Yang et al., 2011).

Previous studies suggested that an estrogenic versus antiestrogenic response was determined by the ERα and ERβ ratio, expression, and binding affinity (Pons et al., 2019; Rutkowska et al., 2016). Mediation of estrogen via ERα resulted in proliferative processes, whereas ERβ resulted in antiproliferative processes and promotion of apoptosis (Rutkowska et al., 2016). XEs also mimic natural estrogens; chemical compounds found in the environment, food, air, and other substances that possessed estrogenic activities exacerbated cellular growth and proliferation (Paterni et al., 2017; Watson et al., 2019). For this reason, both PEs and XEs are considered EDCs that influence the endocrine system and alter hormone functions in either positive or negative ways by competitively binding to estrogen receptors. PE exposure primarily occurs through dietary consumption of soy and bean products. Similarly, human exposure to XEs commonly occurs during food ingestion as a result of environmental contaminants or leeching of food packaging. Diet is the primary route of exposure to exogenous estrogens, specifically dietary PEs and XEs, and the relationship between dietary PEs, XEs, and estrogen-dependent cancers is worthy of further investigation.

The current study may extend existing knowledge of the potential beneficial effects of PEs on human health in reducing development of estrogen-dependent cancers. In addition, the current study may add to the body of scientific knowledge on the potential harmful effect of dietary exposure to XEs for development of estrogen-dependent cancers. I aimed to fill gaps in the literature by assessing the frequency of soy

and bean product consumption and PE urine levels as measures of dietary PE intake. In conjunction, the frequency of bottled drinking water consumption and phthalate urine levels were used as measures of dietary XE exposure. Phthalates are not chemically bound to a polymer matrix (Jeddi et al., 2016). This characteristic of phthalates makes them easily released into food, water, or the surrounding environment directly and/or indirectly. Therefore, individuals who consume bottled drinking water are potentially exposed to small amounts of leaching plastics and phthalates with each drink.

The relationship between dietary PEs, dietary XEs, and estrogen-dependent cancers is not well understood and has not been closely studied in the context of epidemiological studies. Furthermore, previous work focused on exposure to dietary PEs or XEs individually and risk of estrogen-dependent cancers. No researchers had addressed the question of co-exposure to dietary PEs and XEs among the adult population. The purpose of the current study was to determine the association between dietary PE intake and dietary XE exposure, and the development of estrogen-dependent cancer (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adults age 18 years and older in the United States.

Literature Search Strategy

I used the following electronic databases, journal websites, electronically available theses and dissertations, and search engines to identify peer-reviewed articles for the literature review: Google Scholar, ScienceDirect, CINAHL, MEDLINE, PubMed, and ProQuest. The search was performed using single or combination relevant terms that included *estrogen dominance*, *estrogen* and *cancer*, *hormone dependent cancers*, *dietary*

phytoestrogen and *breast cancer*, *isoflavones* and *breast cancer*, *diet* and *hormone dependent cancer*, *dietary factors influencing estrogen metabolism*, *estrogen-related dietary pattern*, *estrogen homeostasis*, *endogenous hormone levels*, *cellular proliferation*, *phytoestrogen* and *breast cancer*, *xenoestrogen* and *cancer*, *diet* and *hormone dependent cancer*, *estrogen* and *colon cancer*, *estrogen receptor mediated* and *cancer*, *environmental XEs*, *dietary XEs*, *exposure to BPA, BPA in bottled water*, *bottled drinking water United States,* and *bottled water phthalates* and *bisphenol a*. The review of articles was focused on publications written in English between 2016 and 2022 to ensure the most recent data on the key variables. The scope of the initial search was expanded to include some earlier work in the discussion of seminal literature and pivotal findings.

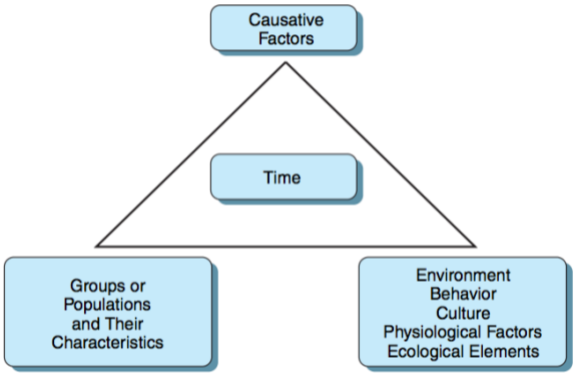
Theoretical Foundation

The theoretical base for the current study was the advanced model of the triangle of epidemiology, which expanded on the foundation of the traditional triangle of epidemiology used in infectious and communicable diseases (see Merrill, 2013). The traditional model explains the cause of infectious and communicable diseases by showing the interaction between the factors that contribute to outbreak over time. According to Merrill, the three components of the traditional epidemiology triangle consists of the agent, the host, and the environment. To include the broader scope of chronic disease and disorders, the advanced model of the epidemiology triangle was developed to incorporate and understand the etiologic factors and elements that contribute to disease over time. Similar to the traditional triangle, the foundation of the advanced model of the triangle of epidemiology asserts that three factors work synergistically to influence the occurrence of

disease over time. In the advanced model of the triangle of epidemiology, Merrill defined the interdependence of epidemiologic factors contributing to disease over time to consist of (a) causative factors; (b) environment, behavior, culture, physiological factors, ecological elements; and (c) groups or populations and their characteristics. Similar to the traditional epidemiology triangle, the advanced model of the triangle of epidemiology was not meant to be all-inclusive; instead, it recognizes the complex causes and contributing factors of chronic diseases. In the context of the current study, this approach indicated that the causative factors, environment/behavior factors, and groups or population and their characteristics were all contributors over time to the development of estrogen-dependent cancers. A depiction of the advanced model of the triangle of epidemiology is presented in Figure 2.

Figure 2

Advanced Model of the Triangle of Epidemiology



Note. Adapted from Merrill (2013).

Application of Advanced Model of the Triangle of Epidemiology to Estrogen-Dependent Cancers

Causative Factors

In the advanced model, estrogen was the agent. Causative factors of estrogen-dependent cancers support the etiology of disease regarding the role of estrogen. Research has demonstrated that estrogen exerts its effects via ERα and ERβ (Yakimchuk et al., 2018). Mediation and modulation of these pathways yield different positive or negative results associated with carcinogenesis (Giudice et al., 2019; Herichova et al., 2019). Substantial in vivo and in vitro data indicated circulating estrogen level's carcinogenic role in development of breast and prostate cancers (Pons et al., 2019; Tang et al., 2018). Although the mechanism of action is not completely understood, the framework supports the idea that increases in ERα stimulate cell proliferation and mutations leading to replication errors, which promotes carcinogenic activity (Henderson et al., 1988; Yue et al., 2013). However, activation of ERβ is more complex because it acts as a physiological regulator for ERα, resulting in antiproliferative and apoptotic activities (Yakimchuk et al., 2018).

Environment/Behavior Factors

Within the advanced model, the components of environment and behavior represented modifiable factors that contribute to estrogen-dependent cancers. This included exposure to environmental exogenous estrogen sources that contributed to increasing breast cancer rates (Gray et al., 2017; Luo et al., 2018; Schettler, 2006) or dietary behaviors that increase PE consumption (Tan et al., 2018) to support increased

protection from breast cancer. According to Ziaei and Halaby (2017), data from several studies have estimated that dietary factors account for 30%–50% of all cancers. The theoretical premise of the advanced model of the epidemiology triangle supports that changes in dietary behavior may affect the occurrence of estrogen-dependent cancer. When examining breast cancer risk factors, Tan et al. (2018) demonstrated a 75% and 60% reduction in risk of breast cancer for women who consumed one cup or more of soymilk per week and soy products once or more per week, respectively.

Populations and Their Characteristics

As supported by previous research, the population and its characteristics, such as race or ethnicity, gender, age, education, and socioeconomic and demographic variables, contributed to estrogen-dependent cancer. One example of the influence of population on dietary behavior was based on the findings from previous meta-analyses that identified an associated reduction of breast cancer in Asian populations but no association in Western populations (Basu & Maier, 2018; H. H. Chen et al., 2018; Darbre & Charles, 2010; Russo et al., 2018; T. T. Zhao et al., 2019). The lower incidence of estrogen-dependent cancer among Asian populations was hypothesized to be related to the overall higher consumption of soy foods or dietary isoflavones in Asian diets.

To examine the role of race/ethnicity as an effect modifier on the association between dietary isoflavone intake and all-cause mortality in breast cancer, F. Zhang et al. (2017) conducted a multiethnic cohort study of women with breast cancer living in the United States. Zhang et al. demonstrated a significant trend of lower all-cause mortality across all racial/ethnic groups. However, Zhang et al. found that Asian American women

had a higher average intake of dietary isoflavones compared to women from other racial/ethnic groups (6.1 vs. 1.3 mg daily; $p < 0.001$). However, these levels of dietary isoflavones were substantially lower than those of women living in Asian countries, who typically have an average daily intake of 45.9 mg (Fritz et al., 2013). The findings by Zhang et al. were consistent with previous research (H. Y. Zhang et al., 2016; Q. Zhang et al., 2017; T. T. Zhao et al., 2019) using migrant and ecological studies that suggested the incidence of estrogen-dependent cancer in Asian populations who migrated to Western countries approached that of the Western population within two generations. The consumption of isoflavones tended to be < 1 mg/day, which was hypothesized to be related to assimilation to a Western diet (Maskarinec et al., 2017).

Justification for the Choice of Advanced Model of the Triangle Epidemiology as the Theoretical Foundation

The advanced model of the triangle epidemiology has been widely used as a theoretical framework to explore complex chronic disease states that have many etiologic factors (Merrill, 2013). The model adequately captures the multifactorial nature of estrogen-dependent cancer that highlights the interaction and contribution of factors to disease over time. In the current study, the advanced model of the epidemiology triangle was the plausible pathway to explain how dietary PE and XE consumption contributes to estrogen-dependent cancer risk. The research questions and associated variables of the current study aligned with the advanced model of the epidemiology triangle to facilitate my exploration of the association between dietary PE intake, dietary XE exposure, and estrogen-dependent cancer.

Literature Review Related to Key Variables/Concepts

The remaining part of this chapter begins by reviewing the pathogenesis, various proposed mechanisms of action and potential pathways, and risk factors associated with the development of estrogen-dependent cancers in the context of dietary PEs and XEs. I then discuss aspects of diet and its impact on estrogen-dependent cancer as associated with PEs and XEs. This is followed by a description of the research assessing the antiestrogenic and estrogenic properties of dietary PEs and XEs, independently, and limited research on co-exposure. Research to support the importance of looking at epidemiological studies and translating the research findings of in vivo and in vitro studies is then discussed. Each of the studies is described in detail, including implications to humans, focusing on how it impacts the development of estrogen-dependent cancers. This chapter ends with a summary of the themes in the literature and a conclusion that elucidates how the current study may fill the gap in the literature and extend existing knowledge.

Epidemiology of Estrogen-Dependent Cancer

Estrogen receptors are critical modulators of estrogen-dependent cancers. Tumor characteristics, such as the expression of specific ERs, provide insight into the etiology of hormone-dependent cancers and strategies for treatment and prevention. The literature supported the hypothesis regarding estrogen's role in the etiology of certain cancers in both men and women. For instance, estrogen is primarily a female sex hormone, but H. Yang et al. (2012) found that lower estrogen levels contributed to the "male gender bias" in esophageal adenocarcinoma, leading to a predominance of this type of cancer

primarily in males. Estrogen played a protective role and high estrogen levels in females contributed to the lower incidence rate where greater expression of ERβ was identified in all patients with esophageal adenocarcinoma (H. Yang et al., 2012). However, among females, estrogen as the female sex hormone promoted breast and ovarian cancers yielding an increased bias against females (Anderson et al., 2003; Trabert et al., 2016).

On the other hand, Herichova et al. (2019) attributed higher colorectal cancer (CRC) diagnoses in males to sex steroid hormones. In CRC, there is a greater expression of ERβ compared to ERα, where E_2 effects are attributed to increased ERβ signaling. It is the overexpression of ERβ that results in disruption of the cycle cell at the G1 stage (leading to suppression of cell cycle progression including prohibition of cell death) and inhibition of proliferation. In all instances, the gender bias among certain types of cancers suggested that there may be a gender-related mechanism that explains the gender difference, but that estrogen is mechanistically related to aspects of cancer development and risk among males and females. Therefore, it was necessary to consider the significant contributing role of estrogen in the development of estrogen-dependent cancers. The biological significance of estrogen and ERs in tumorigenesis has been extensively studied, but there is ongoing debate regarding their impact on the development or prevention of estrogen-dependent cancers. This appears specific to the type of cancer and is depends upon the activation or suppression of ERα or ERβ as a factor of ER-mediated effects.

Circulating Estrogen

It was plausible to suggest that maintaining optimal circulating estrogen levels within the body and obtaining a balance between PE and XE levels, may modulate the risk of estrogen-dependent cancers. The studies (Patel et al., 2018; Rawluszko-Wieczorek et al., 2017; Rod et al., 2009; Williams & Darbre, 2019) found that the onset of chronic and acute diseases can be linked to either hyper or hypo levels of estrogen. In their analysis of circulating estrogens and postmenopausal ovarian cancer, Trabert et al. (2016) demonstrated a risk of ovarian cancer among women with higher levels of estrone (E_1), a weak estrogen and agonist of ERα and ERβ, (OR [odds ratio] for Q [quintile]5 vs. Q1: 1.54; 95% CI [confidence interval]: 0.82– 2.90, *p*-trend = 0.05) and estrogen metabolites, 2- and 4-methoxyestrone metabolites, (OR = 2.03, 95% CI: 1.06–3.88, *p*-trend = 0.02; OR = 1.86; 95% CI: 0.98–3.56), *p*-trend=0.01, respectively).

Trabert's study confirmed previous research associated with breast cancer (Ambrosone et al., 2014) that hypothesized that parity and breastfeeding reduced breast cancer risk by reducing lifetime exposure to circulating estrogen. Similarly for ovarian cancer, research by Traber et al. coincided with the findings by Pike and Spicer, (2000) that suggested that a history of oral contraceptive use reduced ovarian cancer risk by reducing intra-ovarian estrogen levels and the number of lifetime ovulations. Furthermore, Trabert's research was significant to the current study as it validated the need for additional investigation into whether PEs reduced the development of estrogen-dependent cancers.

Estrogen Homeostasis

Additionally, accumulating evidence hypothesized that estrogen level correction can be used to restore the hormonal balance and achieve "estrogen homeostasis" and potentially reduce the risk of estrogen-dependent cancers. A. J. Li et al. (2003) were among the initial researchers to suggest the concept of sex steroid hormone homeostasis based on epidemiologic data on carcinogenesis of ovarian epithelium and altered estrogen homeostasis. A common hypothesis is that long-term exposure to an environment with excessive estrogen results in carcinogenesis by promoting cell proliferation, limiting apoptosis, and promoting abnormal cellular differentiation.

A. J. Li's experiment using cell cultures of human ovarian epithelium and ovarian cancer found the ratio of ERα/ERβ messenger ribonucleic acid expression was 10 times higher among ovarian cancer cultures (9.94 ± 3.90) than normal cultures (1.00 ± 0.16, $P = 0.04$). Similarly, ERα/ERβ protein ratio in ovarian cancer (2.13 ± 0.43) was twice that of normal human ovarian epithelium (1.00 ± 0.13, $P = 0.05$). This finding was relevant as it validated that imbalances in ERα and ERβ expression could have profound effects on ovarian carcinogenesis, specifically the increased ERα expression relative to ERβ. Furthermore, the results highlighted the difference between normal and malignant ovarian epithelium, which supports that the suppression or downregulation of ERβ contributes to carcinogenesis. Although the sample size was small, this did not appear to limit the study's results, as other recent studies (Acconcia et al., 2017; Pons et al., 2019; L. Zhao et al., 2018) found that differences in expression of ERα/ERβ or activation or

suppression of ERα or ERβ, respectively, by endogenous estrogen sources were linked to increased estrogen-dependent cancers.

Mechanisms of Action and Pathways

In more recent research on the regulation of ERα/ERβ and its association with the development of estrogen-dependent cancers, ERα/ERβ ratio is a pivotal mechanism at the impetus of estrogen biosynthesis leading to carcinogenesis. The effects of ERα are related to cell proliferation processes, but ERβ effects are related to anti-proliferative processes. Furthermore, the protective effects of PEs are believed to be a result of up to 30 times more affinity for ERβ than ERα (Kuiper et al., 1998). Compounds that upregulate ERβ activities bind to ERβ with greater affinity than ERα, and this preference in binding affinity has implications for the risk of estrogen-dependent cancers. According to researchers (Acconcia et al., 2017; Pons et al., 2019; Z.-X. Xu et al., 2017; L. Zhao et al., 2018), PE and XE regulation of the ERα/ERβ balance is often associated with estrogen-dependent cancers with de-regulation contributing to pathogenesis.

Pons et al. (2019) found that the PE genistein, commonly found in soy and soy-based products, modulated tumor activation or suppression as a factor of the ERα/ERβ ratio via cell proliferation and reactive oxidative species production. Using 3 breast cancer lines, MCF-7 (high ERα/ERβ ratio), T47D (low ERα/ERβ ratio), and MDA-MB-231 (ERα-), genistein promoted cell proliferation in MCF-7 (+12%), but genistein decreased cell viability in T47D (-6%) and MDA-MB-231 (-5%) as a result of differences in ERα/ERβ ratio. Furthermore, reactive oxidative species production in T47D (-10%) was significantly decreased due to genistein, but MCF-7 and MDA-MB-

231 did not yield any differences. Pon's research identified a potential crucial link between cell proliferation and reactive oxidative species production and pro-inflammatory genes responsible for mediating suppression of proliferation, angiogenesis, apoptosis, invasion, and metastasis. These findings were relevant as they further support the earlier research by A. J. Li et al. (2003) on ovarian cancer regarding imbalances in ERα and ERβ expression also resulting in increased breast cancer. Pon's study confirmed the anti-cancer properties and anti-inflammatory effects of genistein, which was significant to the current study as it supports investigation into the mediating effects of dietary PEs on estrogen-dependent cancers.

Similarly, L. Zhao et al. (2018) identified the molecular mechanism by which ERβ activation increased innate immunity to suppress metastasis of breast cancer. The selective ERβ agonist LY500307 modulated cancer metastasis by suppressing lung metastasis of triple-negative breast cancer 4T1 cell lines. There was also a greater overall survival rate between the LY500307 group compared to the control. The underlying mechanism of LY500307 metastasis suppression was validated as induction of cell death via cleaved caspase 2. The findings corroborated ERβ's potent tumor-suppressive activities via reduced cell proliferation as demonstrated by other research.

On the other hand, Zhao's findings did not confirm ERβ activation to increase significant apoptosis as other research has noted. These findings are meaningful because ERβ expression has been indicated in most melanoma and invasive breast cancer cases, including triple-negative breast cancer. If ERβ expression has proved to be a significant tumor suppressor among aggressive cancers, such as melanoma and triple-negative breast

cancer, increased ERβ activation may be effective in other estrogen-dependent cancers. This research was relevant to the current study as these data suggested use of ERβ agonists, such as dietary PEs, can effectively reduce incidence of estrogen-dependent cancers.

Risk Factors

Outside of specific inherited genetic mutations, such as in *BRCA1* and *BRCA2* (Breast Cancer genes 1 and 2), Patel et al. (2018) attributed most issues related to the body's estrogen imbalance to lifestyle choices. Lifestyle choices are modifiable risk factors. By modifying risk factors, the pathological effects of estrogen can be delayed or prevented. Therefore, the role of diet is important to explore as it offers opportunities for preventive strategies. One such nutrient gaining more interest for its beneficial health properties is dietary PE. In addition to reducing use of EDCs, dietary changes are assumed to aid in proper expression of ER (Patel et al., 2018).

Numerous studies supported the protective effects of PE-rich foods, such as soybeans or lignans, in reducing breast and prostate cancer risk (Russo et al., 2018; Zaineddin et al., 2012). This finding was significant as it contributes to the belief that estrogen-dependent cancer results from many contributing factors and interactions over time. Researchers have long hypothesized that soy foods, which contain high levels of isoflavones, provided protective effects against breast cancer (Fritz et al., 2013; F. Zhang et al., 2017; T. T. Zhao et al., 2019;). However, the findings by Y.-J. Chang et al. (2017), which are discussed in more detail in the following paragraphs, may be a result of the higher levels of isoflavones traditionally found in Asian diets in comparison to Western

diets, suggesting an already reduced risk of breast cancer among Asian populations but not Western populations.

Similarly, southern Italians typically adhere to a Mediterranean diet that contains high levels of isoflavones from soy foods and lignans from citrus fruit suggesting reduced estrogen-dependent cancers among this population (Godos et al., 2017). However, there were varying conclusions on studies' findings on the impact of individual nutrients and food components in decreasing estrogen-dependent cancer incidence (Kyrø et al., 2018; Maxwell et al., 2017; Pons et al., 2019). As I will discuss further, using the potential protective effects of dietary PEs to offset the impact of exposure from dietary XEs may help achieve a level of estrogen homeostasis that can reduce lifetime exposure to estrogen, and subsequently, estrogen-dependent cancers. The current study sought to add to the field of research on determining if a more optimal balance of estrogen levels can be reached through dietary intake of PEs and the potential for dietary PEs to mitigate the effects of exposure to dietary XEs.

Effects of Diet on Estrogen-Dependent Cancers

Phytoestrogens and Dietary Patterns

Estrogen-dependent cancers are the main contributors to the world's cancer burden. The origin of estrogen-dependent cancers is believed to be a combination of genetic and environmental factors. Outside of genetic mutations, researchers have identified lifestyle to be related to the frequency for these types of cancers. A review of the literature suggested that diet and nutrition are modifiable risk factors related to the development and prevention of estrogen-dependent cancers (Y.-J. Chang et al., 2017; De

Cicco et al., 2019; Harris et al., 2015; McKale & Aishwarya, 2019; Parsons et al., 2018; Shivappa et al., 2018). Y.-J. Chang et al. (2017) expanded on the role of nutrients and food components by looking further at the association of dietary patterns as a risk factor for breast cancer among Taiwanese women. Overall, vegetarian diets (OR = 0.42; 95% CI: 0.27–0.65, $P < 0.001$), specifically those containing high isoflavone intake and high albumin levels, protected against developing breast cancer. In comparison, the meat and processed meat diets (OR = 2.25; 95% CI: 1.69–2.98, $P < 0.001$; OR = 1.56, 95% CI: 1.14–2.13, $P = 0.006$, respectively) were significantly associated with increased breast cancer risk. Chang validated the role of diet in the development of estrogen-dependent cancer, which supported the current study's intent to determine the involvement of dietary PEs and XEs. Moreover, the results advanced the notion that dietary patterns as a whole, rather than consumption of individual nutrients and food components alone as suggested by previous research findings (Harris et al., 2015; McKale & Aishwarya, 2019; Russo et al., 2018; Wada et al., 2013; F. Zhang et al., 2017; Ziaei & Halaby, 2017), were adequate in proposing dietary recommendations and lifestyle changes to decrease cancer incidence.

On the other hand, a definitive determination of whether dietary patterns as a whole versus increased consumption of dietary PEs alone provided greater or equal protection against estrogen-dependent cancers remains inconclusive. In comparison to the results by Y.-J. Chang et al. (2017), a case-control study among southern Italians by Russo et al. (2018) established that habitual consumption of dietary PEs were associated with prostate cancer risk independent of a dietary pattern. Patients with prostate cancer

stated consuming significantly higher amounts of lignans (7.00mg/d vs. 3.11mg/d; $p <$ 0.01). Furthermore, the study found that association between PEs and prostate cancer differed by the subclass of compounds. Specifically, isoflavones (Q3 vs. Q1, OR = 0.28, 95% CI: 0.10–0.77) and genistein (Q4 vs. Q1, OR = 0.40, 95% CI: 0.21–0.77) provided significant protection against prostate cancer risk. On the contrary, high intake of lignans (Q4 vs. Q1, OR = 4.72 , 95% CI: 2.34–9.52) was positively associated with prostate cancer.

Consistent with the evidence by Harris et al. (2015), Russo et al. (2018) and F. Zhang et al. (2017) also observed the same protective effect of higher dietary isoflavone intake independent of a dietary pattern for all-cause mortality. Among multi-ethnic women with breast cancer living in the United States, those with the highest dietary intake compared to the lowest dietary intake ($\geq$ 1.5 vs. < 0.3 mg daily, HR[hazard ratio] = 0.79; 95% CI: 0.64–0.97; P_{trend} = 0.01) had a 21% decrease in all-cause mortality. Given the large, ethnically diverse population in the study by Zhang, these findings were significant in establishing the benefit of higher dietary intake of isoflavone independent of dietary patterns across all race/ethnic groups. In addition, Guinter et al. (2018) addressed the inconclusive evidence on dietary patterns by examining the estrogen-related dietary pattern of a previously conducted prospective study of postmenopausal women in The Sister Study. The results did not support previous studies that observed a positive association between estrogen-based dietary patterns and postmenopausal breast cancer risk in all populations.

Additionally, recent studies advanced the role of dietary isoflavones, but greater focus demonstrated that higher intake of soy-based foods specifically achieved the most significant reduction in breast cancer risk. Research by T. T. Zhao et al. (2019) affirmed the earlier work of F. Zhang et al. (2017). However, but T. T Zhao's work further differentiated between specific types of dietary isoflavones with the greatest impact in cancer reduction. Similarly, reductions in all-cause mortality were greatest among the three most common types of isoflavones (genistein, daidzein, and glycitein). However, no increased reduction was associated directly with genistein, a soy isoflavone (F. Zhang et al., 2017). T. T. Zhao et al. explored all possible correlations between intake of different dietary isoflavones or isoflavone-rich foods and breast cancer risk. No significant association was found between consumption of isoflavones or other flavonoid-rich foods and breast cancer risk. T. T Zhao's analysis of sixteen prospective cohort studies found continued support for high intake of soy-based foods compared with a low intake to be associated with a reduced risk of breast cancer (RR [risk ratio] = 0.87; 95% CI: 0.76–1.00; $P = 0.048$).

Admittedly, a recent review of the literature on soy continued to support the protective anti-estrogenic effects on estrogen-dependent cancers, some initial investigations into the impact of soy on human health identified concerns regarding the harmful effects of dietary soy supplementation and the potential for increased breast cancer risk. McMichael-Phillips, et al. (1998) were among the first to further explore PE's role as a weak estrogen agonist among women with benign or malignant breast disease in the United Kingdom. Premenopausal women ($n = 48$) were randomly assigned

to a 60-g soy supplement (equivalent to 45 mg isoflavones) taken daily for 14 days or to maintaining their normal diet. McMichael-Phillips found a strong correlation in the soy supplement group compared to those on a normal diet and found increased proliferation of breast epithelium ($r = 0.868$, $P \leq 0.001$) among the soy group. There was significant breast epithelial proliferation and a small increase in progesterone receptor expression, which suggested breast histology was stimulated by short-term soy supplement. Not only did the study demonstrate the agonist effects of soy, McMichael-Phillips found no evidence of any estrogen antagonist effects. However, the main weakness in their study was the small sample size, and thus the data must be interpreted carefully.

Setchell et al. (1998) investigated similar concerns regarding the potential toxic effects of soy. In their seminal paper, they determined intake of total isoflavones in common soy-based infant formulas in the United States to estimate average PE exposure of infants based on daily milk intake. The daily intake of isoflavones from soy-based infant formula (35–50 mg) was equivalent to adults consuming a moderate soy diet of 50 mg. Based on the understanding of the long plasma half-life of soy isoflavones in adults and the continuous exposure of PE from regular, daily feedings of soy-based infant formula, infants experienced a high steady state plasma concentration of PEs. This was significant because it represented a shift from prior research, moving the focus to concern for significant PE exposure in early life. Setchell pointed out previous research that supported the negative effects identified in animal models based on knowledge of estrogen's role during development. However, in their analysis of the impact of PEs, Setchell et al. highlighted the lack of an animal model for human infants, making it

difficult to extrapolate previous animal data to human infants. Despite prior concerns, more recent evidence from an increasing number of studies (Fink et al., 2006; Fritz et al., 2013; Wada et al., 2013) continued to demonstrate that dietary isoflavone intake, specifically soy, was associated with reduced risk of incidence, recurrence, and mortality for breast and prostate cancers.

Xenoestrogens and Dietary Exposure

Among estrogen-dependent cancers, exposure to exogenous XEs is another strong contributor to carcinogenesis' etiology due to its endocrine disrupting effects. The sources of potentially hazardous exposure to XEs in people's environment include ambient air, water, food, and personal care products. Furthermore, exposure to XEs was most commonly associated with dietary exposure and food ingestion due to of food contaminants, additives, or packaging materials. Dietary exposure to XEs significantly contributes to total human exposure to EDCs. This is a significant public health concern given that the first investigation into exposure to a known environmental XE, Bisphenol A (BPA), in the United States, found BPA in 90% of the population (Calafat et al., 2008).

A recent literature review on this topic also found a link with dietary XE exposure causing health issues in reproductive, lung, breast, kidney, pancreas, and brain cancers (Jafer et al., 2018). In addition, given the strong correlation between dietary exposures to XEs and breast and prostate cancers, current research indicated the need to further evaluate the impact of specific agents. Subsequently, in defining these specific agents, there was also the need to better understand the impact of cumulative lifetime exposure to dietary XEs through daily use conditions on development of estrogen-dependent cancers.

Weak Estrogens

In multiple bodies of environmental cancer literature, researchers (Bilancio et al., 2017; Fucic et al., 2012; Jafer et al., 2018; Paterni et al., 2017; Prins et al., 2017; Watson et al., 2019) hypothesized that increased exposure to environmental XEs, such as BPA, phthalates, and other plasticizers, have increased hormone-dependent cancers through activation of estrogen in the body. As a result of the BPA being an EDC, evidence suggested that the BPA exposure induced cell proliferation leading to increased incidence of estrogen-dependent cancer. Specifically, Williams and Darbre (2019) reached a similar conclusion, finding a direct link between low-dose exposure to environmental EDCs and breast cancer.

The in vitro research by Williams and Darbre (2019) on human breast cancer cells confirmed that despite their weak binding ability, XEs could upregulate aromatase activity, induce E_2 biosynthesis, and stimulate estrogen-sensitive cell proliferation. These environmental molecular factors all contributed to carcinogenesis and the rising incidence of breast cancer. The results demonstrated significant positive correlations by Spearman Rank coefficients in all three human breast cell lines studied, MCF-7 and ZR-75-1 breast cancer cells, and HMF3A breast fibroblasts (all $p < 0.05$). There was increased aromatase enzyme activity in all breast cancer cells, but the greatest increase occurred in HMF3A breast fibroblasts (MCF-7 rho 0.663, $p < 0.002$; ZR-75-1 rho 0.687, $p < 0.001$; HMF3A rho 0.809, $p < 0.0001$). Similarly, for E_2 biosynthesis, significantly increased 17β-estradiol biosynthesis was reported, and the greatest increase occurred in HMF3A breast fibroblasts as well (MCF-7 rho 0.506 $p < 0.02$; ZR-75-1 rho 0.577 $p < 0.02$; HMF3A rho

0.725 $p < 0.0002$). Increased aromatase-induced biosynthesis resulted in increased endogenous estradiol production and ERα+ breast cell proliferation.

The finding by Williams and Darbre was crucial, as it highlighted the direct impact of XE exposure at environmentally relevant, low-dose concentrations suggesting that ongoing inadvertent dietary XE exposure is a significant contributing factor to breast cancer. This finding was pertinent to the current study as it affirms the potential for low-dose dietary XE exposure to increase the risk of estrogen-dependent cancers. In addition, contrary to previous research (Basu & Maier, 2018), this recent evidence confirms the need for public health concern even over weak estrogen compounds such as XEs, since it showed the significant affect weak estrogen receptor binding can still have on E_2 biosynthesis in stimulating breast cancer cell growth.

The impact of dietary XEs on breast cancer was similarly seen among prostate cancer patients, showing that exposure to XEs exacerbated growth of prostate cancer cells. Therefore, to control the growth rate of prostate cancer, it was necessary to better understand the mechanism that controls the tumor-promoting effects of XEs. Androgens are known for inducing cell proliferation among tumors associated with the male reproductive system, Watson et al. (2019) hypothesized that maintenance of E_2 levels equivalent to those of young males may prevent the growth of prostate cancers. Specifically, Watson presented evidence that dietary XEs exacerbated prostate cancer cell growth by acting rapidly and potently to interfere with physiological actions of endogenous estrogens through nongenomic signaling pathways.

As confirmed by Williams and Darbre (2019), Watson et al. (2019) found that BPA within a range of concentrations significantly increased prostate tumor cell numbers. The dose-response curve reflected that of a potent agonist with the exponential growth of cells at various BPA concentrations (10^{-12} to 10^{-7} M). In addition, prostate cancer cells treated with BPA for 3 days did not initiate the most common mechanisms that cause cell death or inhibition of cell proliferation, which was hypothesized to explain the growth response to BPA. Watson's findings plausibly confirmed the link between BPA exposure and increased risk of prostate cancer. Furthermore, the studies by Watson et al. and Williams and Darbre corroborated evidence that dietary XEs can exert estrogenic effects, despite being deemed weak estrogenic compounds with low binding affinity for ERs. In addition, both studies concluded that exposure to XE concentrations at various levels, particularly low levels, can induce cancer cell growth among estrogen-dependent cancers.

Leaching of XEs

However, the findings by Watson et al. (2019) and Williams and Darbre (2019) are contrary to the claims of several previous researchers that the effects of increased circulating estrogen levels, increased E_2 biosynthesis, and up-regulation of ER expression only occurred with high exposure to EDCs. Moreover, in contrast to the views by Watson et al. and Williams and Darbre, particularly as this association between increased estrogen activities and high EDC exposure applied to dietary XEs, other researchers (H. Li et al., 2019) hypothesized that dietary exposure to BPA and other plasticizers did not yield sufficient estrogenic effects to impact carcinogenesis.

For example, H. Li et al. (2019) provided a detailed analysis of the polyethylene terephthalate (PET)-bottled drinking water samples to assess them as a potential sources of phthalate ester (PAE) exposure among people in China. Globally, PET is the most commonly used thermoplastic polymer resin in commercially bottled drinking water (Jeddi et al., 2016; H. Li et al., 2019; Santana et al., 2014; Sax, 2010). Some preliminary work carried out in the 1990s and early 2000s (Montuori et al., 2008; Sauvant et al., 1995; Sax, 2010; M. Wagner & Oehlmann, 2009) found that PET bottling could leach EDCs, such as PAEs, under daily use conditions. These studies suggested that leaching from plasticizers occurred because PAEs are easily released from containers due to their nonchemical bonding to polymers. The preliminary works in this field were well grounded, making it acceptable to assume there is potential risk associated with EDC exposure as part of daily normal consumption of bottled water. Consequently, the adverse effects of PAEs have been confirmed in epidemiological and toxicity studies (Bornehag et al., 2004; Colón et al., 2000; Selcuklu et al., 2012).

In order to assess the impact to human health of PET leaching, H. Li et al. (2019) used 60 bottled drinking water samples from 10 commercial brands, 6 samples from each brand. The findings confirmed the presence of 17 of the 21 PAEs under study in all the bottled drinking water samples, with dibutyl phthalate, diisobutyl phthalate, and dimethyl phthalate being the most predominant compounds. PET bottles were assessed based on the physical parameters of thickness, weight, density, and internal surface area to determine their relationship to PAE concentrations. Overall correlation analysis confirmed PET bottles as a potential source of PAEs in PET-bottled drinking water. PAE

levels in water ranged from 0.010 to 0.51 μg/L; yet all levels were lower than the allowable concentration (3 μg/L) for drinking water per China's regulation. PAE concentrations in PET bottles ranged from 0.45 to 383.38 ng/g and were detected at frequencies from 10% to 100%. However, the findings about the evidence of previous researchers concerning the impact of PAEs in PET-bottled drinking water remains mixed.

Despite the confirmed presence of PAEs in all PET-bottled drinking water samples, H. Li et al. (2019) suggested that the carcinogenic risk posed by 4 of the PAEs was "extremely low." Conversely, this argument was weakened because H. Li acknowledged that the human risk assessment determined by the non-cancer hazard quotient and excess cancer risks was only estimated for the 4 PAEs for which toxicity data were available. Possible carcinogenicity to humans for the remaining 17 PAEs under study remained unknown. Therefore, it was impossible to completely rule out the potential for carcinogenicity and toxicity of the other PAEs for which data are unavailable. The results by H. Li were significant as they validated the unknown carcinogenic impact of numerous other PAEs frequently found in bottled drinking water. Furthermore, the findings were significant to the current study as they substantiated both the concern for the abundance of PAEs found in all bottled drinking water and the need for the current study to further assess risk of estrogen-dependent cancers as a result of consumption of bottled drinking water.

In comparison, a recent study by Aneck-Hahn et al. (2018) assessed the health risks related to consumption of bottled water in South Africa by determining the estrogenic activity of selected plasticizers. In comparison to H. Li et al. (2019), the

findings by Aneck-Hahn et al. did not show the same significant impact of leaching from PET bottles based on storage temperature. The researchers stated that the storage conditions mimicked those of a warehouse for 10 bottled water samples incubated for 10 days in the dark at 20°C, representing normal storage, or at increased temperature of 40°C. Overall, the findings by Aneck-Hahn suggested there were no human health risks from plasticizer exposure due to leaching of PET bottles as a result of storage temperature.

However, this was based the following exposure parameters assumptions: "[consumption] events per year 350; [an individual with] body weight 70 kg; [over the course of a] lifetime 70 years; ingestion rate 1 L of water per day; chronic exposure duration 30 year." No estrogenic activity or toxicity was observed from the recombinant yeast estrogen screen in vitro bioassay analysis of the South African bottled water. However, T47D-Kbluc human breast cancer cell lines denoted increased levels of estrogenic activity associated with increased temperature (0.001 to 0.003 ng/L); yet these values did not meet the trigger value for estrogenic activity identified for the study, 0.7 ng/L. Conversely, BPA was detected in all bottled water samples (0.9 ng/L to 10.06 ng/L), likely contributing to the estrogenic activity identified. Furthermore, the mean BPA concentrations for samples at 20°C (2.78 ng/L) and 40°C (6.61 ng/L), respectively, were well above the trigger value. Finally, many potential limitations of the study need to be considered.

First, as Aneck-Hahn acknowledged, given the small sample size, caution must be exercised regarding interpretation of study findings. H. Li et al. (2019) analyzed 60

bottled water samples compared to Aneck-Hahn's 10 bottled water samples. Second, the pH of the water samples was adjusted to 3 before extraction, yielding highly acidic water when a pH is lower than 7, potentially contaminating the analysis and the results. However, whether or not the change to an acidic pH value of the water samples positively or negatively impacted the results was unknown. No rationale was provided to determine why this step to adjust the pH was done. Third, as was mentioned above by H. Li et al. (2019), leaching of EDCs can occur under daily use conditions.

The conditions used in the study by Aneck-Hahn et al. (2018) mimicked storage conditions of a dark warehouse and did not account for daily use conditions anticipated for consumers, such as a longer storage duration on store shelves, storage in sunlight, or multiple temperature scenarios. For example, to assess normal conditions by consumers, a survey by X. Xu et al. (2019) determined that "more than 80% of consumers frequently stored bottled water in car trunks for up to 4 weeks." Fourth, H. Li et al. (2019) results were more rigorous as they were more comprehensive in their inclusion of potential PAEs. Li investigated the occurrence of 21 PAEs in bottled water samples, yet Aneck-Hahn et al. (2018) only assessed 5 PAEs. Fifth, as demonstrated by previous research (Setchell et al., 1998), Aneck-Hahn used yeast estrogen screen as the in vitro bioassay, which may limit the generalizability of the results in humans, and found no estrogenic activity. T47D-Kbluc gene assay may be more reflective of the effect of PAEs in bottled drinking water in humans, making the results from yeast estrogen screen questionable.

Unfortunately, the argument by H. Li et al. (2019) that PET bottled water is a noteworthy source of dietary XEs and the claim by Watson et al. (2019) and Williams

and Darbre (2019) that dietary XEs have the ability to exacerbate breast and prostate cancer cell growth was weakened by Li's contradictory statement that PET bottled water posed "little or no non-carcinogenic health risk." Li's statement initially diminished the overall human health risk of XEs even though the study's findings could only be applied to 4 of the PAEs for which toxicity data were available and only 1 PAE is considered possibly carcinogenic to humans. However, Li did go on to contest this initial statement. Li later noted that the health risks associated to exposure to the 21 PAEs found in bottled drinking water should not be ignored because of their pervasive presence; particularly since in the study, only 6 PAEs were controlled by the Environmental Protection Agency, the remaining 15 were uncontrolled.

Li's claims seemed to be somewhat inaccurate because research has consistently identified PAEs in bottled drinking water. Many studies suggested that XE exposure from dietary consumption represents a minor component of overall human exposure and has limited impact on human health. However, this assessment has been made in the context of PAEs in isolation, without considering other sources of dietary exogenous estrogen, such as PEs. Furthermore, research has also continued to support that certain factors exacerbate PAE concentrations. PAE exposure from PET bottled drinking water is necessary to evaluate as a potential risk for estrogen-dependent cancers due to the increasing consumption of bottled drinking water globally.

Factors Associated With XE Leaching

There may be more contributors to leaching of XEs to bottled drinking water than initially assumed, and greater care must be taken to assess these factors to understand the

total potential of EDC exposure. Regression analysis by H. Li et al. (2019) indicated a positive association between the physical parameters of PET bottles and levels of PAEs in bottled drinking water, which conflicted with the findings of previous researchers. Bo et al. (2007), Mazzaglia et al. (2016), Montuori et al. (2008), and Nawrocki et al. (2002) were among the first researchers to note a link between water source, temperature, and time in storage to PAE levels in bottled drinking water. In addition, Sax (2010) hypothesized that recycled PET versus original PET composition and lower pH promoted leaching of PAEs from PET bottle walls.

This current study brings awareness to the potential health risks associated with bottled drinking water consumption, which is important as it challenged conventional wisdom among the general public on the risk of estrogen-dependent cancer. Early research on PAE exposure in bottled drinking water tended to de-emphasize the health impact, particularly the role of PAE exposure as a contributing factor to estrogen-dependent cancers. In addition, recent literature (Dhaini & Nassif, 2014; Santana et al., 2014; X. Xu et al., 2019) further highlighted time and storage conditions to be significant factors contributing to leaching of PAEs into PET-bottled drinking water. One illustration of this was research by X. Xu et al. (2019) that confirmed storage condition, primarily temperature and time, affected the leaching of PAEs from PET bottles.

In the study by X. Xu et al. (2019), leaching characteristics of PAEs from PET bottled drinking water in Beijing, China were examined through concentrations of PAEs in PET bottles and PET bottled water. In order to mimic normal consumer conditions, samples were taken from 10 brands of bottled drinking water stored at temperatures of

40°C, 50°C, 60°C, and 70°C, respectively, for 24 hours. All 10 PET bottled waters contained 3 of the most common PAEs, diethyl phthalate, dimethyl phthalate, and dibutyl phthalate, ranging from 101.97 μg/kg to 709.87 μg/kg. Furthermore, the findings appeared to be in general agreement with the previous research that established the leaching of PAEs from PET bottles into water as a component of storage conditions.

Under simulation of indoor storage conditions, PET concentrations ranged from 0.18 μg/kg to 0.71 μg/kg, but simulation of outdoor storage conditions yielded a slight increase in PAE concentrations ranging from 0.19 μg/kg to 0.98 μg/kg. Overall, the results suggested that PAEs in PET bottled water posed "a negligible risk to consumers if they followed the recommendations" on storage temperature, placement away from sunlight, and limited total storage time before consumption. Similar to the findings by Aneck-Hahn et al. (2018), the findings by X. Xu et al. (2019) needed to be taken with care. It was important to note the study's incubation time prior to sampling was only 24 hours, which as confirmed by the consumer survey was substantially less than the reality of expected storage condition times by consumers. In addition, the researchers acknowledged that risk of PAEs was only evaluated for 4 PAEs individually. This limited assessment did not account for the potential of additional PAEs of unknown toxicity as highlighted by H. Li et al. (2019). Admittedly, the PAEs under study were assessed individually and did not suggest the impact of PAEs in PET bottled water when assessed in real-world conditions where people may be exposed to numerous sources of dietary and/or environmental exogenous estrogens.

PAEs Found in Bottled Drinking Water Globally

It may be easy to attribute the significant presence of EDCs in bottled drinking water in China (H. Li et al., 2019; X. Xu et al., 2019) to the country's sub-standard food and water regulations (W. Zhang & Xue, 2016; Zhu et al., 2019), but the presence of BPA and other PAEs have been confirmed in bottled drinking water in countries around the world. Using methods such as gas/liquid chromatography-mass spectrometry and bioassays, estrogenic activity was detected in bottled drinking water from Germany (M. Wagner & Oehlmann, 2009), Italy (Montuori et al., 2008), Spain (Guart et al., 2014), Lebanon (Dhaini & Nassif, 2014), Iran (Jeddi et al., 2016), Qatar (Al-Otoum et al., 2017), South Africa (Aneck-Hahn et al., 2018), and South Korea (Park et al., 2017). However, similar direct studies quantifying or confirming the presence of PAEs in bottled drinking water in the United States could not be found in the literature. Nonetheless, the growing body of literature has confirmed the presence of BPA and PAEs in bottled drinking water globally. The ongoing presence of BPA and PAEs in bottled drinking water around the world makes a strong argument that EDCs are likely present in U.S. bottled drinking water as well and is a relevant concern in the United States, which requires further investigation on the potential health impact, particularly as it relates to the potential development of estrogen-dependent cancers.

Bottled Drinking Water in the United States and NHANES Data

In the United States , the growth of the bottled water industry and increased bottled water consumption may have important consequences for public health. No specific studies on PAEs in bottled drinking water in the United States could be

identified, LaKind and Naiman (2011) was among the first to use the urinary levels of BPA and its metabolites to estimate daily BPA exposure among a nationally representative sample from the 2005–2006 NHANES. The study focused on using NHANES data to identify possible XE exposure pathways and sources but also incorporating demographic information to evaluate these factors for their association with urinary BPA levels.

Total urinary BPA was obtained in a 24-hour urine sample to approximate exposure in the previous 24 hours. Urinary BPA concentrations were combined with 24-hour urine output volume to estimate the daily excretion of BPA. Bottled water consumption was inversely associated with urinary BPA; however, the association was only identified for data from the second interview day (Day 1: $P = 0.32$ vs. Day 2: $P = 0.012$). Additionally, age ($P < 0.00001$), being female ($P = 0.0002$), and being a current smoker ($P = 0.012$) were negatively associated with urinary BPA. A serious shortcoming of their assumption regarding expected leaching of BPA from polycarbonate bottles has been recognized. Their analysis identified no association between increased urinary BPA and bottled water consumption, but as acknowledged by the researchers, no information on bottle type was included in the 2005–2006 NHANES data.

However, as confirmed by the literature (Jeddi et al., 2016; H. Li et al., 2019; Santana et al., 2014; Sax, 2010), PET is the most commonly used thermoplastic polymer resin in bottled drinking water. Therefore, as supported by LaKind and Naiman's analysis, the lack of an observed association of urinary BPA with bottled water consumption would be expected if leaching of PAEs, rather than BPA, occurred with

PET bottled water. The key implication drawn from this literature for the current study was that it further substantiates the appropriateness of phthalate urine level to determine an association with bottled water consumption. In addition, from this pivotal research, LaKind and Naiman underscored the feasibility and importance of using NHANES cross-sectional data for hypothesis-generating analysis.

Given the contradictory and inconclusive findings on the risk to human health from dietary XE exposure, research indicated the need for further epidemiologic studies to evaluate the potential effects of chronic PAE exposure from PET bottled drinking water consumption. At the time of the current study, a recent review of the literature on overall bottled drinking water consumption found no information suggesting a decline of bottled drinking water consumption in the United States since the preliminary work by LaKind and Naiman in 2011. There are a few significant factors that could influence bottled drinking water consumption among adults in the United States: race/ethnicity, education, and income. This is relevant as it is necessary to consider the confounding effects of these factors associated with the increased bottled drinking water consumption among certain populations and the potential for increased estrogen-dependent cancers. The literature (Rosinger et al., 2018; Vieux et al., 2020) supported using NHANES to provide a large, nationally representative population sample to assess bottled drinking water consumption in the United States as proposed for the current study.

Dietary PEs and XEs in Combination

After reviewing the extensive literature regarding the individual effects of dietary PEs and XEs on the development of estrogen-dependent cancers, further insight and

investigation into the potential effects of dietary PEs and XEs in combination was necessary. The combined co-exposure to dietary PEs and XEs has been poorly studied and the results have often been conflicting. Furthermore, there has been little investigation of the combined effects of dietary PEs and XEs in humans, particularly in epidemiologic studies. A literature review found that most research on the combined effects was conducted in in vivo and in vitro studies that used BPA as the sole XE agent with the PE genistein. Additionally, studies that investigated phthalates as the dietary XE exposure in combination with soy were not identified in the literature.

In Vitro Research

Many researchers have explored the association between genistein and BPA and the cellular and molecular actions related to cancer through in vitro and in vivo studies. Researchers have suggested regulation of ERα and ERβ is complicated due to the number of co-regulators that determine signaling specificity and intensity (J. Wang et al., 2014). Furthermore, in vitro research is complex, as the pathways identified among animal cell lines may not translate into humans due to numerous pathways for signaling, making the results of in vitro studies conflicting or inconclusive. Even more so, combination co-exposure studies have been considered too complex to be studied (J. Wang et al., 2014).

For instance, the first investigation into the interaction between and the combined effects of dietary PEs and XEs conducted by Hwang et al. (2012) found that genistein was able to inhibit cell proliferation mediated by ERα when BG-1 ovarian cancer cells were exposed to E_2 or BPA. E_2 and BPA worked in two ways to increase proliferative activity: (a) increased expression of cyclin D1, which is responsible for the cell cycle

transition from G1/S or (b) decreased expression of p21, a potent cyclin-dependent kinase inhibitor responsible for cell cycle arrest at the G1 phase. On the other hand, genistein was able to correct cell growth through the decreased expression of cyclin D1 and increased p21 expression, thereby, counteracting the effects of E_2 and BPA in ovarian cancer cells. This finding was noteworthy because genistein's inhibitory effect on the cell proliferation of estrogen-dependent cancers when exposed to E_2 or BPA is confirmed. This was relevant to the current study as it substantiated the ability for dietary PEs intake to counteract the potential effects of dietary XE exposure from bottled drinking water.

Contrary to the findings by Hwang et al. (2012), Katchy et al. (2014) suggested that genistein and BPA acted additively to exert magnified estrogenic effects and increase the risk for estrogen-dependent cancers. The in vitro analysis was conducted to assess the future implications of breast cancer among neonates based on their potential for increased endogenous estrogen following co-exposure to infant soy-based formula and BPA in combination in early life. The study demonstrated that the proliferative and transcriptional effects of genistein and BPA mirrored those of E_2 yielding a synergistic effect, and therefore, combined exposure to these compounds can produce significant biological effects in infants. A serious criticism of the study is that Katchy's findings significantly disagreed with those in previous and recent literature regarding the proposed mechanism of action for the PEs and XEs. The study suggested that PEs and XEs "activate the same ERα target genes as E_2 does" in MCF7 breast cell lines. In contrast, the literature contended that PEs target increase activation of ERβ and suppression of tumor

cell proliferation in line with the anti-proliferative effect of ERβ to yield chemopreventative effects.

Admittedly, Hwang et al. (2012) were not the only researchers that demonstrated the chemopreventative roles of and ability to inhibit carcinogenesis by PEs in the presence of co-exposure to other XEs, such as BPA, and E_2. For instance, Lee et al. (2018) similarly found that PEs could restore induced cell proliferation back to control level following co-exposure to XEs. Specifically, co-treatment with either PEs Kaempferol (30 μM) or 3,3'-diindolylmethan (15 μM) effectively inhibited the induced anti-apoptotic activities of triclosan (0.1-10 μM) and E_2 (0.01-0.0001 μM) in Vm7LUC4E2 breast cancer cells. Additionally, Kaempferol and 64iindolylmethane inhibited breast cancer cell proliferation induced by triclosan and BPA. This finding was significant as it continued to substantiate the ability to obtain hormonal balance, achieve "estrogen homeostasis" and reduce the risk of estrogen-dependent cancers through the restorative capabilities of dietary PEs when exposed to dietary XEs. Lee's research elucidated the mechanisms of the opposite effects of dietary XEs versus PEs via upregulation of Bxl-xl gene expression for anti-apoptotic protein and upregulation of the apoptotic protein BAX, respectively.

In Vivo Research

Animal studies were conducted to reproduce the in vitro research described above. Researchers who conducted in vivo research have documented the consistent ability of BPA to enhance cell proliferation and decrease apoptosis in the cells of rodents and humans through upregulation of estrogen or increased estrogen biosynthesis (Jadhav

et al., 2017; Lee et al., 2018; Patisaul et al., 2012; J. Wang et al., 2014; Yakimchuk et al., 2018). On the other hand, studies conducted with genistein exposure in the presence of BPA yielded conflicting results regarding their additive estrogenic effects (Katchy et al., 2014) versus the ability of genistein to reduce or counter the carcinogenic properties of BPA (Jadhav et al., 2017; Patisaul et al., 2012; J. Wang et al., 2014; Yakimchuk et al., 2018). For instance, Jadhav et al. (2017) conducted a study of prepubertal co-exposure in rats to BPA and genistein, alone or in combination, and found the mechanism for altering epigenetic effects was differential deoxyribonucleic acid methylation in specific genes. BPA exposure led to hypermethylation of many loci, but loci hypermethylation in genistein alone and BPA+genistein were significantly lower.

As previous research (Pons et al., 2019; J. Wang et al., 2014; Williams & Darbre, 2019) established the susceptibility to BPA and genistein in breast cancer, the differentially methylated genes in rats were mapped with gene expression in the Cancer Genomic Atlas to assess gene level differential regulation in breast cancer patients. Jadhav et al. (2017) found large overlap in the expression of these genes among ERα+ and ERα- breast cancer patients compared to normal tissue. Of the genes investigated, 12 were linked to overall survival outcome; specifically, 4 were strong predictors of poor survival and 8 were predictive of long-term survival. In the rat BPA exposure, 9 of the 12 genes were hypermethylated. Genes corresponding to long-term patient survival were hypomethylated in BPA single and BPA+genistein combination co-exposures. Poor survival genes were hypermethylated in the BPA single exposure yet hypomethylated in genistein single exposure.

This finding was noteworthy because it demonstrated that prepuberal exposure to genistein alone or in combination with BPA were hypomethylated, confirming the tumor suppressive property of genistein. The use of exposure and control groups further strengthened the study's findings. Additionally, in their analysis, the researchers determined that confirmation of genistein's ability to mitigate the negating effects of BPA on gene expression could be obtained by assessing gene methylation after exposure. This evidence was critical in supporting the research question of the current study in assessing the association between consumption of soy and bean products and bottled drinking water and estrogen-dependent cancer with the potential for an antagonistic effect.

The findings by Jadhav et al. (2017) were consistent with earlier investigations into combination co-exposure to BPA and genistein conducted by J. Wang et al. (2014). However, a unique aspect of Wang's research was that it involved assessing co-exposures in prepubertal and adult rats to not only address the effects of combinational co-exposure to BPA and genistein in breast cancer, but also to determine if there was an age effect. Aligning with the findings from other studies on the effects of BPA, the researchers found BPA exposure in adult rats resulted in cell proliferation of mammary glands, which was associated with an increased risk of breast cancer. In comparison, BPA exposure resulted in no significant effect on cell proliferation and apoptosis among prepubertal rats with values being similar to those of the control.

On the other hand, genistein exposure in prepubertal rats also increased cell proliferation 50% compared to controls, but this was correlated with mammary gland

maturation [differentiation from terminal end buds that are most susceptible to mammary carcinogenesis to lobules that are least susceptible] and protective effects. Genistein exposure in adult rats resulted in increased apoptosis that reduced the risk of carcinogenesis due to increased cell death and reduction in DNA damaged cell replication. The results of the combination of BPA+genistein co-exposure in both prepubertal and adults rats was similar to the results demonstrated for genistein alone. In prepubertal rats, combination co-exposure increased cell proliferation, but decreased cell proliferation and increased apoptosis in adult rats. This was relevant as it strengthened the argument for the protective effects of genistein, but subsequently supports the hypothesis that genistein co-exposure in both early and later in life can reduce the potential carcinogenic effects of BPA in development of breast cancer. This analysis provided further justification for an epidemiological study to determine if such an association exists between estrogen-dependent cancers and co-exposure to other dietary PEs and XEs in combination, such as soy and bean products and bottled drinking water, respectively. Additionally, J. Wang et al. (2014) affirmed these results could be interpreted to mean that early exposure to genistein functions as a "biochemical blueprint" by programming mammary glands to suppress carcinogenic susceptibility.

Previous studies have reported genistein's anticancer activity and beneficial properties during co-exposure with BPA in non-estrogen-dependent cancers and other diseases. For example, exposure to either BPA or dietary genistein reduced proliferation and promoted apoptosis, respectively, via induction of the estrogen-dependent regulation of ERβ in mouse and human lymphomas in vivo (Yakimchuk et al., 2018). Notably to

highlight that this was one of the only instances in the literature where oral exposure to BPA (50 μg/kg BW/day) was beneficial. Moreover, lymphoma tumor growth was inhibited at higher doses of BPA; yet no change in growth was identified at lower dose levels, 1 μg/kg BW/day or 0.02 μg/kg BW/day.

In line with other researchers, Yakimchuk found that genistein exposure significantly suppressed lymphoma tumor growth at doses of 10 and 1 mg/kg BW/day, but the 0.1 mg/kg BW/day dose was insufficient to generate an effect. This minimum dose effect of ≥ 1mg/kg BW/day is equivalent to a daily soy intake of 70 g/day, corresponding to consumption as part of the typical Japanese diet. Likewise, a similar mitigating effect of soy with early life BPA exposure in rat amygdala associated with behavioral effects has been confirmed (Patisaul et al., 2012). Aside from carcinogenic effects, BPA also induced anxiogenic responses or anxiety-induced behavior among juvenile rats that consumed a soy-free diet via downregulation of ERβ and 2 melanocortin receptors.

A significant strength of the study and its findings were the 5 comprehensive exposure groups, which included a control: (a) BPA only (soy-free diet plus water containing BPA); (b) Soy only (soy diet); (c) BPA+Soy combination (soy diet plus water containing BPA); (d) Soy-free (soy-free diet); (e) Control (soy-free diet plus water contain estradiol). The exposure groups were able to distinguish the direct of exposure on anxiety-like behavior. Since no effect of BPA was found among rats fed the soy diet with water containing BPA, this confirmed a significant modifying effect of diet. Furthermore,

as even low dose BPA exposure was sufficient to induce anxiogenic response, the soy diet could counter the effects of BPA in inducing anxiety-like behavior.

This was relevant to the current study as it suggested the potential for dietary PEs to counter the effects of PAE leaching in bottled drinking water consumption on the development of estrogen-dependent cancers. This warranted further epidemiological research on the association between dietary PEs and XEs and the effects in humans, which the current study sought to investigate. Consistent with an age effect confirmed by T. Wang et al. (2018), research by Patisaul et al. (2012) concluded that the developmental impact of BPA persisted into adulthood. Yet a soy diet was able to still yield protective effects and alleviated effects of the early life BPA exposure. This was significant as it highlighted the potential for a similar effect of concomitant administration of a soy-based diet to be possible in humans to reduce future incidence of estrogen-dependent cancers due to BPA exposure.

Human Research

Interest in the combined effects of dietary PEs and XEs is growing. However, human studies are lacking to examine the potential association between dietary PE intake and dietary XE exposure in the development of estrogen-dependent cancers. A review of the literature on combination co-exposure to dietary PEs and XEs was found to be scant. Nonetheless, the findings of the combined effects of dietary PEs and XEs in present and prior in vitro and in vivo studies have implications for patients with estrogen-dependent cancers. The hypothesis that ongoing lifetime exposure to EDCs, such as BPA and phthalates, and that dietary PEs, such as soy and bean products, can mitigate the impact

of exogenous estrogen was supported by parallel work in the in vitro and in vivo studies. The cellular and molecular mechanisms identified for mediating ER responses in rodents and primates, including humans, were critical to determine if effects observed in animal models have implications for human health. Furthermore, as data have shown the potential for dietary XE exposure to increase risk of estrogen-dependent cancer, it has shown the potential for those effects to be modified and mitigated by dietary PEs.

Summary and Conclusion

Estrogen-dependent cancers represent a significant disease burden among men and women and a major public health concern within the United States and globally. Various sources of exogenous estrogens in daily life contribute to and increase lifetime exposure to circulating estrogens. However, these circulating estrogens play a significant role in carcinogenesis among estrogen-dependent cancers. A wide range of research indicates that overall diet, the intake of specific foods, and exposure to estrogen in the diet can affect the onset and progression of estrogen-dependent cancers. In the literature, there were a surprising number of inconsistent and inconclusive findings on the impact of the various sources of dietary estrogen exposure in combination. The effect of co-exposure to dietary PEs and XEs and how these interacted to contribute to increased risk of estrogen-dependent cancers, particularly in human or epidemiological studies, was still uncertain. Research has suggested that there may be an association between high soy and soy-based products intake, phthalate exposure from bottled drinking water consumption, and estrogen-dependent cancer outcomes. Furthermore, the opposing antiestrogenic and estrogenic properties of dietary PEs and XEs, respectively, added further support to the

suggested association between them. In general, no studies have been conducted that directly examined the potential association between dietary intake of soy and bean products, bottled drinking water consumption, and estrogen-dependent cancer within the U.S. population.

The NHANES database presented a novel opportunity to address this gap in the literature. The data from NHANES allowed for an accurate assessment of diet, estrogen-dependent cancer diagnosis, urine levels of phytoestrogen and phthalate, and a potential association between them. Therefore, my aim with the current study was to examine the potential association between soy and bean product intake, bottled drinking water consumption, and estrogen-dependent cancers. The design and methodological approached used in the current study are described in Chapter 3.

Chapter 3: Research Method

The purpose of this quantitative study was to determine the association between dietary PE intake and dietary XE exposure and estrogen-dependent cancers among a sample of adults age 18 years and older in the United States in the 2003–2006 NHANES. At the time of the current study, there was limited research on the association of co-exposure to dietary PEs and XEs with estrogen-dependent cancer incidence in epidemiological studies, and I sought to add to the current body of knowledge. This chapter includes a discussion of the research design and rationale of the study. The chapter's methodology section includes the sample population and sampling procedures used in the 2003–2006 NHANES. Because I employed secondary data, the chapter includes a description of the methods for collecting dietary PE and XE data, including the description and analysis of proxy laboratory measurements, from the original NHANES data sets. Furthermore, I describe the methodology for determining the use of proxy measures for PE and XE urine levels and explain the data analyses and statistical procedures to test the study's hypotheses. Finally, I discuss the study's threats to validity and ethical considerations.

Research Design and Rationale

Quantitative Method

I employed a quantitative survey design using secondary data from the 2003–2004 and 2005–2006 iterations of NHANES to assess the potential relationship between dietary PE intake and dietary XE exposure and estrogen-dependent cancers in the United States. The independent variables were daily PE intake and daily XE exposure,

phytoestrogen urine levels, phthalate urine levels, and interaction effect between the two independent variables, PEs and XEs. The dependent variable was estrogen-dependent cancer (breast, cervical, colorectal, endometrial, ovarian, and prostate) diagnosis or no cancer diagnosis. Confounders included age, gender, race, education level, and marital status. A quantitative approach was best for the current study because the research questions addressed factors, dietary PEs and XEs, that influence an outcome, estrogen-dependent cancer diagnosis (see Creswell & Creswell, 2018).

A qualitative research approach is appropriate for understanding a concept or phenomenon to be explored, which was not the case for the current study. In addition, a qualitative approach would not have been appropriate to evaluate whether dietary PEs and XEs are associated with estrogen-dependent cancer diagnoses using NHANES data, because NHANES data did not contain narrative information or open-ended questions to address the current study's research questions. Unlike qualitative data collected from observations, NHANES collected quantitative data obtained from instruments using questionnaires and structural interviews that allowed for appropriate assessment of the current study's research questions in determining whether a relationship exists between dietary intake/exposures and cancer outcome. Furthermore, a quantitative research design allowed for testing of the hypotheses of the research questions by examining the relationship among the independent and dependent variables (see Allen, 2017; Creswell & Creswell, 2018).

Survey Design

The NHANES data sets were selected for the current study because they provided comprehensive numeric data using an extensive sampling of a nationally representative U.S. population. Using NHANES data sets, researchers cannot adopt an experimental design because treatment conditions cannot be assigned when using secondary data, and NHANES uses survey instruments. The survey research from NHANES data sets contains quantitative measures of dietary PE/XE intake and PE/XE urine exposure levels. Because diet is the primary route of exposure to dietary PEs and XEs, dietary PEs and XEs may represent possible contributing factors to estrogen-dependent cancer (Deng et al., 2020; Schettler, 2006). The 2003–2006 iterations of NHANES were selected because they were the most current surveys that included laboratory testing of PE urine levels and XE urine levels, which were accurate proxies for PE intake and XE exposure levels, respectively (see LaKind & Naiman, 2011).

The observational nature of epidemiological studies makes cohort, case-control, cross-sectional, and ecologic study designs the most commonly used research designs in public health research (Szklo & Nieto, 2014). The cross-sectional designs are also appropriate when using secondary data such as that from NHANES, because NHANES is a cross-sectional survey of the U.S. population (Avila-Tang et al., 2013; Dwyer et al., 2003). NHANES data capture information on a population of interest to observe a pattern of exposure as a snapshot of a specific period in time, such as in the selected NHANES iteration years. Unlike in experimental studies, it is impossible to establish causality from a cross-sectional study design using survey methods; instead, a researcher can identify

associations by assessing exposure and outcome at a single point in time (Creswell & Creswell, 2018; Szklo & Nieto, 2014).

For these reasons, the cross-sectional design was selected for the current study. The cross-sectional design was appropriate to investigate an association that had not been examined in the literature. The choice of a cross-sectional design was consistent with research designs needed to advance knowledge in the public health discipline because this design can ascertain factors associated with health-related behaviors to promote a healthier diet and reduce the incidence of estrogen-dependent cancers. If there was a predictable association between dietary PE intake and XE exposure and estrogen-dependent cancers, the results could assist with measures to prevent cancer, such as by providing more public awareness and implementing changes to public health and policy promotion. Based on the operational, technical, and economic feasibility of conducting a cross-sectional study with NHANES data, a cross-sectional design was appropriate when assessing dietary risk factors for estrogen-dependent cancers among a large U.S. population represented by NHANES 2003–2006.

Methodology

Population

The study population included both men and women in the 2003–2006 NHANES, and their data were obtained from the publicly available 2003–2006 NHANES data sets (see CDC, 2020c). The 2003–2006 range encompassed two cycles of NHANES data sets: the 2003–2004 and the 2005–2006 NHANES. The sample sizes were 10,122 for the 2003–2004 NHANES and 10,348 for the 2005–2006 NHANES, for a combined sample

size of 20,470. The NHANES assesses children's and adults' health and nutritional status in the United States and collects information from a nationally representative sample that includes participants of various races and ethnicities (CDC, 2020d). In the current cross-sectional analysis, the sample population consisted of all participants 18 years and older. Although most estrogen-dependent cancers are diagnosed at 50 years and older, the inclusion of participants 18–49 years of age in the current study was relevant because estrogen-dependent cancer diagnoses occur within this younger age range (Assi et al., 2013; Cathcart-Rake et al., 2021; Felix et al., 2017; Kotsopoulos et al., 2018; Manjelievskaia et al., 2017; Sopik et al., 2017).

Sampling and Sampling Procedures

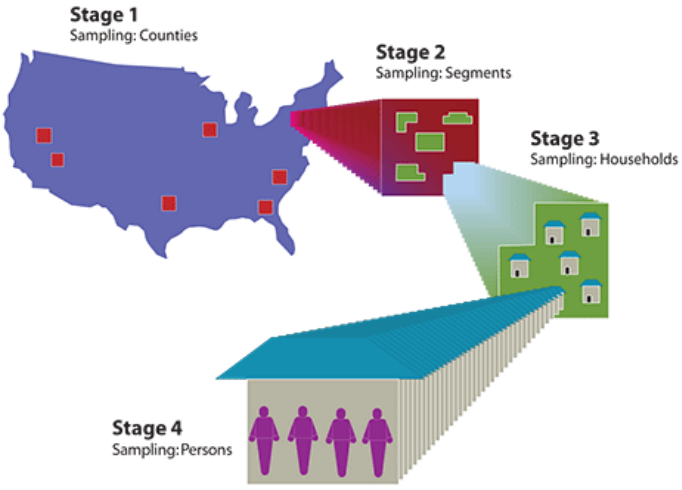
NHANES uses a complex sampling procedure designed to assess adults' and children's health and nutritional status in the United States annually. The multistage probability sampling design obtains a representative sample of the civilian, noninstitutionalized U.S. population by selecting approximately 5,000 individuals (CDC, 2020c). The NHANES sampling procedure consists of four stages, as shown in Figure 3, with each sampling broken into smaller population segments called primary sampling units (CDC, 2020c). Stage 1 consists of selecting primary sampling units from single counties or groups of contiguous counties in the United States, where the groups combine to form 15 counties that make up the NHANES surveys for each year (CDC, 2018). Stage 2 involves sampling smaller groups (segments) by census blocks/combinations of blocks or their equivalent within each county. Stage 3 encompasses sample selection from

dwelling units (households; CDC, 2020c). For Stage 4, individuals are chosen from a list of all individuals living in the selected households.

Furthermore, to ensure a representative population of the United States in the sample, individuals are randomly selected within the dwelling units designated by age-sex-race/ethnicity screening subdomains (CDC, 2020c). The inclusion of these subdomains generates robust screening rates to produce the desired number of sample participants for the most challenging race and Hispanic origin-sex-age-income domains in the minority stratum (CDC, 2020d). Oversampling of specific individuals is also intentionally done to ensure the sample selected represents the U.S. population. Individuals oversampled include those 80 and older, African Americans, Asians, Hispanics, and those at or below the federal poverty level (CDC, 2020c). To stabilize the statistical estimates from 1-year data, NHANES data are publicly released in 2-year cycles.

Figure 3

How was I selected?



Note. Adapted from CDC (2018).

In addition, the current study included as many participants as possible from the 2003–2006 NHANES data sets for which data were complete to ensure an appropriate sample size was obtained. Participants included in the current study completed dietary data to assess PE intake and XE exposure and urine laboratory samples for testing of PE urine levels and XE urine levels, and they responded positively or negatively to having a diagnosis of estrogen-dependent cancers. Respondents that reported a diagnosis of types of cancers other than estrogen-dependent cancers were excluded. Individuals age 17 years and under were excluded.

Power Analysis

The use of a power analysis was necessary to determine a sufficient sample size, which was obtained by using G*Power 3.1.9.6 for macOS (see Faul et al., 2007). By using the sample size suggested from the power analysis, I was confident that there

would be sufficient data to make a reasonable decision regardless of the *p* value. Furthermore, the power analysis ensured a high probability for correct rejection of the null hypothesis (Creswell & Creswell, 2018). An a priori power analysis computed the sample size (*N*) needed to detect some level of effect based on the alpha (α), power (1-β err prob), and effect size during the design stage of the study. Logistic regression analyses were used to answer the study's research questions. To determine sample size, I used the following input parameters: *z* tests, logistic regression, a priori power analysis, two tails, odds ratio of 0.5 for medium effect size, power of 0.80, R^2 for other controls = 0, normal distribution, X parm μ = 0, and X parm σ = 1. The resulting sample size estimate in G*Power for logistic regression analysis was 113 participants. The statistical power of 80% is typically used to achieve an improved probability of rejecting a false null hypothesis (Whitley & Ball, 2002), and this was the power I used. An alpha of 0.05 ($p < 0.05$ threshold for statistical significance) is the most common significance value, and it was used in the current study. Based on similar food frequency studies with this analysis, the average effect size ranged from 0.5 to 0.7 for nutrient intakes (Melzer et al., 2010; Willett, 2013).

Use of Archival Data

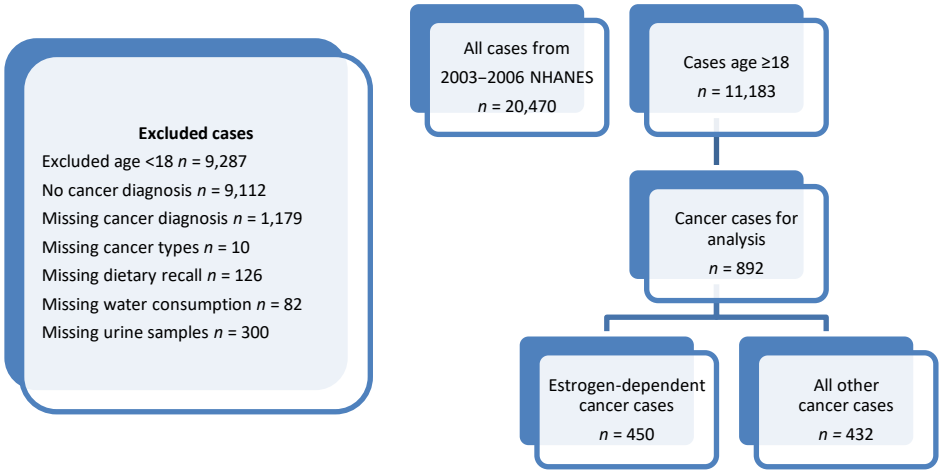
Data from the 2003–2006 NHANES were collected from participants through household interviews, diagnostic testing, and medical health examinations. A trained interviewer conducted all interviews and administered all questionnaires for the household interview component (CDC, 2020c). The questionnaire was used to obtain self-reported, individual-level information on various health outcomes and behaviors

such as oral health, physical activity, and medical conditions (CDC, 2020c). Following the completion of the household interview, study participants were asked to visit a mobile examination center (MEC) where interviewers administered a 24-hour dietary recall questionnaire (CDC, 2020c). Questionnaires were also used to collect data on more sensitive topics such as depression, drug use, and reproductive health (CDC, 2020c). Urine and blood samples were obtained in addition to assessments such as body measurements, electrocardiography, spirometry, and X-rays (CDC, 2020c). Some samples were analyzed in the MEC laboratory, but most of the analyses occurred at contract laboratories (CDC, 2020c). Data collected from the NHANES are intended for public use, with consent provided by participants to allow the future use of collected data; therefore, additional permissions for data use were not necessary.

Following Walden University Institutional Review Board (11-01-21-0436046) approval, I downloaded the secondary data sets from NHANES. The data for the current study were obtained from the 2003–2006 NHANES data sets related to the variables of interest in the study for demographic, dietary, laboratory, and health outcome assessments. Preparation of the 2003–2006 NHANES data set followed the process described in this chapter to form a complete data set for the study. The initial combined 2003–2006 NHANES data set included 20,470 participants. This consisted of 10,122 from the 2003–2004 NHANES data set and 10,348 from the 2005–2006 NHANES data set. As shown in Figure 4, I removed cases according to the exclusion criteria for the current study to reduce the study sample size to address each research question.

Figure 4

Cases Available for Analysis After Applying Criteria



Instrumentation and Operationalization of Constructs

The data collection instruments used to obtain data for the current study consisted of NHANES survey questionaries and laboratory sample collection. Since 1960, the National Center for Health Statistics (NCHS), a part of the Centers for Disease Control and Prevention (CDC), conducts the NHANES program as a series of health examination surveys used to collect data on health topics from different population groups (CDC, 2020e). NHANES data are useful in determining disease prevalence and risk factors for disease to develop health promotion and disease prevention activities (CDC, 2020b). NHANES data were appropriate for use in the current study since data from this survey were used in population-based epidemiological studies (CDC, 2020b). In addition, NHANES data contained the appropriate variables that would allow for examination of

the dietary and lifestyle risk factors for estrogen-dependent cancer among the U.S. adult population for this study.

The data for the current study was obtained from the 2003-2006 NHANES data sets related to the variables of interest in the study for demographic, dietary, laboratory, and health outcome assessments. Trained interviewers obtained this information from participants during interviews, examinations, and laboratory sample collection. Interviewers administered NHANES questionnaires to participants on two separate occasions, once in their home and once in the MEC trailers. The specific questions from the 2003-2006 NHANES questionnaire used to obtain the data can be found in Appendix 1. The 2003-2006 NHANES questionnaire instruments included screener modules and the "Family Questionnaire" to obtain information on demographics and food consumption; the "Sample Person Questionnaire" to collect data on medical history and dietary behavior; and a MEC examination that included a health exam, laboratory testing on blood and urine, and food recall (CDC, 2020f). Interviewers obtained food frequency consumption information from participants through 24-hour dietary recall interviews conducted at two independent time points to better assess the usual dietary intake of the U.S. population. Participants completed the in-person recall survey in the MEC trailers, followed by the second nutritional recall by phone three to 10 days after the initial in-person interview (CDC, 2020g). The 2003-2006 NHANES laboratory data included specimens collected at the MECs that included blood, urine, and swabs (CDC, 2020h). Trained laboratory staff consisting of medical technologists and phlebotomists collected laboratory specimens. To ensure the integrity of the samples collected, strict guidelines

and protocols were adhered to associated with the collection and processing of blood and urine samples.

The NHANES data release and access policy addresses "when, to whom, and in what form" the NHANES data are available. NHANES data are available on the internet for public use through the release of data nine months after completion of each two-year data collection cycle. Although publicly available, NHANES data for the current study was accessed after Walden Institutional Review Board (IRB) approval was obtained. The NHANES findings are used in and are the basis for publications on public health topics, reports on exposure to environmental chemicals, and health indicators of diet and nutrition.

Study Variables

Dependent Variables

The dependent variable for the current study was cancer diagnosis (MCQ220) and was operationally defined as a reported estrogen-dependent cancer diagnosis (MCQ230A), which includes breast, cervical, colorectal, endometrial, ovarian, and prostate (coded as 14, 15, 16, 31, 38, 28, and 30, respectively). The value of the dependent variable was determined based on participant responses to the following two questions: "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?" for which responses included a nominal measurement of Yes = 1 and No = 0, and "What kind of cancer was it?" for which responses were also on a nominal level of measurement. Cancer types were limited to 29 possible answers and respondents were able to provide up to three kinds of cancers.

However, for the purposes of this study, only the initial response provided for the type of cancer was used to determine and code if the respondent had a diagnosis of estrogen-dependent cancer. There were also choices for "Other (39)," "Refused (77)," and "Don't Know (99)."

Independent Variables

The independent variables for the current study were daily PE intake and daily XE exposure, phytoestrogen urine levels, phthalate urine levels, and interaction effect between the two independent variables, PEs and XEs. Moderate soy consumption among U.S. adults was defined as one to two servings daily of soy foods, where 1 serving is equivalent to 25 mg isoflavones (American Institute for Cancer Research, 2019). In comparison, high soy consumption among Asian populations averaged three servings/day or up to 100 mg/day of isoflavones (AICR, 2019). Correspondingly, the American dietary guidelines for adults for consumption of beans and legumes are five servings per week, where the average serving is ½ cup of dried beans (American Heart Association, 2017). Recent literature on dietary intake trends among adults in the United States, specifically for soy and bean products, suggested that overall PE consumption was low and that contributions to PE intake primarily come from consuming coffee, tea, and dietary supplements (Huang et al., 2020). This finding was consistent with overall low consumptions of fruits, vegetables, and whole grains among U.S. adults in relation to current daily nutritional recommendations in the 2015-2020 Dietary Guidelines for Americans (Huang et al., 2020; U.S. Department of Agriculture, 2015).

To assess PE intake, participants were asked individually about soy and bean product frequency consumption, which for soy consumption included the question, "How often did you eat tofu, soy burgers, or soy meat-substitutes?" (Question FFQ0056). Next, to determine bean product consumption, participants were asked, "How often did you eat cooked dried beans (such as baked beans, pintos, kidney, blackeyed peas, lima, lentils, soybeans, or refried beans, excluding bean soups or chili)?" (Question FFQ0096). For each of the soy and bean product consumption questions, the participants could select from the following ordinal choice options, 1 = *never*, 2 = *1-6 times per year*, 3 = *7-11 times per year*, 4 = *1 time per month*, 5 = *2-3 times per month*, 6 = *1 time per week*, 7 = *2 times per week*, 8 = *3-4 times per week*, 9 = *5-6 times per week*, 10 = *1 time per day*, and 11 = *2 or more times per day*. The specific questions from the 2003-2006 NHANES questionnaire used to obtain the data can be found in Appendix 1.

Since research (Huang et al., 2020) confirmed that the overall intake of PEs among U.S. adults was lower than the recommended dietary guidelines, with most adults not meeting the recommendations for even moderate consumption of one to two servings daily, I adjusted the dietary PE consumption to operationalize "high" consumption of PEs at a lower daily intake value to account for lower overall PE consumption in the U.S. population. To address Research Question 1 (RQ1), the daily PE intake was operationally defined as "high consumption" (at least 3-4 times per week or greater) of soy (FFQ0056, coded as 8, 9, 10, & 11) and/or bean products (FFQ0096, coded as 8, 9, 10 & 11). Subsequently, "moderate" consumption of the daily PE intake was operationally defined as between 1 time per month to 2 times per week of soy (FFQ0056, coded as 4, 5, 6, & 7)

and/or bean products (FFQ0096, coded as 4, 5, 6, & 7). Finally, “low” consumption of the daily PE intake was operationally defined as from never to 7-11 times per year of soy (FFQ0056, coded as 1, 2, & 3) and/or bean products (FFQ0096, coded as 1, 2, & 3). I recoded and reduced the number of groups for the soy and bean product intake variables each into 3 ordinal variables. The responses for the newly coded variables then appropriately reflected the operational definitions for high, moderate, and low PE intake in RQ1.

Daily XE exposure was operationally defined as presence or absence of bottled drinking water consumed by participants on a nominal scale. Each participant’s XE exposure was calculated by averaging the grams of bottled drinking water consumed in two, non-consecutive, 24-hour dietary recalls (DR1BWATR, coded as 0-9472; DR2BWATR, coded as 0 – 7577.6, respectively). Then I recoded the amount of total bottled water consumed per day by participants from a continuous ratio scale to binary variables on a nominal categorical scale. The daily XE exposure was operationally defined as “Yes” (any value > 0, coded as 1) and “No” (value equal to 0, coded as 0).

Additional independent variables for the current study included urine PE and urine phthalate metabolite levels used as proxy measurements for PE consumption and XE exposure. The use of urine biomarkers minimized the possibility for self-reporting bias and the potential measurement error in 24-hour dietary recall for assessing soy and bean product intake and bottled drinking water consumption (Ahluwalia et al., 2016; Kirkpatrick et al., 2019; McKeown et al., 2001; Va et al., 2019). The urine PE and XE values were measures of circulating exogenous estrogen. Such biomarkers of PE were

needed to establish “reference ranges for these compounds and evaluate their potential effects on human health” (CDC, 2020a). The literature established the validity of urine levels (Clarke et al., 2020; Environmental Protection Agency [EPA], 2015; LaKind & Naiman, 2011; Valentín-Blasini et al., 2003) as proxy measures for exogenous estrogen, which included six common measures of PE and seven of the most frequently found phthalate metabolites in humans (EPA, 2015; Blount et al., 2000).

For both urine PEs and XEs levels, the total values were measured as continuous interval variables, and individual PE and XE intake values were adjusted to total average PE and XE intake values in nanograms per milliliter (ng/mL) to provide a more accurate reflection of overall exposure for disease outcomes in epidemiologic analysis (Clarke et al., 2020; Willett, 2013; Willett & Lenart, 1998). Then I recoded the total average urine PE and phthalate values from a continuous ratio scale to 3 ordinal variables. The urine PE levels were operationally defined as “high” presence (> 288 ng/mL, coded as 3); “moderate” presence (235 – 287 ng/mL, coded as 2); and “low” presence (< 234 ng/mL, coded as 1). Similarly, the urine phthalate levels were operationally defined as “high” presence > 109 ng/mL, coded as 3); “moderate” presence (88 – 108 ng/mL, coded as 2); “low” presence (< 87 ng/mL, coded as 1). Urine PEs and XEs in the study were quantified as isoflavones (daidzein, o-desmethylangolensin, equol, genistein,); lignans (enterodiol, enterolactone); and phthalate metabolites (mono-n-butyl phthalate; mono-ethyl phthalate; mono-2-ethyl-5-hydroxyhexyl; mono-2-ethyl-hexyl phthalate; mono-isobutyl phthalate; mono-2-ethyl-5-oxohexyl; mono-benzyl phthalate).

Covariates identified as potential confounders to be controlled for and which are available in NHANES included age, gender, race, education level, and marital status (Hilz & Wagner, 2018; House et al., 1990; Kahlert et al., 2017; Kato et al., 1989; LaKind & Naiman, 2011; Rosinger et al., 2018; Sakharkar & Kahaleh, 2017; Vieux et al., 2020). Table 1 provides a description of the data dictionary for the dependent variable, independent variable, and covariates. Table 2 provides a description of the variable coding and operationalization.

Table 1

Data Dictionary

Variable (variable name)	Variable description	Variable type	Value option (code)
Dependent variable (DV)			
• Cancer (MCQ220)	Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?	Nominal, dichotomous (binary)	1= Yes, 2 = No, 7 = Refused, 9 = Don't Know
Type (MCQ230A)	What kind of cancer was it?	Nominal	10 = Bladder, 11 = Blood, 12 = Bone, 13 = Brain,14 = Breast, 15 = Cervical, 16 = Colon, 17 = Esophageal, 18 = Gallbladder, 19 = Kidney, 20 = Larynx/Windpipe, 21 = Leukemia, 22 = Liver, 23 = Lung, 24 = Lymphoma/Hodgkins' Disease, 25 = Melanoma, 26 = Mouth/Tongue/Lip, 27 = Nervous System, 28 = Ovarian, 29 = Pancreatic, 30 = Prostate, 31 = Rectal, 32 = Skin (non-melanoma), 33 = Skin (don't know what kind), 34 = Soft Tissue (muscle or fat), 35 = Stomach, 36 = Testicular, 37 = Thyroid, 38 = Uterine, 39 = Other, 66 = More Than 3 Kinds, 77 = Refused, 99 = Don't Know
Independent variable (IV)			
• Bean consumption (FFQ0096)	How often did you eat cooked dried beans (such as baked beans, pintos, kidney, blackeyed peas, lima, lentils, soybeans, or refried beans? (Please don't include bean soups or chili.)	Ordinal	1 = never, 2 = 1-6 times per year, 3 = 7-11 times per year, 4 = 1 time per month, 5 = 2-3 times per month, 6 = 1 time per week, 7 = 2 times per week, 8 = 3-4 times per week, 9 = 5-6 times per week, 10 = 1 time per day, 11 = 2 or more times per day
• Soy consumption (FFQ0056)	How often did you eat tofu, soy burgers, or soy meat-substitutes?	Ordinal	1 = never, 2 = 1-6 times per year, 3 = 7-11 times per year, 4 = 1 time per month, 5 = 2-3 times per month, 6 = 1 time per week, 7 = 2 times per week, 8 = 3-4 times per week, 9 = 5-6 times per week, 10 = 1 time per day, 11 = 2 or more times per day
• Bottled drinking water consumption (Day 1 – DR1BWATR; Day 2 – DR2BWATR)	Total bottled water drank yesterday (gm)	Ratio, continuous	0 – 9472 0 – 7577.6
• Urine PE			
○ Soy:			
▪ Daidzein (URXDAZ)	Daidzein (ng/mL)	Interval, continuous	0.2 to 29200
▪ o-Desmethylangolensin (URXDMA)	o-Desmethylangolensin (O-DMA) (ng/mL)	Interval, continuous	2.46 to 3890
▪ Equol (URXEQU)	Equol (ng/mL)	Interval, continuous	0.2 to 8040
▪ Genistein (URXGNS)	Genistein (ng/mL)	Interval, continuous	0.2 to 25700
○ Bean:	Enterodiol (ng/mL)	Interval, continuous	0.2 to 16400
▪ Enterodiol (URXETD)			
▪ Enterolactone (URXETL)	Enterolactone (ng/mL)	Interval, continuous	0.2 to 42100

Variable (variable name)	Variable description	Variable type	Value option (code)
• Urine phthalate o Mono-n-butyl phthalate (URXMBP)	Mono-n-butyl phthalate (ng/mL)	Interval, continuous	0.3 to 5143.2
o Mono-ethyl phthalate (URXMEP)	Mono-ethyl phthalate (ng/mL	Interval, continuous	2.31 to 30589.02
o Mono-(2-ethyl-5-hydroxyhexyl) (URXMHH)	Mono-(2-ethyl-5-hydroxyhexyl) (ng/mL)	Interval, continuous	0.2 to 3141.4
o Mono-(2-ethyl)-hexyl phthalate (URXMHP)	Mono-(2-ethyl)-hexyl phthalate (ng/mL)	Interval, continuous	0.6 to 718
o Mono-isobutyl phthalate (URXMIB)	Mono-isobutyl phthalate (ng/mL)	Interval, continuous	0.2 to 359.1
o Mono-(2-ethyl-5-oxohexyl) (URXMOH)	Mono-(2-ethyl-5-oxohexyl) (ng/mL)	Interval, continuous	0.4 to 1953.5
o Mono-benzyl phthalate (URXMZP)	Mono-benzyl phthalate (ng/mL)	Interval, continuous	0.056 to 862.272
Covariates variables			
• Age (RIDAGEYR)	Best age in years of the sample person at time of screening.	Interval, continuous	0-84, ≥85
• Gender (RIAGENDR)	Gender of the sample person	Nominal, dichotomous	Men = 1, Women = 2
• Race (RIDRETH1)	Recode of reported race information	Nominal	1 = Mexican American, 2 = Other Hispanic, 3 = Non-Hispanic White, 4 = Non-Hispanic Black, 5 = Other Race (including Multi-Racial)
• Education level (DMDEDUC2)	What is the highest grade or level of school you have completed or the highest degree you have received?	Ordinal	1 = Less than 9^{th} grade, 2 = $9\text{-}11^{th}$ grade, 3 = High School Grad/GED or equivalent, 4 = Some College or AA degree, 5 = College Graduate or above
• Marital status (DMDMARTL)	Now married, widowed, divorced, separated, never married or living with a partner?	Nominal	1 = Married, 2 = Widowed, 3 = Divorced, 4 = Separated, 5 = Never married, 6 = Living with partner, 77 = Refused, 99 = Don't know
• Annual household income (INDHHINC)	Total household income (reported as a range value in dollars	Ordinal	1 = $0-$4,999, 2 = $5,000-$9,999, 3 = $10,000-$14,999, 4 = $15,000-$19,999, 5 = $20,000-$24,999, 6 = $25,000-$34,999, 7 = $35,000-$44,999, 8 = $45,000-$54,999, 9 = $55,000-$64,999, 10 = $65,000-$74,999, 11 = $75,000 and over, 12 = Over $20,000, 13 = Under $20,000

Table 2

Variable Coding and Operationalization

Variable name	Operational definition	Recoded
Cancer	Presence of cancer	0 = No, 1 = Yes
Estrogen-dependent cancer	Presence of estrogen-dependent cancer	0 = No, 1 = Yes
Bean consumption	• Low: < 1 time per month bean products • Moderate: ≥ 1 time per month to < 3-4 times per week bean products • High: ≥ 3-4 times per week bean products	1 = Never through 7-11 times per year [low bean consumption], 2 = 1 time per month to 2 times per week [moderate bean consumption] 3 = 3-4 times per week to 2 or more times per day [high bean consumption] 88, 99 = Missing
Soy consumption	• Low: < 1 time per month soy products • Moderate: ≥ 1 time per month to < 3-4 times per week soy products • High: ≥ 3-4 times per week of soy products	1 = Never through 7-11 times per year [low PE consumption], 2 = 1 time per month to 2 times per week [moderate PE consumption] 3 = 3-4 times per week to 2 or more times per day 88, 99 = Missing
Bottled Water Exposure	Response of bottled water consumed	0 = No, 1 = Yes
PE urine level	• Low: < average 234 ng/mL • Moderate: ≥ average 234 ng/mL to < average 287 ng/mL • High: ≥ average 288 ng/mL	1 = < average 234 ng/mL 2 = ≥ average 234 ng/mL to < average 287 ng/mL 3 = ≥ average 288 ng/mL
Phthalate urine level	• Low: average < 87 ng/mL • Moderate: ≥ average 87 ng/mL to < average 108 ng/mL • High: ≥ average 109 ng/mL	1 = < average 87 ng/mL 2 = ≥ average 87 ng/mL to < average 108 ng/mL 3 = ≥ average 109 ng/mL
Interaction bean consumption and bottled drinking water	Bean consumption*Bottled drinking water Control/Reference – 3-4 times per week to 2 or more times per day [high bean consumption]	• Low bean consumption*Bottled drinking water • Moderate bean consumption*Bottled drinking water • High bean consumption*Bottled drinking water
Interaction soy consumption and bottled drinking water	Soy consumption*Bottled drinking water Control/Reference – 3-4 times per week to 2 or more times per day [high soy consumption]	• Low soy consumption*Bottled drinking water • Moderate soy consumption*Bottled drinking water • High soy consumption*Bottled drinking water
Interaction PE and phthalate Urines	PE urine levels*phthalate urine levels Control/Reference – High PE urine*High Phthalate urine	• High PE urine*High Phthalate urine • Low PE urine*Low Phthalate urine • Low PE urine*Moderate Phthalate urine • Low PE urine*High Phthalate urine • Moderate PE urine*Low Phthalate urine • Moderate PE urine*Moderate Phthalate urine • Moderate PE urine*High Phthalate urine • High PE urine*Low Phthalate Urine • High PE urine*Moderate Phthalate Urine

Data Analysis Plan

All analyses for the current study used the statistical package for social sciences (SPSS) version 27. In order to create a complete data set that includes all variables required for analysis, the data used in the current study was appropriately organized, cleaned, and extracted into SPSS from the SAS transport (.XPT) file that NHANES data were saved in. Subsequently, an assessment of the final data set was conducted to ensure that all assumptions were met for each statistical procedure used to test the study hypotheses. These assumptions are further discussed in Chapter 4.

Research Questions and Hypotheses

RQ1: Is there an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$1: There is no association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$1: There is an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ2: Is there an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$2: There is no association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$2: There is an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ3: Is there an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$3: There is no association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$3: There is an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among

adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ4: Is there an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$4: There is no association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$4: There is an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ5: Is there an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$5: There is no association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial,

ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$5: There is an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

RQ6: Is there an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$6: There is no association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$6: There is an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

Descriptive statistics were calculated to characterize the sample population in terms of measures of central tendency (median, mode) and dispersion (minimum, maximum, range, percentile, and frequency distribution). Frequency distribution tables reporting the number and percentage of occurrence were provided for all categorical variables to summarize demographic information, including gender, race, education level, marital status, income, and cancer type. The measures of central tendency (mean, median, mode) and dispersion (minimum, maximum, range, percentile, frequency distribution, and standard deviation) were provided for continuous variable, age (Marshall & Jonker, 2010). The continuous variables were examined to determine whether they met assumptions for statistical analysis of normality, skewness, and kurtosis. To control for confounders when using secondary data, statistical methods needed to be employed to adjust for the effects of confounding variables on both the dependent and independent variables (Pourhoseingholi et al., 2012). For this study, multivariable regression analysis was used to control for confounding in the data analysis, since this avoids the limitation on the number of factors that can be stratified in the stratification method (Kahlert et al., 2017).

Inferential statistics was used to answer the research questions to test the null hypotheses of the study using a p value of < 0.05. An odds ratio with 95% confidence intervals was presented to determine statistical significance needed in order to reject the null hypotheses. Binary logistic regression was the appropriate statistical test to examine the relationship between one or more independent variables and the dependent variable when the dependent variable is categorical and dichotomous (with two categories)

(Sullivan, 2012). Binomial logistic regression was used to analyze the relationship between the dichotomous outcome of estrogen-dependent cancers and the ordinal predictor of dietary PE consumption and dichotomous predictor of bottled drinking water consumption for RQ1 and RQ2, respectively, in a main effects model. For RQ3 and RQ4, the relationship between the dichotomous outcome of estrogen-dependent cancers and the ordinal predictors of PE and phthalate urine levels, respectively, were also analyzed by binominal logistic regression in a main effects model. Finally, for RQ5 and RQ6, the relationship between the dichotomous outcome of estrogen-dependent cancers and the interaction terms, [PE consumption*bottled drinking water] and [PE urine level*phthalate urine level] were analyzed by binominal logistic regression. In addition, to carrying out a logistic regression, the Box-Tidwell Transformation Test was conducted to test for linearity between the continuous independent variables and the logit transformation of the dependent variable (Sullivan, 2012). The test of the interaction was conducted using the Wald chi-squared test comparing models with and without the interaction term. A goodness of fit to assess how well a model fits the data for logistic regression was done by using the Hosmer-Lemeshow test (Sullivan, 2012).

In order to directly examine co-exposure to both dietary PEs and XEs in combination and the potential association with cancer, it was necessary to evaluate the interaction effect between the two independent variables, PEs and XEs. An interaction effect occurs when the relationship between one independent variable and the dependent variable depends on the value of another independent variable (Fisher, 1926). The interaction effects between the independent variables used to operationalize PE intake

(daily PE intake; PE urine level) and XE exposure (daily XE exposure; phthalate urine level) and the dependent variable (estrogen-dependent cancer) needed to be examined in this current study's remaining research questions. To address RQ5 and RQ6, I operationalized the interaction effect by creating multiple new product variables for each of the interaction terms, PE consumption*bottled drinking water and PE urine level*phthalate urine level, respectively. The interaction coefficient represented the multiplicative effect on the logit of the variable for the dummy comparisons. The interaction indicated the odds of estrogen-dependent cancers for each increment of bottled drinking water consumption among each dietary PE consumption category.

For RQs that had ordinal measurements, the interaction variables were recoded as dichotomous variables through the use of dummy variables to create a set to compare each level of the variable to the reference level, where "0" denotes none of the attribute and "1" represents the presence of an attribute (W. Wagner, 2017). The number of dummy variables created in the set was dependent on the number of categories in the independent variable, which was one less dummy variable than the number of categories in the variable (W. Wagner, 2017). Dummy variables for PE consumption for each of the independent variables [bean consumption and soy consumption] were created. Since the number of categories was reduced from 11 to 3, both consumption variables have 3 categories that will be transformed into a "0-1" dichotomy for each category in the interaction terms. This led to the creation of 2 dummy variables and one category as a reference category, with the latter being "3-4 times per week through 2 or more times per day" for high PE consumption. Moderate PE consumption of soy and bean products each

had 3 levels [“1 time per month”, “2-3 times per month”, “1 times per week”, “2 times per week”]. Low PE consumption for soy and bean products each have 3 levels [“never”, “1-6 times per year”, time per day”, “7-11 times per year”]. First, “3-4 times per week” with the old value of “1” was coded as “1” in the new variable. All other values were coded as “0.” Similarly, this was repeated for the remaining 3 categories, where “5-6 times per week” was coded as “1,” and all other values were coded as “0;” “1 time per day” was coded as “1,” and all other values were coded as “0;” then “2 times or more times per day” was coded as “1,” and all other values were coded as “0.”

Once the 2 dummy variables for high PE consumption were created, then the new variables for the 3 interaction terms for PE consumption at each level by bottled water consumption were created. The reference group was the “3-4 times per week to 2 or more times per day” for high PE consumption. This process of creating dummy variables was repeated to generate the 9 interaction terms for PE urine levels by phthalate urine levels as well. The reference group was High PE urine*High Phthalate urine.

Table 3

Statistical Tests for Dependent and Independent Variables

Research question	Dependent variable (level of measurement)	Independent variable (level of measurement)	Statistical test
RQ1	• Estrogen-dependent cancer (dichotomous)	• Bean consumption (ordinal) • Soy consumption (ordinal)	• Binomial logistic regression
RQ2	• Estrogen-dependent cancer (dichotomous)	• Bottled Water Exposure (dichotomous)	• Binomial logistic regression
RQ3	• Estrogen-dependent cancer (dichotomous)	• PE urine level (ordinal)	• Binomial logistic regression
RQ4	• Estrogen-dependent cancer (dichotomous)	• Phthalate urine level (ordinal)	• Binomial logistic regression
RQ5	• Estrogen-dependent cancer (dichotomous)	• Interaction terms [Bean consumption*Bottled drinking water (ordinal)] • Interaction terms [Soy consumption*Bottled drinking water (ordinal)]	• Binomial logistic regression
RQ6	• Estrogen-dependent cancers (dichotomous)	• Interaction terms [PE urine levels and phthalate urine levels (ordinal)]	• Binomial logistic regression

Threats to Validity

Construct Validity

When surveys and questionaries are used in a research study, such as in NHANES, it is necessary to assess construct validity and threats to construct validity. Construct validity evaluates whether whatever is supposed to be measured has been measured, since this affects the interpretation of the results and attribution of observed effects (Creswell & Creswell, 2018; Matthay & Glymour, 2020). Evaluating the construct of dietary intake represented a challenge when studying its association to disease, since various foods are consumed each day that contain known or unknown chemicals that may not be well quantified, are poorly characterized, or are unmeasurable (Freedman et al., 2015, 2018; Yuan et al., 2018). More specifically, methods that evaluate dietary intake proved the most difficult to validate, because true intake levels in retrospective observational studies can never be known with absolute certainty (Food and Agriculture

Organization of the United Nations, 2018). For this reason, mono-method bias was the primary threat to construct validity in the current study. Mono-method bias refers to the use of only one operational method of measurement, such as self-reported dietary intake in NHANES, which can be avoided by incorporating additional methods to measure the construct (Matthay & Glymour, 2020).

In order to minimize the threat of mono-method bias, multiple approaches were used to measure the construct of dietary intake, specifically the use of urine biomarkers to measure PE and XE associated chemicals and their metabolites. Since food frequency questionnaires (FFQ) and 24-hour dietary recall are commonly used in epidemiological studies (Freedman et al., 2018; Willett, 2013; Yuan et al., 2018) to obtain information on "dietary intakes and patterns" and "to assess diet-disease associations," both were used in the current study in addition to the evaluation of biomarkers in urine (Food and Agriculture Organization of the United Nations, 2018). Researchers concluded that there was high reproducibility and validity when a FFQ was used as a tool to measure diet, but researchers also recommended the use of biomarkers to complement a FFQ rather than substitute for it (Kabagambe et al., 2001; McKeown et al., 2001; Ocké & Kaaks, 1997). Similarly, 24-hour dietary recalls, particularly two non-consecutive 24-hour dietary recalls, used to investigate dietary patterns were used to validate FFQs as well and found that 24-hour dietary recalls were closely correlated (Nurul-Fadhilah et al., 2012).

Statistical Conclusion Validity

Considerable attention must be paid to ensure the conclusions of a study are based on acceptable data analysis, which is the intent of assessing statistical conclusion validity.

Threats to statistical conclusion validity can result in an incorrect conclusion regarding the relationship of the variables, and two types of errors could occur (García-Pérez, 2012; Petursdottir & Carr, 2018). A Type I error (false positive) occurs when a null hypothesis should not be rejected but is incorrectly rejected; therefore, the results conclude that a relationship between the variables exists when there is no relationship (Banerjee et al., 2009; Sullivan, 2012). Correspondingly, a Type II error (false negative) occurs when a relationship does exist between the variables, but this relationship is not identified from the results (Sullivan, 2012). A Type II error leads to the failure to reject the null hypothesis that should be rejected.

Type I and Type II errors cannot be avoided altogether in research, but the likelihood of these errors can be reduced by taking appropriate measures. A Type I error, α, is the probability of rejecting the null hypothesis when it should not be rejected; a false positive (Sullivan, 2012). Type I errors can be minimized by purposely selecting a small value for the level of significance to control the probability of committing a Type I error. For example, if the threshold for $\alpha = 0.05$, then there is a 5% probability of a Type I error, where most investigators are comfortable and confident in rejecting a null hypothesis (Sullivan, 2012). A Type II error, β, is the probability of failing to reject a null hypothesis when it is false; a false negative. The probability of a Type II error is influenced by additional factors such as α, the hypothesis, and the sample size. In addition, β is related to a study's power calculation, where power = $1 - \beta$. Unlike Type I errors that can be directly minimized through selection of a smaller α, β cannot be purposely chosen to be small; instead increasing power increases the sample size which

then decreases β and lowers probability of committing Type II errors (Sullivan, 2012). Type I and II errors were threats to statistical conclusion validity in this study. Type II errors are of more significant concern when utilizing a single NHANES data set iteration with just a two-year data set cycle, since the sample size available for analysis is smaller (CDC, 2006).

For this reason, "combining two or more 2-year cycles of the continuous NHANES" was recommended, since doing so produces greater statistical reliability for rare events and demographic domains (CDC, 2006). To address the threat of Type II error, the 2003–2004 and 2005–2006 iterations of NHANES were combined to increase sample size and statistical power and reduce β. Furthermore, NHANES sample designs specifically allow for the combination of two or more cycles to increase sample size. As such, each 2-year cycle and any combinations of 2-year cycles yield a nationally representative sample.

Ethical Procedures

The current study has a cross-sectional design utilizing secondary data from the 2003–2004 and 2005–2006 iterations of NHANES, which provided an opportunity to measure the prevalence of health outcomes at these specific points in time. Access to data were provided by the NCHS through its downloadable "public-use data" files which provided access to questionnaires, data sets, and documentation in a format that allowed for data manipulation as needed for appropriate analyses (CDC, 2018a). Users of the "public-use data files" must comply with the terms of use that state the data were solely used for statistical analysis or reporting and any attempts to identify participants are

prohibited and violates Federal confidentiality laws (CDC, 2018b). The use of NHANES secondary data posed no ethical concerns related to data access, data collection, participant recruitment, or treatment of participants, and all data were collected confidentially. In addition, NCHS takes every effort to remove any personal identifying characteristics, and no identifiable data were disclosed without the consent of the individual per section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)) and under protection of confidentiality laws. To ensure the ethical conduct of this study, research did not proceed without Walden University Institutional Review Board approval. In order to meet protection guidelines for confidential data, the data for the current study will be maintained for 2 years following completion of the study and then destroyed. Furthermore, all data for the current study will be password protected on a cloud-based storage server.

Summary

This chapter aimed to explain of the study design, research questions, and other relevant aspects associated with the study's methodology. The current study was a quantitative observational study using archival data previously collected by NHANES to assess the potential relationship between dietary PE intake, dietary XE exposure and estrogen-dependent cancers in the United States. To accomplish this, the cross-section study design used dietary intake, biomarker urine samples, demographic, and socioeconomic data from the 2003–2006 iterations of NHANES. The current study's few threats to construct and statistical conclusion validity were acknowledged and efforts to

minimize the threats were highlighted. The results of the statistical analysis in the current study are described in Chapter 4.

Chapter 4: Results

The purpose of the current study was to determine whether there was an association between dietary PE intake and dietary XE exposure and estrogen-dependent cancers among adults age 18 years and older in the United States, and whether age, gender, race, education level, and marital status were confounders in the association. This chapter includes the results from statistical analyses of data from the 2003–2006 NHANES that I used to answer the study's research questions. In this chapter, I present an overview of descriptive statistics for study cases and a review of the findings from binominal logistic regression analyses. I conclude the chapter with a summary of statistical results related to each research question.

Research Questions and Hypotheses

RQ1: Is there an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$1: There is no association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$1: There is an association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers (breast, cervical, colorectal,

endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ2: Is there an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$2: There is no association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$2: There is an association between consumption of bottled drinking water that may contain increased levels of dietary XEs and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ3: Is there an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$3: There is no association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$3: There is an association between PE urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ4: Is there an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders?

$H_0$4: There is no association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$4: There is an association between phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

RQ5: Is there an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$5: There is no association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary

XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$5: There is an association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

RQ6: Is there an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and if there is an association, is there an antagonistic effect?

$H_0$6: There is no association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders.

$H_1$6: There is an association between both PE and phthalate urine levels and estrogen-dependent cancers (breast, cervical, colorectal, endometrial, ovarian, and prostate) among adult participants in the 2003–2006 NHANES after adjusting for relevant confounders, and there is an antagonistic effect.

Results

Demographic Characteristics of the Sample

I generated descriptive statistics for all participants in the study sample. As shown in Table 4, the average age of all participants was 67.27 years (*SD* = 15.437). There were more women (55.3%, *n* = 493) than men (44.7%, *n* = 399). Those identifying as White were the largest racial segment of the study population and accounted for 78.4% (*n* = 699), followed by those identifying as Black at 13.1% (*n* = 117). In addition, 47.1% (*n* = 417) of participants had completed at least some college or were college graduates or above. Finally, annual household incomes were as follows: < $25,000 at 32.1% (*n* = 286), $25,000–$54,999 at 34.8% (*n* = 310), $55,000–$74,999 at 9.5% (*n* = 85), and $75,000 and over at 16% (*n* = 143). The top three most frequently reported cancers were skin (nonmelanoma) cancer (*n* = 139) that accounted for 15.8% of cases, followed by breast cancer 16.2% (*n* = 143) and prostate cancer 13.9% (*n* = 123).

To ensure that the sample was representative of the general noninstitutionalized U.S. population, I compared the demographic proportions for the study sample against available data from the 2020 U.S. Census Bureau. The general U.S. population had 57.8%, 12.1%, 18.7%, and 11.4% of people identifying as White, Black, Hispanic, and other races or multiracial, respectively (U.S. Census Bureau, 2020). Similar to the U.S. population, the study sample consisted primarily of those who identified as White. However, there were more Hispanics than Blacks in the U.S. population, whereas the opposite was true for the study sample. The proportions of females and males in the U.S. population were 50.8% female and 49.2% male in 2020, compared to 55.3% and 44.7%,

respectively, in the study sample (U.S. Census Bureau, 2020). Individuals who identified as Hispanic and other races or multiracial were slightly underrepresented in the study sample by approximately 12% and 9%, respectively, however, Whites were overrepresented by approximately 21% in the current study compared to the U.S. population.

The participants with a diagnosis of all other cancers (nonestrogen) accounted for 49.1% of the study sample. The average age of participants with all other cancer was 66.92 (*SD* = 14.89) years old. Fewer of the participants with all other cancers were women (44.0%, *n* = 190), whereas men accounted for 56.0% (*n* = 242). The most frequently reported non-estrogen-dependent cancer was skin (nonmelanoma) (*n* = 139) that accounted for 32.1% of cases, followed by skin (“don’t know what kind”) (*n* = 73) that made up 16.9%, and melanoma 12.0% (*n* = 52).

Table 4

Demographic Data for Study Sample

Variable	All cancer *N* = 892 (%)	Nonestrogen-dependent cancer *n* = 432 (%)	Estrogen-dependent cancer *n* = 450 (%)
Age (years)			
Mean ± *SD*	67.27 ± 15.44	66.92 ± 14.89	67.46 ± 16.002
Min-max (range)	20-85	20-85	20-85
Gender			
Men	399 (44.7)	242 (56.0)	151 (33.6)
Women	493 (55.3)	190 (44.0)	299 (66.4)
Race			
White	699 (78.4)	384 (88.9)	306 (68.0)
Black	117 (13.1)	25 (5.8)	91 (20.2)
Hispanic	57 (6.4)	15 (3.5)	42 (9.3)
Other race – including multiracial	19 (2.1)	8 (1.9)	11 (2.4)
Education level			
Less than high school	242 (27.2)	93 (21.6)	143 (31.8)
High school diploma (including GED)	229 (25.7)	113 (26.2)	114 (25.3)
Some college and college graduate or above	419 (47.1)	225 (52.2)	192 (42.7)
Marital status			
Married	538 (60.3)	286 (66.2)	249 (55.3)
Widowed	184 (20.6)	72 (16.7)	108 (24.0)
Divorced	129 (14.5)	57 (13.2)	71 (15.8)
Single	41 (4.6)	17 (3.9)	22 (4.9)
Income			
<$25,000	286 (32.1)	121 (27.9)	161 (35.8)
$25,000–$54,999	310 (34.8)	148 (34.2)	159 (35.3)
$55,000–$74,999	85 (9.5)	48 (11.1)	37 (8.2)
>$75,000	143 (16.0)	82 (18.9)	60 (13.3)
All other cancers (nonestrogen)			
Bladder	17 (1.9)	17 (3.9)	
Blood	1 (0.1)	1 (0.2)	
Bone	4 (0.5)	4 (0.9)	
Brain	4 (0.5)	4 (0.9)	
Esophagus (esophageal)	5 (0.6)	5 (1.2)	
Kidney	15 (1.7)	15 (3.5)	
Larynx/windpipe	3 (0.3)	3 (0.7)	
Leukemia	8 (0.9)	8 (1.9)	
Liver	3 (0.3)	3 (0.7)	
Lung	23 (2.6)	23 (5.3)	
Lymphoma/Hodgkin's disease	19 (2.2)	19 (4.4)	
Melanoma	52 (5.9)	52 (12.0)	
Mouth/tongue/lip	6 (0.7)	6 (1.4)	
Skin (nonmelanoma)	139 (15.8)	139 (32.2)	
Skin ("don't know what kind")	73 (8.3)	73 (16.9)	
Soft tissue (muscle or fat)	2 (0.2)	2 (0.5)	
Stomach	6 (0.7)	6 (1.4)	
Testis (testicular)	6 (0.7)	6 (1.4)	
Thyroid	17 (1.9)	17 (3.9)	
Other	29 (3.3)	29 (6.7)	
Estrogen-dependent cancer types			
Breast	143 (16.2)		143 (31.8)
Cervical	72 (8.2)		72 (16.0)
Colon	55 (6.2)		55 (12.2)
Ovarian	13 (1.5)		13 (2.9)
Prostate	123 (13.9)		123 (27.3)
Rectal	3 (0.3)		3 (0.7)
Uterine	41 (4.6)		41 (9.1)

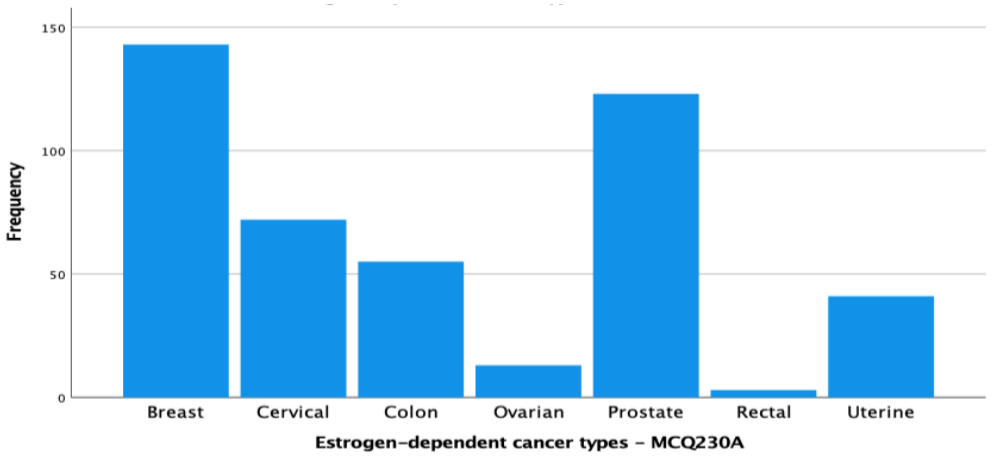
Note. Totals will vary due to missing data for some variables.

Demographic Characteristics of Participants With Estrogen-Dependent Cancers

The participants with a diagnosis of estrogen-dependent cancer accounted for 50.4% of the study sample. The prevalence of estrogen-dependent cancers among participants in the current study was higher than the 42.2% nationally among U.S. adults in 2022 (American Cancer Society, 2022). The average age of participants with estrogen-dependent cancers was 67.46 years (*SD* = 16.002). Twice as many of the participants with estrogen-dependent cancers were women (66.4%, *n* = 299), but men accounted for only 33.6% (*n* = 151). The most frequently reported estrogen-dependent cancer was breast cancer (*n* = 143) that accounted for 31.8% of cases, followed by prostate cancer (*n* = 123) that made up 27.3%, and cervical and colorectal cancers 16.0% (*n* = 72) and 12.2% (*n* = 55) of cases, respectively (see Table 4 and Figure 6). Similar to the overall sample, those identifying as White were the largest racial segment of those with estrogen-dependent cancers, accounting for 68.0% (*n* = 306). However, among those with estrogen-dependent cancer, those identifying as Black made up a larger proportion of participants at 20.2% (*n* = 91) than in the overall sample.

Figure 5

Numbers of Estrogen-Dependent Cancers Among 2003–2006 NHANES Participants



Statistical Assumptions

The statistical assumptions that needed to be taken into consideration were the size and nature of the sample used for binominal logistic regression. The number of cases in the sample population needed to maintain a power of 80% with an alpha of 0.05 was 113 participants. This sample size was met for all of the research questions.

RQ1 Results

A binary logistic regression analysis was conducted to determine whether there was an association between consumption of soy and bean products and estrogen-dependent cancers after adjusting for relevant confounders. The dependent variable was estrogen-dependent cancer diagnosis. The independent variables were bean and soy consumption (defined as low/moderate/high), and the possible confounders were age, gender, race, education, and marital status.

Table 5 displays a binary logistic regression analysis showing the unadjusted association between bean consumption and estrogen-dependent cancers. The unadjusted odds ratio was .949 for moderate bean consumption and 1.679 for high consumption. The results of this analysis were not statistically significant ($p > 0.05$) for any level of bean consumption.

Table 5

Binary Logistic Regression (Unadjusted) Assessing Association Between Bean Consumption and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bean consumption				
Low bean consumption	.351			
Moderate bean consumption	.745	.949	.690	1.304
High bean consumption	.192	1.679	.771	3.657
Constant	.812	1.029		

Note: The reference category is low PE bean consumption, $n = 640$.

Table 6 displays a binary logistic regression showing the adjusted association between bean consumption and estrogen-dependent cancers, and controlled for confounders. Age, gender, race, education, and marital status were all confounding variables and were included in the final model. The results of this analysis were not significant ($p > 0.05$) for any level of bean consumption.

Table 6

Binary Logistic Regression (Adjusted) Assessing Association Between Consumption of Bean and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bean consumption				
Low bean consumption	.974			
Moderate bean consumption	.944	.988	.698	1.398
High bean consumption	.845	1.092	.453	2.630
Age	.159	1.009	.996	1.022
Gender*	.000	.394	.274	.565
Race				
White*	.000			
Hispanic*	.002	3.793	1.611	8.934
Black*	.000	6.674	3.332	13.367
Other – Including Multi-Racial	.907	1.066	.368	3.083
Education				
Less than High School	.307			
High School Diploma (including GED)	.494	.844	.520	1.372
Some College and College Graduate or Above	.132	.718	.467	1.105
Marital Status				
Single	.835			
Married	.943	.967	.386	2.420
Widowed	.806	1.134	.416	3.092
Divorced	.749	1.176	.436	3.171
Constant	.703	.788		

Note: The reference categories are: Low bean consumption; Women; White; Less than High School; Single
**Results that were statistically significant ($p < 0.05$)*

Table 7 displays a binary logistic regression analysis showing the unadjusted association between soy consumption and estrogen-dependent cancers. The unadjusted odds ratio was .922 for moderate soy consumption and .787 for high consumption. The results of this analysis were not significant ($p > 0.05$) for any level of soy consumption.

Table 7

Binary Logistic Regression (Unadjusted) Assessing Association Between Consumption of Soy and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Soy consumption				
Low soy consumption	.918			
Moderate soy consumption	.826	.922	.448	1.899
High soy consumption	.723	.787	.209	2.959
Constant	.839	1.017		

Note: The reference category is: Low PE bean consumption, $n = 647$

Table 8 displays a binary logistic regression showing the adjusted association between soy consumption and estrogen-dependent cancers, and controlled for confounders. Unlike bean consumption, age was not a confounding variable. Gender, race, education, and marital status were confounding variables and were included in the final model. The result of this analysis was not significant ($p > 0.05$) for any level of soy consumption.

Table 8

Binary Logistic Regression (Adjusted) Assessing Association Between Consumption of Soy and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio Lower	Upper
Soy consumption				
Low soy consumption	.934			
Moderate soy consumption	.744	1.137	.525	2.464
High soy consumption	.876	.895	.223	3.596
Gender*	.000	.398	.283	.561
Race				
White*	.000			
Hispanic*	.002	3.977	1.643	9.625
Black*	.000	5.952	3.036	11.670
Other – Including Multi-Racial	.986	1.010	.344	2.961
Education				
Less than High School	.225			
High School Diploma (including GED)	.699	.911	.567	1.463
Some College and College Graduate or Above	.114	.709	.463	1.086
Marital status				
Single	.469			
Married	.937	1.037	.421	2.554
Widowed	.427	1.473	.566	3.836
Divorced	.722	1.197	.445	3.218
Constant	.582	1.301		

Note: The reference categories are: Low soy consumption; Women; White; Less than High School; Single
**Results that were statistically significant ($p < 0.05$)*

RQ2 Results

A binary logistic regression analysis was conducted to investigate if there was an association between bottled drinking water exposure and estrogen-dependent cancers after adjusting for relevant confounders. The dependent variable was estrogen-dependent cancer diagnosis. The independent variable was bottled drinking water consumption

(defined as yes or no), whereas the possible confounders were age, gender, race, education, and marital status.

Table 9 displays the binary logistic regression showing the unadjusted association between bottled drinking water exposure and estrogen-dependent cancers. The unadjusted odds ratio was .936, and the result of this analysis was not statistically significant ($p > 0.05$).

Table 9

Binary Logistic Regression (Unadjusted) Assessing Association Bottled Water Exposure and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bottled Water Exposure	.672	.936	.687	1.273
Constant	.596	1.073		

Note: The reference category is: Yes bottled water exposure, $n = 787$

Table 10 displays a binary logistic regression showing the adjusted association between bottled drinking water exposure and estrogen-dependent cancers, and controlled for confounders. Education and marital status were not confounding variables. Age, gender, and race were confounding variables and were included in the final model. The result of this analysis was not significant ($p > 0.05$) for bottled drinking water exposure.

Table 10

Binary Logistic Regression (Adjusted) Assessing Association Between Bottled Water Exposure and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bottled Water Exposure	.596	1.098	.778	1.549
Age*	.004	1.016	1.005	1.026
Gender*	.000	.336	.246	.460
Race				
White*	.000			
Hispanic*	.000	4.411	2.157	9.023
Black*	.000	5.854	3.462	9.898
Other – Including Multi-Racial	.315	1.651	.621	4.388
Constant	.016	.414		

Note: The reference categories are: Yes bottled water exposure; Women; White
**Results that were statistically significant (p < 0.05)*

RQ3 Results

A binary logistic regression analysis was conducted to investigate if there was an association between PE urine levels and estrogen-dependent cancers after adjusting for relevant confounders. The dependent variable was estrogen-dependent cancer diagnosis. The independent variable was PE urine levels (defined as low/moderate/high), whereas the possible confounders were age, gender, race, education, and marital status.

Table 11 displays the binary logistic regression showing the unadjusted association between PE urine levels and estrogen-dependent cancers. The unadjusted odds ratio was 1.462 for moderate bean consumption and .907 for high consumption. The results of this analysis were not statistically significant ($p > 0.05$).

Table 11

Binary Logistic Regression (Unadjusted) Assessing Association Between PEs in Urine and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
PE urine level				
Low PEs in Urine	.729			
Moderate PEs in Urine	.504	1.462	.480	4.450
High PEs in Urine	.738	.907	.512	1.607
Constant	.038	1.368		

Note: The reference category is: Low PE in Urine, $n = 260$

Table 12 displays a binary logistic regression showing the adjusted association between PE urine levels and estrogen-dependent cancers, and controlled for confounders. Age and marital status were not confounding variables. Gender, race, and education were confounding variables and were included in the final model. The results of this analysis were not significant ($p > 0.05$) for any PE urine level.

Table 12

Binary Logistic Regression (Adjusted) Assessing Association Between PEs in Urine and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
PE urine level				
Low PE urine	.208			
Moderate PEs urine	.191	2.315	.658	8.149
High PEs urine	.160	1.587	.833	3.023
Gender*	.000	.277	.157	.488
Race				
White*	.001			
Hispanic*	.032	3.649	1.114	11.951
Black*	.000	6.976	2.457	19.807
Other – Including Multi-Racial	.340	2.442	.390	15.283
Education				
Less than High School	.155			
High School Diploma (including GED)	.058	.467	.213	1.026
Some College and College Graduate or Above	.143	.592	.294	1.194
Constant	.015	2.276		

Note: The reference categories are: Low PEs in Urine; Women; White; Less than High School
**Results that were statistically significant (p < 0.05)*

RQ4 Results

A binary logistic regression analysis was conducted to investigate if there was an association between phthalate urine levels and estrogen-dependent cancers after adjusting for relevant confounders. The dependent variable was estrogen-dependent cancer diagnosis. The independent variable was phthalate urine levels (defined as low/moderate/high); whereas the possible confounders were: age, gender, race, education, and marital status.

Table 13 displays the binary logistic regression showing the unadjusted association between phthalate urine levels and estrogen-dependent cancers. The unadjusted odds ratio was .816 for low phthalate urine levels and 1.250 for moderate phthalate urine levels. The results of this analysis were not statistically significant ($p > 0.05$).

Table 13

Binary Logistic Regression (Unadjusted) Assessing Association Between Phthalate in Urine and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Phthalate urine level				
High phthalate urine	.889			
Low phthalate urine	.728	.816	.260	2.564
Moderate phthalate urine	.869	1.250	.089	17.653
Constant	.410	1.600	.470	.570

Note: The reference category is: High phthalate in Urine, $n = 265$

Table 14 displays a binary logistic regression showing the adjusted association between phthalate urine levels and estrogen-dependent cancers, and controlled for confounders. Age was not a confounding variable. Gender, race, education, and marital status were confounding variables and were included in the final model. The results of this analysis were not significant ($p > 0.05$) for any phthalate urine level.

Table 14

Binary Logistic Regression (Adjusted) Assessing Association Between Phthalate in Urine and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Phthalate urine level				
High phthalate urine	.982			
Low phthalate urine	.897	.918	.251	3.355
Moderate phthalate urine	.939	1.127	.052	24.575
Gender*	.000	.297	.170	.519
Race				
White*	.006			
Hispanic*	.040	3.532	1.058	11.793
Black*	.002	4.688	1.754	12.529
Other – Including Multi-Racial	.689	1.392	.276	7.025
Education				
Less than High School	.143			
High School Diploma (including GED)	.053	.465	.213	1.011
Some College and College Graduate or Above	.132	.585	.292	1.175
Marital Status				
Single	.591			
Married	.677	1.348	.330	5.504
Widowed	.410	1.859	.425	8.131
Divorced	.359	2.046	.443	9.437
Constant	.519	1.910		

Note: The reference categories are: High phthalate in Urine; Women; White; Less than High School; Single
**Results that were statistically significant ($p < 0.05$)*

RQ5 Results

A binary logistic regression analysis was conducted to investigate if there was an association between estrogen-dependent cancers and the interaction term of consumption of soy and bean products and consumption of bottled drinking water after adjusting for relevant confounders, and if there was an antagonistic effect. The dependent variable was estrogen-dependent cancer diagnosis. The independent variable was the interaction term of consumption of soy and bean products (both defined as low/moderate/high) and consumption of bottled drinking water (defined as yes or no exposure); whereas the possible confounders were age, gender, race, education, and marital status.

Table 15 displays the binary logistic regression showing the unadjusted association between estrogen-dependent cancers and the interaction term of bean

consumption and bottled drinking water consumption. The unadjusted odds ratio was .988 for the interaction between moderate bean consumption and bottled drinking water consumption, and 1.306 for the interaction between high bean consumption and bottled drinking water consumption. The results of this analysis were not statistically significant ($p > 0.05$).

Table 15

Binary Logistic Regression (Unadjusted) Assessing Association of the Interaction Between Consumption of Bean and Bottled Drinking Water and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bean consumption*Bottled drinking water				
Low bean consumption*Bottled drinking water	.830			
Moderate bean consumption*Bottled drinking water	.941	.988	.714	1.367
High bean consumption*Bottled drinking water	.555	1.306	.538	3.171
Constant	.838	1.021		

Note: The reference category is: Low PE bean consumption; Yes bottled water exposure, $n = 639$

Table 16 displays a binary logistic regression showing the adjusted association between estrogen-dependent cancers and the interaction term of bean consumption and bottled drinking water, and controlled for confounders. Age and marital status were not confounding variables. Gender, race, and education were confounding variables and were included in the final model. The Hosmer-Lemeshow goodness-of-fit was not significant ($p > 0.05$) indicating the model was correctly specified. Additionally, the -2 log Likelihood = 826.666 and the Nagelkerke R squared = .118. The result of this analysis was not significant ($p > 0.05$) for any level of bean consumption and bottled drinking water consumption; there was no significant effect modification identified.

Table 16

Binary Logistic Regression (Adjusted) Assessing Association of the Interaction Between Consumption of Bean and Bottled Drinking Water and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Bean consumption*Bottled drinking water				
Low bean consumption*Bottled drinking water	.892			
Moderate bean consumption*Bottled drinking water	.633	1.089	.767	1.547
High bean consumption*Bottled drinking water	.981	1.012	.378	2.712
Gender*	.000	.404	.288	.567
Race				
White*	.000			
Hispanic*	.004	3.436	1.500	7.870
Black*	.000	6.460	3.256	12.814
Other – Including Multi-Racial	.983	1.011	.353	2.901
Education				
Less than High School	.179			
High School Diploma (including GED)	.387	.810	.502	1.306
Some College and College Graduate or Above*	.067	.75	.443	1.029
Constant	.053	1.512		

Note: The reference categories are: Low PE bean consumption; Women; White; Less than High School
**Results that were statistically significant ($p < 0.05$)*

For soy consumption, Table 17 shows the unadjusted association between estrogen-dependent cancers and the interaction term of soy consumption and bottled drinking water consumption. The unadjusted odds ratio was .883 for the interaction between moderate soy consumption and bottled drinking water consumption, and .490 for the interaction between high soy consumption and bottled drinking water consumption. The results of this analysis were not statistically significant ($p > 0.05$).

Table 17

Binary Logistic Regression (Unadjusted) Assessing Association Between Consumption of Soy and Bottled Drinking Water and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Soy consumption*Bottled drinking water				
Low soy consumption*Bottled drinking water	.692			
Moderate soy consumption*Bottled drinking water	.789	.883	.354	2.202
High soy consumption*Bottle drinking water	.413	.490	.089	2.697
Constant	.810	1.019		

Note: The reference category is: Low PE soy consumption, $n = 647$

Table 18 displays a binary logistic regression showing the adjusted association between estrogen-dependent cancers and the interaction term of soy consumption and bottled drinking water consumption, and controlled for confounders. Age and marital status were not confounding variables. Gender, race, and education were confounding variables and were included in the final model. The Hosmer-Lemeshow goodness-of-fit was not significant ($p > 0.05$) indicating the model is correctly specified. Additionally, the -2 log Likelihood = 805.793 and the Nagelkerke R squared = .173. The results of this analysis were not significant ($p > 0.05$) for any level of soy consumption and bottled drinking consumption, and there was no significant effect modification identified.

Table 18

Binary Logistic Regression (Adjusted) Assessing Association Between Consumption of Soy and Bottled Drinking Water and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Soy consumption*Bottled drinking water				
Low soy consumption*Bottled drinking water	.866			
Moderate soy consumption*Bottled drinking water	.975	1.015	.390	2.644
High soy consumption*Bottled drinking water	.594	.621	.108	3.578
Gender*	.000	.378	.270	.530
Race				
White*	.000			
Hispanic*	.003	3.718	1.551	8.913
Black*	.000	5.955	3.060	11.590
Other – Including Multi-Racial	.977	.985	.342	2.835
Education				
Less than High School	.195			
High School Diploma (including GED)	.672	.903	.563	1.448
Some College and College Graduate or Above	.097	.700	.459	1.067
Constant	.031	1.531		

Note: The reference categories are: Low soy consumption; Women; White; Less than High School
**Results that were statistically significant (p < 0.05)*

RQ6 Results

A binary logistic regression analysis was conducted to investigate if there was an association between estrogen-dependent cancers and the interaction term of PE and phthalate urine levels after adjusting for relevant confounders. The dependent variable was estrogen-dependent cancer diagnosis. The independent variable was the interaction of PE and phthalate urine levels (both defined as low/moderate/high); whereas the possible confounders were: age, gender, race, education, and marital status.

Table 19 displays the binary logistic regression showing the unadjusted association between estrogen-dependent cancers and the interaction term of PE and phthalate urine levels. The unadjusted odds ratio was .875 for the interaction between low PE urine and low phthalate urine; .682 for the interaction between low PE urine and moderate phthalate urine; 6.210 for the interaction between low PE urine and high

phthalate urine; 1.364 for the interaction between moderate PE urine and low phthalate urine; .667 for the interaction between moderate PE urine and moderate phthalate urine; .575 for the interaction between moderate PE urine and high phthalate urine; .958 for the interaction between high PE urine and low phthalate urine; and 1.145 for the interaction between high PE urine and moderate phthalate urine. The results of this analysis were not statistically significant ($p > 0.05$).

Table 19

Binary Logistic Regression (Unadjusted) Assessing Association Between Both PE and Phthalate Urine Levels and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio Lower	Upper
PE and phthalate urine levels				
High PE urine*High Phthalate urine	.854			
Low PE urine*Low Phthalate urine	.638	.875	.503	1.524
Low PE urine*Moderate Phthalate urine	.789	.682	.041	11.329
Low PE urine*High Phthalate urine	.087	6.210	.765	50.386
Moderate PE urine*Low Phthalate urine	.603	1.364	.423	4.392
Moderate PE urine*Moderate Phthalate urine	.471	.667	.221	2.009
Moderate PE urine*High Phthalate urine	.214	.575	.240	1.376
High PE urine*Low Phthalate Urine	.884	.958	.539	1.703
High PE urine*Moderate Phthalate Urine	.635	1.145	.654	2.006
Constant	.106	1.467		

Note: The reference category is: High PE urine*High Phthalate urine, $n = 260$

Table 20 displays a binary logistic regression showing the adjusted association between estrogen-dependent cancers and the interaction term of PE and phthalate urine levels, and controlled for confounders. Age was not a confounding variables. Gender, race, education, and marital status were confounding variables and were included in the final model. The interaction between low PE urine and low phthalate urine was borderline significant ($p = 0.058$), and this significance value denotes some evidence against the null hypothesis. The Hosmer-Lemeshow goodness-of-fit was not significant ($p > 0.05$) indicating the model was correctly specified. Additionally, the -2 log

Likelihood = 300.275 and the Nagelkerke R squared = .252. The results of this analysis were not significant ($p > 0.05$) for any other levels of PE and phthalate urine; there was no significant effect modification identified.

Table 20

Binary Logistic Regression (Adjusted) Assessing Association Between Both PE and Phthalate Urine Levels and Estrogen-Dependent Cancers

	p	Odds ratio	95% CI for odds ratio Lower	Upper
PE and phthalate urine levels				
High PE urine*High Phthalate urine	.178			
Low PE urine*Low Phthalate urine	.058	.544	.290	1.020
Low PE urine*Moderate Phthalate urine	.528	.270	.005	15.780
Low PE in urine*High Phthalate in urine	.128	5.521	.612	49.789
Moderate PE urine*Low Phthalate urine	.651	1.357	.361	5.101
Moderate PE in urine*Moderate Phthalate in urine	.276	.499	.143	1,743
Moderate PE in urine*High Phthalate in urine	.161	.496	.186	1.321
High PE in Urine*Low Phthalate in Urine	.168	1.576	.826	3.009
High PE in Urine*Moderate Phthalate in Urine	.294	.713	.380	1.341
Gender*	.000	.274	.152	.494
Race				
White*	.001			
Hispanic*	.034	3.713	1.101	12.521
Black*	.000	6.607	2.327	18.755
Other – Including Multi-Racial	.296	2.712	.417	17.623
Education				
Less than High School	.151			
High School Diploma (including GED)	.054	.453	.202	1.013
Some College and College Graduate or Above	.158	.593	.287	1.225
Marital status				
Single	.515			
Married	.698	1.327	.317	5.554
Widowed	.423	1.850	.411	8.323
Divorced	.324	2.193	.461	10.444
Constant	.218	2.636		

Note: The reference categories are: High PE urine*High Phthalate urine; Women; White; Less than High School; Single
**Results that were statistically significant ($p < 0.05$)*

Summary

The results of the data analyses used to address RQ1, RQ2, RQ3, RQ4, RQ5, and RQ6 showed no statistically significant associations. For these reasons, the null hypotheses for all research questions in the current study were not rejected. The results from the logistic regressions used to address RQ1 and RQ2 indicated no association between soy and bean products and estrogen-dependent cancer. For RQ1, no associations

were identified, gender and race confounded the association between soy and bean consumption and development of estrogen-dependent cancers. For RQ2, age, gender, and race all confounded the association between bottled drinking water exposure and development of estrogen-dependent cancers. The results from the logistic regressions used to address RQ3 and RQ4 indicated no association between PE and phthalate urine levels, respectively, and estrogen-dependent cancer. For both RQ3 and RQ4, gender and race confounded the association between PE and phthalate urine levels, respectively, and development of estrogen-dependent cancers.

The results from RQ5 showed no association when there was co-exposure to both dietary PEs and XEs. Similarly, the results from RQ6 showed no association when co-exposure to PE and phthalate urine levels were assessed simultaneously. For RQ5, gender and race confounded the association between estrogen-dependent cancers and the interaction term of bean consumption and bottled drinking water consumption; and the association between estrogen-dependent cancers and the interaction term of soy consumption and bottled drinking water consumption. Similarly for RQ6, gender and race confounded the association between estrogen-dependent cancers and the interaction term of PE and phthalate urine levels.

In Chapter 5, I summarize the key findings with an interpretation and comparison of the results from the current study with what was in the literature. Further description of how the findings contribute to the current body of knowledge are noted. In addition, the next chapter includes a discussion of the study's results and how they potentially impact

positive social change. Finally, Chapter 5 concludes with an overview of the study's findings.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this quantitative cross-sectional study was to assess the association between dietary PE intake and XE exposure, and the development of estrogen-dependent cancers among adults in the United States. To reduce the global burden of estrogen-dependent cancers, it was necessary to gain insight into modifiable lifestyle factors, particularly dietary ones, that may help reduce cancer risk. A key objective of this epidemiological study was to identify risk factors for estrogen-dependent cancers and quantify their significance (see Ressing et al., 2010). The differences examined were between levels of exposure for soy, bean, and bottled drinking water both independently and in combination. After reviewing the effects of independent exposure, I looked at the potential combined co-exposure effects of varying levels of soy, bean, and bottled water consumption, and how these exposures may interact to contribute to the overall risk of estrogen-dependent cancers. At the time of this study, limited epidemiological studies assessed the association between dietary intake of PEs and XE exposure, and incidence of estrogen-dependent cancers.

The nature of the current study entailed hypothesis testing using data from the 2003–2006 NHANES data set to identify individual factors that may influence differences in dietary PEs and XEs in adults with and without an estrogen-dependent cancer diagnosis. The analyses from the current study indicated that none of the levels of soy, bean, or bottled drinking water consumption, when tested independently, were statistically significant ($p > 0.05$) to predict the development of estrogen-dependent cancers. Similarly, co-exposures to dietary PEs and XEs in combination were also not

statistically significant ($p > 0.05$) predictors of development of estrogen-dependent cancers for any level of soy, bean, or bottled drinking water consumption. This chapter includes interpretating these findings to further address the research questions. Additionally, I review study limitations, offer recommendations for future research, discuss implications for social change, and provide conclusions.

Interpretation of the Findings

Dietary PEs and Estrogen-Dependent Cancers

According to the findings of this study, there was no association between consumption of soy and bean products and estrogen-dependent cancers. Previous studies demonstrated that increased PE consumption played a protective role and was associated with a reduced risk of incidence, recurrence, and mortality for breast and prostate cancers (Y.-J. Chang et al., 2017; Fink et al., 2006; Fritz et al., 2013; Russo et al., 2018; Tan et al., 2018; Wada et al., 2013; Yakimchuk et al., 2018; H. Y. Zhang et al., 2016; Q. Zhang et al., 2017; T. T. Zhao et al., 2019). However, the results from the current study did not suggest the same association among adult participants in the 2003–2006 NHANES. In this current study, no level of soy consumption was associated with reduced risk of estrogen-dependent cancers, despite prior studies (Y.-J. Chang et al., 2017; Fink et al., 2006; Fritz et al., 2013; Russo et al., 2018; Wada et al., 2013; H. Y. Zhang et al., 2016; Q. Zhang et al., 2017; T. T. Zhao et al., 2019) that demonstrated higher dietary isoflavone intake, specifically soy, played a protective role against developing breast and prostate cancers.

Additionally, the reduced risk of estrogen-dependent cancers was not associated with any level of bean consumption in the current study. This contrasts with research (Bahrami et al., 2021; Ghanavati et al., 2021; Godos et al., 2017; Jang et al., 2022; Maskarinec et al., 2017; Rattanaburee et al., 2021; Russo et al., 2018) involving diets high in beans that showed an inverse association with risk of breast and colorectal cancers. There are several possible explanations for why findings and conclusions in the current study differed from prior studies. One explanation for the observed findings is that the daily intake of soy and bean products in the current study, even at the highest levels, may not have been sufficient to reduce the likelihood of estrogen-dependent cancers because Western diets are known to have lower overall soy and bean consumption when compared to Asian diets (Maskarinec et al., 2017; F. Zhang et al., 2017; H. Y. Zhang et al., 2016; Q. Zhang et al., 2017; T. T. Zhao et al., 2019; Ziaei & Halaby, 2017). The average daily dietary soy intake in Asian countries was 30–50 mg, whereas the United States's per capita intake was less than 3 mg (Ziaei & Halaby, 2017). The average consumption of dietary beans worldwide was 21 g/day, whereas the United States's per capita intake is less than 9.3 g/day (Semba et al., 2021). The intake levels of soy and bean products in the current study were unknown due to the use of retrospective data.

Another explanation for the findings in the current study is that the study population was predominantly White at 78.4% (*n* = 699), and Whites comprised 68% (n = 306) of the cases of estrogen-dependent cancers in this study. The NHANES selection process collects information from a nationally representative sample meant to include

participants of various races and ethnicities. Furthermore, oversampling of specific individuals is meant to ensure the sample selected includes African Americans, Asians, and Hispanics in proportions representative of the U.S. population. Despite these efforts, the population in the current study included a disproportionate number of Whites, which may have contributed to the study population's overall lower consumption of soy and bean products. Moreover, the 2003–2006 NHANES did not include a racial category for Asians, and studies (Y.-J. Chang et al., 2017; F. Zhang et al., 2017; T. T. Zhao et al., 2019) had reported Asian diets to be high in soy foods.

In addition, with a larger proportion of the study population composed of Whites, there may be differences in its genetic predispositions compared to those found in the literature. The meta-analysis by F. Zhang et al. (2017) included studies conducted in Europe, East Asian, and North America. Researchers noted that extrapolating other populations from different genetic backgrounds should be done cautiously. Similar research (Franke et al., 2014; Iino et al., 2019; Russo et al., 2018; Song et al., 2006) indicated that there may be variations in metabolism of PEs in individuals of different races due to differences in gut microflora resulting in different capacities to produce PE metabolites.

The findings by Franke et al. (2014), Russo et al. (2018), and Song et al. (2006) extended the concept of variations in metabolism of PEs in individuals of different races. They indicated that Asian populations may have higher PE metabolite levels than Western populations. Additionally, the use of secondary data in the current study to assess soy and bean consumption limited the types of soy and bean products to those

defined within the NHANES FFQs, and this could be another explanation for the observations. NHANES dietary intake of soy was defined by consumption of tofu, soy burgers, and soy meat substitutes. NHANES dietary intake of beans was defined by consumption of cooked dried beans, such as baked beans, pinto beans, kidney beans, black-eyed peas, lima beans, lentils, soybeans, and refried beans. If participants had high dietary PE intakes but consumed PEs other than the soy and bean products in the questionnaire, their high dietary PE intakes would not have been accounted for in this study.

Another explanation for the differences observed between the current study and other studies is that this was a cross-sectional study, which limited my ability to assess exactly how much the average consumption was in this sample. The average consumption may have been well below what was observed as protective in prior studies. There is the time of first exposure to soy and bean products in a person's lifetime and overall duration of exposure that could not be assessed in the current study that may be responsible for the differing findings. Prior studies (Korde et al., 2009; Shu et al., 2001; Wu et al., 2002) demonstrated a reduced risk of developing breast cancer when high soy consumption occurred during childhood, and the risk was further reduced with continued soy intake in adulthood. Furthermore, M. Chen et al. (2022) found that prenatal exposure through maternal consumption can reduce the risk of developing breast cancer by regulating offspring gut microbiome, indicating that even the earliest soy intake can have beneficial effects. A longitudinal study in which researchers collect soy and bean intake

and follow individuals prospectively for diagnosis of incident estrogen-dependent cancers may yield different results regarding an association with estrogen-dependent cancers.

Although FFQs are widely used in large epidemiological studies, assessing dietary intake remains challenging for researchers. Researchers (Eysteinsdottir et al., 2011; Shim et al., 2014) have worked to refine assessment methods and test the validity of retrospective dietary information. Considering the population difference between the literature and the current study, the results of the current study cannot be applied to Western populations due to the multitude of differences in dietary, lifestyle, environmental, and genetic factors. This is relevant because it is important to consider how profound the influence of the vertexes (causative factors; environment, behavior, culture, physiological factors, ecological elements; and groups or populations and their characteristics) of the advanced model of the epidemiology triangle may be to disease over time. Moreover, researchers need to examine the possibility that one factor within the epidemiology triangle, such as genetics, may have disproportional influencing power on the triangle despite other factors. An example of this may be that a population's genetics limits the overall benefits of dietary PE consumption. No matter how many dietary PEs are consumed (causative factors) by Whites, their dietary PE consumption cannot substantially affect the development of estrogen-dependent cancers in a positive way when compared to Asians due to the positive genetic predisposition held by Asian populations (groups or populations and their characteristics).

In a multiethnic cohort study of women, F. Zhang et al. (2017) investigated race/ethnicity as an effect modifier of the association between all-cause breast cancer

mortality and dietary PE intake. They found that Asian American women had a higher average intake of dietary isoflavones than women from other racial/ethnic groups. Zhang et al.'s research supported the hypothesis that the population's characteristics (higher consumption of soy foods in Asian diets) led to lower incidence of estrogen-dependent cancer among Asian populations. However, the findings by Zhang et al. did not address the influence of ethnic origin (genetic differences, pharmacogenomics) as the cause for the effect modifier in preventing estrogen-dependent cancers among Asians. In such cases, population differences in pharmacokinetics may be associated with interethnic differences in the frequencies of genetic variants that have a functional consequence for relevant PE metabolizing enzymes, which may be of clinical consequence (Hirano et al., 2021). Research suggested that soy consumption inhibited to cancer-inducing enzymes and reduced cytochrome P450 activity, which may contribute to cancer prevention. As a result of interethnic differences, Asian populations have been found to have greater isoflavone pharmacokinetics and bioavailability (Lepri et al., 2018; Vergne et al., 2009). This is relevant because the current study addressed PE and XE metabolites in a person's urine as proxy measurements for PE consumption and XE exposure. The findings from the current study may contribute to understanding why differences were observed in urinary PE and XE excretion among women of different races and the impact on estrogen-dependent cancer risk.

Based on the current study's findings, the null hypotheses were not rejected in the tests of association between consumption of soy and bean products (high in dietary PEs) and estrogen-dependent cancers. Although the current study's results for the effects of

soy and bean product consumption on the occurrence of estrogen-dependent cancers were not significant, the findings support the complex nature of this potential relationship among humans and the need for further research. Although the literature (Gray et al., 2017; Hwang et al., 2012; Luo et al., 2018; Schettler, 2006; Tan et al., 2018; Ziaei & Halaby, 2017) provided insight into the etiology of hormone-dependent cancers and the role diet plays in chronic diseases such as cancer, there are many etiologic factors interacting (Merrill, 2013). This makes it difficult to assess potential factors that directly contribute to the development of estrogen-dependent cancers in humans. Given the multifactorial nature of cancer and the role early life and young adulthood exposures play (Ugai et al., 2022), the findings from the current study affirm the need for additional prospective cohort studies to obtain a better understanding of the relationship between hormone-dependent cancers and diet in humans by identifying exposures, quantifying them, and understanding their impact on future health outcomes.

Dietary XEs and Estrogen-Dependent Cancers

Additionally, I did not find an association between consumption of bottled drinking water and estrogen-dependent cancers among adult participants in the 2003–2006 NHANES. My findings did not support previous researchers who found environmental XE exposure to contribute to increasing cancer rates (Gray et al., 2017; Jafer et al., 2018; H. Li et al., 2019; Luo et al., 2018; Schettler, 2006; Watson et al., 2019; Williams & Darbre, 2019). No level of bottled drinking water consumption was associated with increased risk of estrogen-dependent cancers in the current study, despite the finding of Williams and Darbre (2019) of a direct link between low-dose exposure to

environmental XEs and breast cancer. The results of the current study also did not align with findings from Hashemipour et al. (2018), Park et al. (2017), and Wagner and Oehlmann (2009), who reported a positive association between consumption of bottled water and biomarker concentrations of XEs. My findings are aligned with the findings that dietary exposure to XEs do not yield sufficient estrogenic effects to impact carcinogenesis (H. Li et al., 2019).

Based on my findings, the null hypothesis was not rejected in the test of association between consumption of bottled drinking water, which may contain increase levels of dietary XEs, and estrogen-dependent cancers in this current study. Although my research results differed from those of previous studies (Chuang et al., 2020; Park et al., 2017; M. Wagner & Oehlmann, 2009; Williams & Darbre, 2019), there are some aspects of the prior bottled drinking water studies that need to be taken into consideration. In studies assessing XE exposure, leaching of XEs into bottled drinking water was the most critical of these factors due to the variability it can introduce into a study and its results. Bo et al. (2007), Montuori et al. (2008), and Nawrocki et al. (2002) reported a link between the varying XE levels in bottled drinking water and water source, temperature, and time in storage. However, none of these factors that describe the bottled drinking water (water source, temperature, and time in storage) were included in the 2003–2006 NHANES to assess the XE levels associated with leaching. Without the descriptive factors of bottled drinking water (water source, temperature, and time in storage), I could not assess the accurate values of XE levels. XE levels in bottled drinking water vary due

to water source, temperature, and time in storage; therefore, information on the descriptive factors needs to be current to reflect current exposure levels.

Another possible explanation for the lack of association observed in the current study is that I used urine XE levels instead of the plasma XE levels used by many other researchers (Ahern et al., 2019; Chuang et al., 2020; Wu et al., 2021; F. Zhang et al., 2017). Although there was no evidence in the literature to suggest a difference in results between studies that use plasma and urine, accumulation and/or metabolism of XE metabolites may differ in urine compared to plasma.

Finally, another possible explanation for why the results of the current study differed from the literature is the effect of confounding factors in the former. Research by Rosinger et al. (2018) examined the demographic and socioeconomic disparities among people drinking tap water versus those consuming bottled drinking water. The findings revealed that greater proportions of Hispanics (52.9%) and Blacks (46.0%) consumed bottled water compared to Whites (26.3%) and Asians (37.8%). Females had higher odds of consuming bottled water (OR = 1.28; 95% CI: 1.11–1.47) than males. Rosinger hypothesized that people with demographic and population characteristics such as being foreign-born Hispanic and Black or having lower education and income were more likely to consider tap water unsafe based on previous life experiences, leading to greater bottled drinking water consumption. This is relevant because it is necessary to consider the confounding effects of these factors associated with increased bottled drinking water consumption among specific populations, and the potential for increased estrogen-dependent cancers.

Co-Exposure to Dietary PEs and XEs and Estrogen-Dependent Cancers

Finally, the primary research questions addressed in the current study were related to assessing the relationship between consumption of both soy and bean products and bottled drinking water and estrogen-dependent cancers. The current study's findings indicated that there was no association between consumption of soy and bean products and bottled drinking water and estrogen-dependent cancers. Based on the results of my study, when PE and XE intake occurred together, there was no interaction effect in this population. This analysis's results were not significant ($p > 0.05$) for any level of bean, soy, or bottled drinking water consumption, and no significant effect modification was identified.

Some possible explanations for the results from this current study varying from those in the literature. Previous work on the risk of estrogen-dependent cancers was not without concerns, since that research primarily focused on exposure to dietary PEs or XEs individually (Hwang et al., 2012; Katchy et al., 2014; Lee et al., 2018; Schmidt et al., 2006; J. Wang et al., 2014; Yakimchuk et al., 2018). Combination co-exposure studies had been considered too complex to be done (J. Wang et al., 2014), and the limited research available had been conducted in in vitro and in vivo studies (Hwang et al., 2012; Jadhav et al., 2017; Lee et al., 2018; Patisaul et al., 2012; Pons et al., 2019; Yakimchuk et al., 2018). The inconsistent findings among these studies (Hwang et al., 2012; Jadhav et al., 2017; Katchy et al., 2014; Lee et al., 2018; Patisaul et al., 2012; J. Wang et al., 2014; Yakimchuk et al., 2018) speaks to the complex nature of co-exposure studies. The further complexity of co-exposure studies in humans is a possible

explanation for the difference in results of the current study from the literature. For example, the multiple external lifestyle factors influencing human diets add complexity and make in vivo and in vitro results difficult to extrapolate to humans. Additionally, previous studies focused on early in utero exposure to PEs and XEs as having a more significant impact on estrogen-dependent cancers developed later in life (Lite et al., 2022; Stillwater et al., 2020; Ugai et al., 2022). However, unlike animal studies, it is difficult to assess in humans the in utero and early life co-exposure to PEs and XEs and subsequent estrogen-dependent cancer diagnosis later in life without a prospective longitudinal study.

No association was found for the individual exposures in the current study (RQ1, RQ2, RQ3, and RQ4), and there was no observed association for the interactions in the current study as well (RQ5 and RQ6), which aligns with the methodologic concept by Bedeian and Mossholder (1994). However, Lorah (2020) suggested that when an interaction effect is not significant, it may be due to a lack of power rather than no actual effect. Therefore, the study would need to be powered sufficiently to detect an interaction. A significantly larger sample size is required to detect an effect for an interaction, since the analysis for an interaction takes the difference-in-differences between two groups making the standard error having four terms instead of two. Gelmann et al. (2022) suggested that a sample size 4 times larger is needed to estimate an interaction the same size as the main effect. Therefore, for RQ5 and RQ6, the sample must have been at least $n = 472$ compared to $n = 113$ for the main effect sample size. The smaller sample size available for RQ5 and RQ6 in the current study to assess the interactions may have contributed to the inability to observe interactions.

The null hypotheses were not rejected in the tests of association between consumption of both soy and bean products (high in dietary PEs) and bottled drinking water (may contain increased dietary XEs) and estrogen-dependent cancers. No statistical significance was observed for any research questions in this study. However, the current study did build on existing knowledge by retrospectively assessing this association of co-exposure in a human population. Substantial gaps exist in research on the impact of co-exposure, and whether PEs can reduce the toxicity of XEs among humans. The current study begins to fill this gap in the literature by investigating the dietary impact of co-exposure of PEs and XEs on estrogen-dependent cancers in a human population. The current study goes beyond investigating co-exposure impact in that it also investigates whether there are optimal levels of PEs necessary to minimize the effects of XEs which may result in a reduced risk of estrogen-dependent cancers. The current study begins to fill that gap with the next steps being further research using prospective cohort studies.

Theoretical Framework

My findings aligned with the employed advanced model of the epidemiology triangle. The model suggests three things that work synergistically to influence the occurrence of disease over time – causative factors, environmental/behavioral factors, and the group or population and its characteristics. According to the model, all of these contribute over time to estrogen-dependent cancer diagnosis. The framework explores complex chronic disease states with many etiologic factors (Merrill, 2013). In the current study, the increased presence of estrogen, increased soy or increased bottled water consumption, and specific population characteristics could be used to better predict the

potential for development of estrogen-dependent cancers. As reflected in research by Hwang et al. (2012), genistein, the phytoestrogen found in soy products, plays a preventive role in estrogen-dependent cancer development due to its anti-estrogenic properties that regulate cell lifecycles and inhibit cell proliferation. Furthermore, as mentioned in the review of the literature, genistein can reduce the impact of phthalates and the potential for estrogen-dependent cancer diagnoses. Therefore, individuals consuming significant amounts of soy and bean products and more significant amounts of bottled water should be able to reduce their risk of estrogen-dependent cancers.

Limitations of the Study

The data set used in these analyses was secondary data originally collected by NHANES for purposes other than those of the current study. This was the most significant limitation since it required modification of my initial research question. Some independent variables were not collected in a way that would allow them to be analyzed in a way that would answer the original question. My ability to ask the specific questions needed to examine these associations was limited by the independent variables collected in the data and how they were measured or operationalized. The current study examined dietary estrogen intake using soy and bean product consumption as the primary source of PEs. However, the NHANES data set also included soy intake through consumption of soy milk. Soy milk consumption was excluded from the current study as it was not in line with the literature; the current study only included consumption of solid soy products rather than liquid soy products. This differentiation in soy product types is relevant because there are potential implications for variability in the results when including solid

and liquid products due to differences in metabolism and absorption. This additional source of soy intake was not accounted for in the current study, and it is possible that it could contribute to reducing the risk of estrogen-dependent cancer.

Similarly, the cancer diagnosis variable in NHANES allowed for up to three kinds of cancers to be reported by participants. The current study assumed that the first cancer entry reported in NHANES was the primary cancer diagnosed. The study's analyses did not include any additional second or third cancer entries, if reported. Conversely, excluding these secondary and tertiary cancers may have inadvertently biased the results by excluding any additional diagnoses of estrogen-dependent cancer that may have been reported.

This secondary data set contained some cases for which critical data as described in Figure 4, such as cancer diagnosis, cancer types, dietary recall, etc., were missing, so these cases could not be included in the analyses. Again, this may have reduced the sample size for the number of total estrogen-dependent cancer cases. In addition, the data were obtained using self-reporting and interviewer questionnaires, which introduce the possibility of both recall and interviewer bias, intentionally or non-intentionally. Finally, given the current study's cross-sectional design, it was impossible to establish any temporality between the dependent and independent variables.

Recommendations

The results from the current study should be used as a starting point to further investigate the impact of dietary intake and exposure during an individual's life on the development of estrogen-dependent cancers. Nevertheless, a longitudinal study would be

recommended to elucidate any potential temporal relationship between dietary intake and estrogen-dependent cancers. In addition, a more comprehensive examination of the potential relationship between dietary intake of PEs and dietary exposure to XEs should include co-exposure during multiple stages of life to assess the development of estrogen-dependent cancers in adulthood.

There is a further need to understand whether the time of exposure is the key factor in the development of estrogen-dependent cancers in adulthood, since exposure to exogenous estrogens during periods of development may alter an individual's susceptibility to cancer. As suggested by other researchers (Korde et al., 2009; Lite et al., 2022; Shu et al., 2001; Stillwater et al., 2020; Ugai et al., 2022; Wu et al., 2002), future research needs to include investigation at different stages of development (i.e., in utero, perinatal, peripubertal, adolescence, and adulthood), dosing of exposure, and any cumulative effect of lifetime exposure to assess the potential impact of exposure on risk of estrogen-dependent cancers. Similarly, data on time of exposure and a longitudinal assessment might make it possible to determine if intake and exposure have a cumulative effect. The multiple sources of exogenous estrogen increase lifetime exposure, which may contribute to the carcinogenesis of estrogen-dependent cancers (Fucic et al., 2012; LaKind & Naiman, 2011). There continues to exist a need for more research studies on estrogen-dependent cancers to determine which specific dietary factors contribute most to the development of estrogen-dependent cancers, and whether other dietary factors provide the most protective effects with co-exposure, particularly in the context of epidemiological data. Public health practitioners could use results from such future

research to develop interventions aimed at reducing the risk of estrogen-dependent cancers, which would yield positive implications for social change.

Implications for Social Change

This research can contribute to positive social change by providing cancer researchers with a starting point to continue investigating dietary estrogen exposure pathways and assessing these pathways' carcinogenesis risk in an epidemiologic context. This current study was one of the first studies of its type in a Western population. Future research can improve knowledge of pathogenesis to inform strategies in promoting prevention efforts, early detection of cancer, and treatment, all of which have broader public health implications. Understanding the etiological role dietary PE and XE exposures play in carcinogenesis can raise awareness among healthcare and public health officials to promote healthy diet and lifestyle behaviors. Such behaviors are modifiable and can potentially to support or promote that increased consumption of soy and bean products and/or the reduction in exposure to dietary phthalates and other plasticizers leached from packaging materials, as well as other food contaminants. The current study can serve as the basis for future researchers to expand on and continue to investigate not only the potential association between PEs and XEs and the development of estrogen-dependent cancer but to quantify the levels at which prevention may occur. Identification and quantification of these dietary sources of environmental risk factors, and their influence on estrogen-dependent cancers remain elusive. Quantifying the association between dietary PEs and XEs and cancer outcomes in future studies can provide evidence of the need for appropriate control and prevention measures. Further implications for

positive social change may come from utilizing knowledge of this topic to inform public health recommendations and develop interventions to reduce estrogen-dependent cancer incidence, morbidity, and mortality.

Conclusion

There has been a significant increase in the global incidence of many types of cancer among those under 50, including many estrogen-dependent cancers investigated in the current study (breast, cervical, colorectal, endometrial, and prostate). Even though the reasons are not completely clear, previous research had suggested that specific risk factors, such as dietary exposure during early life and young adulthood may explain the rise in these types of cancers. Previous research has also concluded that most estrogen-dependent cancers are influenced by ongoing exposure to certain environmental risk factors, and it is critical to identify these potential carcinogenic substances. Diet is an essential route of lifetime EDC exposure and may play a role in the prevention of estrogen-dependent cancers. Lifestyle and dietary factors appear to be correlated with these estrogen-dependent cancers, making cancer prevention an important avenue for this public health issue. Available epidemiologic studies have been inconsistent and inconclusive on the association between dietary intake of PEs and dietary XE exposure, and incidence of estrogen-dependent cancers. Greater exploration of the association between dietary PE intake and XE exposure and the development of estrogen-dependent cancers is needed to elucidate this potential relationship. Public health practitioners could use results from further research to develop interventions aimed at reducing the risk of estrogen-dependent cancers, which would yield positive implications for social change.

References

Acconcia, F., Fiocchetti, M., & Marino, M. (2017). Xenoestrogen regulation of ERα/ERβ balance in hormone-associated cancers. *Molecular and Cellular Endocrinology*, *457*, 3–12. https://doi.org/10.1016/j.mce.2016.10.033

Ahern, T. P., Broe, A., Lash, T. L., Cronin-Fenton, D. P., Ulrichsen, S. P., Christiansen, P. M., Cole, B. F., Tamimi, R. M., Sørensen, H. T., & Damkier, P. (2019). Phthalate exposure and breast cancer incidence: A Danish nationwide cohort study. *Journal of Clinical Oncology*, *37*(21), 1800–1809. https://doi.org/10.1200/JCO.18.02202

Ahluwalia, N., Dwyer, J., Terry, A., Moshfegh, A., & Johnson, C. (2016). Update on NHANES dietary data: Focus on collection, release, analytical considerations, and uses to inform public policy. *Advances in Nutrition, 7*(1), 121–134. https://doi.org/10.3945/an.115.009258

Alipour, S., Jafari-Adli, S., & Eskandari, A. (2015). Benefits and harms of phytoestrogen consumption in breast cancer survivors. *Asian Pacific Journal of Cancer Prevention, 16*(8), 3091-3096. https://doi.org/10.7314/apjcp.2015.16.8.3091

Allen, M. (2017). *The Sage Encyclopedia of Communication Research Methods*. https://doi.org/10.4135/9781483381411

Al-Otoum, F., Al-Ghouti, M. A., Costa, O. S., Jr., & Khraisheh, M. (2017). Impact of temperature and storage time on the migration of antimony from polyethylene terephthalate (PET) containers into bottled water in Qatar. *Environmental Monitoring and Assessment*, *189*(12), 631. https://doi.org/10.1007/s10661-017-

6342-3

Ambrosone, C. B., Zirpoli, G., Ruszczyk, M., Shankar, J., Hong, C.-C., McIlwain, D., Roberts, M., Yao, S., McCann, S. E., Ciupak, G., Hwang, H., Khoury, T., Jandorf, L., Bovbjerg, D. H., Pawlish, K., & Bandera, E. V. (2014). Parity and breastfeeding among African-American women: Differential effects on breast cancer risk by estrogen receptor status in the Women's Circle of Health Study. *Cancer Causes & Control*, *25*(2), 259–265. https://doi.org/10.1007/s10552-013-0323-9

American Cancer Society. (2022). *Cancer facts & figures 2022*. Retrieved from www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf

American Cancer Society. (2023). *What is cancer?* Retrieved from https://www.cancer.org/cancer/understanding-cancer/what-is-cancer.html

American Heart Association. (2017). *Suggested servings from each food group*. www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/suggested-servings-from-each-food-group

American Institute for Cancer Research. (2019). *AICR food facts*. www.aicr.org/cancer-prevention/food-facts/soy/

An, J., Tzagarakis-Foster, C., Scharschmidt, T. C., Lomri, N., & Leitman, D. C. (2001). Estrogen receptor β-selective transcriptional activity and recruitment of coregulators by phytoestrogens. *Journal of Biological Chemistry*, *276*(21), 17808–17814. https://doi.org/10.1074/jbc.M100953200

Anand, P., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., Sung, B., & Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research*, *25*(9), 2097–2116. https://doi.org/10.1007/s11095-008-9661-9

Anderson, G. L., Judd, H. L., Kaunitz, A. M., Barad, D. H., Beresford, S. A., Pettinger, M., Liu, J., McNeeley, S. G., Lopez, A. M., & Women's Health Initiative Investigators (2003). Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*, *290*(13), 1739–1748. https://doi.org/10.1001/jama.290.13.1739

Aneck-Hahn, N. H., Van Zijl, M. C., Swart, P., Truebody, B., Genthe, B., Charmier, J., & Jager, C. D. (2018). Estrogenic activity, selected plasticizers and potential health risks associated with bottled water in South Africa. *Journal of Water and Health*, *16*(2), 253-262. https://doi.org/10.2166/wh.2018.043

Assi, H. A., Khoury, K. E., Dbouk, H., Khalil, L. E., Mouhieddine, T. H., & El Saghir, N. S. (2013). Epidemiology and prognosis of breast cancer in young women. *Journal of Thoracic Disease*, *5*, S2–S8. https://doi.org/10.3978/j.issn.2072-1439.2013.05.24

Avila-Tang, E., Al-Delaimy, W. K., Ashley, D. L., Benowitz, N., Bernert, J. T., Kim, S., Samet, J. M., & Hecht, S. S. (2013). Assessing secondhand smoke using biological markers. *Tobacco Control*, *22*(3), 164–171. https://doi.org/10.1136/tobaccocontrol-2011-050298

Bahrami, A., Makiabadi, E., Jalali, S., Heidari, Z., Assadi, M., & Rashidkhani, B. (2021).

Dietary intake of polyphenols and the risk of breast cancer: A case-control study. *Clinical Nutrition Research*, *10*(4), 330–340. https://doi.org/10.7762/cnr.2021.10.4.330

Banerjee, A., Chitnis, U. B., Jadhav, S. L., Bhawalkar, J. S., & Chaudhury, S. (2009). Hypothesis testing, Type I and Type II errors. *Industrial Psychiatry Journal*, *18*(2), 127–131. https://doi.org/10.4103/0972-6748.62274

Basree, M. M., Shinde, N., Koivisto, C., Cuitino, M., Kladney, R., Zhang, J., Stephens, J., Palettas, M., Zhang, A., Kim, H. K., Acero-Bedoya, S., Trimboli, A., Stover, D. G., Ludwig, T., Ganju, R., Weng, D., Shields, P., Freudenheim, J., Leone, G. W., … Ramaswamy, B. (2019). Abrupt involution induces inflammation, estrogenic signaling, and hyperplasia linking lack of breastfeeding with increased risk of breast cancer. *Breast Cancer Research*, (1), 1. https://doi.org/10.1186/s13058-019-1163-7

Basu, P., & Maier, C. (2018). Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives. *Biomedicine & Pharmacotherapy*, *107*, 1648–1666. https://doi.org/10.1016/j.biopha.2018.08.100

Bedeian, A., & Mossholder, K. (1994). Simple question, not so simple answer: Interpreting interaction terms in moderated multiple regression. *Journal of Management*, *20*(1), 159–165. https://doi.org/10.1177/014920639402000108

Berger, C., Qian, Y., & Chen, X. (2013). The p53-estrogen receptor loop in cancer. *Current Molecular Medicine*, *13*(8), 1229–1240.

https://doi.org/10.2174/15665240113139990065

Bilancio, A., Bontempo, P., Di Donato, M., Conte, M., Giovannelli, P., Altucci, L., Migliaccio, A., & Castoria, G. (2017). Bisphenol A induces cell cycle arrest in primary and prostate cancer cells through EGFR/ERK/p53 signaling pathway activation. Oncotarget, 8(70), 115620–115631. https://doi.org/10.18632/oncotarget.23360

Blount, B. C., Silva, M. J., Caudill, S. P., Needham, L. L., Pirkle, J. L., Sampson, E. J., Lucier, G. W., Jackson, R. J., & Brock, J. W. (2000). Levels of seven urinary phthalate metabolites in a human reference population. *Environmental Health Perspectives*, *108*(10), 979–982. https://doi.org/10.1289/ehp.00108979

Bo, S., Ciccone, G., Baldi, C., Benini, L., Dusio, F., Forastiere, G., Lucia, C., Nuti, C., Durazzo, M., Cassader, M., Gentile, L., & Pagano, G. (2007). Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. *Journal of General Internal Medicine*, *22*(12), 1695–1703. https://doi.org/10.1007/s11606-007-0399-6

Bornehag, C. G., Sundell, J., Weschler, C. J., Sigsgaard, T., Lundgren, B., Hasselgren, M., & Hägerhed-Engman, L. (2004). The association between asthma and allergic symptoms in children and phthalates in house dust: A nested case-control study. *Environmental Health Perspectives*, *112*(14), 1393–1397. https://doi.org/10.1289/ehp.7187

Bradley, C. J., Yabroff, K. R., Dahman, B., Feuer, E. J., Mariotto, A., & Brown, M. L. (2008). Productivity costs of cancer mortality in the United States: 2000-2020.

Journal of the National Cancer Institute, *100*(24), 1763–1770. https://doi.org/10.1093/jnci/djn384

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Bronowicka-Kłys, D. E., Lianeri, M., & Jagodziński, P. P. (2016). The role and impact of estrogens and xenoestrogen on the development of cervical cancer. *Biomedicine & Pharmacotherapy*, *84*, 1945–1953. https://doi.org/10.1016/j.biopha.2016.11.007

Calafat, A. M., Ye, X., Wong, L. Y., Reidy, J. A., & Needham, L. L. (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environmental Health Perspectives*, 116, 39–44. https://doi.org/10.1289/ehp.10753

California Breast Cancer Research Program. (n.d.). *Etiology and Prevention*. Retrieved from https://www.cbcrp.org/priorities/etiology-and-prevention.html

Carroll, R. J., Midthune, D., Subar, A. F., Shumakovich, M., Freedman, L. S., Thompson, F. E., & Kipnis, V. (2012). Taking advantage of the strengths of 2 different dietary assessment instruments to improve intake estimates for nutritional epidemiology. *American Journal of Epidemiology*, 175, 340-347. https://doi.org/10.1093/aje/kwr317

Cathcart-Rake, E. J., Ruddy, K. J., Bleyer, A., & Johnson, R. H. (2021). Breast cancer in

adolescent and young adult women under the age of 40 years. *JCO Oncology Practice*, *17*(6), 305-313. https://doi.org/10.1200/OP.20.00793

Centers for Disease Control and Prevention. (2020a). *National Center for Health Statistics – National Health and Nutrition Examination Survey (NHANES 2003-2004)*. Retrieved from https://wwwn.cdc.gov/nchs/nhanes/

Centers for Disease Control and Prevention. (2020b). *About the National Health and Nutrition Examination Survey - Introduction*. Retrieved from https://www.cdc.gov/nchs/nhanes/about_nhanes.htm

Centers for Disease Control and Prevention. (2020c). *National Health and Nutrition Examination Survey Tutorials -Module 2: Sample Design* . Retrieved from https://wwwn.cdc.gov/nchs/nhanes/tutorials/module2.aspx

Centers for Disease Control and Prevention. (2020d). *NHANES Survey Methods and Analytic Guidelines* . Retrieved from https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#sample-design

Centers for Disease Control and Prevention. (2020e). *National Health and Nutrition Examination Survey Tutorials - NHANES 2003-2004 Questionnaire Data Overview*. Retrieved from https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/OverviewQuex.aspx?BeginYear=2003

Centers for Disease Control and Prevention. (2020f). *NHANES Survey Methods and Analytic Guidelines.* Retrieved from https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#sample-design

Centers for Disease Control and Prevention. (2020g). *Measuring Guides for the Dietary Recall Interview*. Retrieved from https://www.cdc.gov/nchs/nhanes/measuring_guides_dri/measuringguides.htm

Centers for Disease Control and Prevention. (2020h). *NHANES 2003-2004 Laboratory Data Overview.* Retrieved from https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/OverviewLab.aspx?BeginYear=2003

Centers for Disease Control and Prevention. (2019a). *Colorectal (colon) cancer*. Retrieved from https://www.cdc.gov/cancer/colorectal/statistics/index.htm

Centers for Disease Control and Prevention. (2019b). *Prostate Cancer*. Retrieved from https://www.cdc.gov/cancer/prostate/statistics/index.htm

Centers for Disease Control and Prevention. (2018a). *Data Access - Public-Use Data Files and Documentation.* Retrieved from https://www.cdc.gov/nchs/data_access/ftp_data.htm

Centers for Disease Control and Prevention. (2018b). *Confidentiality.* Retrieved from https://www.cdc.gov/nchs/nhanes/participant/participant-confidentiality.htm

Centers for Disease Control and Prevention. (2006). *Analytic and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES).* Retrieved from https://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf

Centers for Disease Control and Prevention. (2018). *NHANES – Survey participants.*

Retrieved from https://www.cdc.gov/nchs/nhanes/participant/participant-selected.htm

Center for Innovation in Research and Teaching (CIRT). (n.d.). *An overview of quantitative research.* Retrieved from https://cirt.gcu.edu/research/developmentresources/research_ready/quantresearch/overview_quant

Chang, Y.-J., Hou, Y.-C., Chen, L.-J., Wu, J.-H., Wu, C.-C., Chang, Y.-J., & Chung, K.-P. (2017). Is vegetarian diet associated with a lower risk of breast cancer in Taiwanese women? *BMC Public Health*, 17(1), 800. https://doi.org/10.1186/s12889-017-4819-1

Chen, H. H., Chen, S. P., Zheng, Q. L., Nie, S. P., Li, W. J., Hu, X. J., & Xie, M. Y. (2018). Genistein promotes proliferation of human cervical cancer cells through estrogen receptor-mediated PI3K/Akt-NF-κB pathway. *Journal of Cancer*, *9*(2), 288. https://doi.org/10.7150/jca.20499

Chen, M., Li, S., Arora, I., Yi, N., Sharma, M., Li, Z., Tollefsbol, T. O., & Li, Y. (2022). Maternal soybean diet on prevention of obesity-related breast cancer through early-life gut microbiome and epigenetic regulation. *Journal of Nutritional Biochemistry, 110*. https://doi.org/10.1016/j.jnutbio.2022.109119

Cheng, H. G., & Phillips, M. R. (2014). Secondary analysis of existing data: opportunities and implementation. *Shanghai Archives of Psychiatry*, *26*(6), 371–375. https://doi.org/10.11919/j.issn.1002-0829.214171

Chisamore, M., Wilkinson, H., Flores, O., & Chen, J. (2009). Estrogen-related receptor-a

antagonist inhibits both estrogen receptor-positive and estrogen receptor-negative breast tumor growth in mouse xenografts. *Molecular Cancer Therapeutics*, 8, 672–681. https://doi.org/10.1158/1535-7163.MCT-08-1028

Choi, S. M., Yoo, S. D., & Lee, B. M. (2004). Toxicological characteristics of endocrine-disrupting chemicals: Developmental toxicity, carcinogenicity, and mutagenicity. *Journal of Toxicology and Environmental Health*, Part B, *7*(1), 1-24. https://doi.org/10.1080/10937400490253229

Chuang, S., Chen, H., Sun, C., Chen, Y., Wang, Y., Chiang, C., Chen, C., Wang, S., & Chen, C. (2020). Phthalate exposure and prostate cancer in a population-based nested case-control study. *Environmental Research, 181*. https://doi.org/10.1016/j.envres.2019.108902

Chung, S. H., Franceschi, S., & Lambert, P. F. (2010). Estrogen and ERalpha: Culprits in cervical cancer?. *Trends in Endocrinology and Metabolism: TEM*, *21*(8), 504–511. https://doi.org/10.1016/j.tem.2010.03.005

Clarke, E. D., Rollo, M. E., Pezdirc, K., Collins, C. E., & Haslam, R. L. (2020). Urinary biomarkers of dietary intake: A review. *Nutrition Reviews*, *78*(5), 364–381. https://doi.org/10.1093/nutrit/nuz048

Cleveland Clinic. (2013). *Estrogen dependent cancers*. Retrieved from https://my.clevelandclinic.org/health/diseases/10312-estrogen-dependent-cancers

Colón, I., Caro, D., Bourdony, C. J., & Rosario, O. (2000). Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environmental Health Perspectives*, *108*(9), 895–900.

https://doi.org/10.1289/ehp.108-2556932

Corcoran, M. P., McKay, D. L., & Blumberg, J. B. (2012). Flavonoid basics: Chemistry, sources, mechanisms of action, and safety. *Journal of Nutrition in Gerontology and Geriatrics*, *31*(3), 176-189. https://doi.org/10.1080/21551197.2012.698219

Creswell, J. W., & Creswell, J. D. (2018). *Research design: Qualitive, quantitative, & mixed methods approaches*. SAGE Publications.

Darbre, P. D., & Charles, A. K. (2010). Environmental oestrogens and breast cancer: Evidence for combined involvement of dietary, household and cosmetic xenoestrogens. *Anticancer Research*, *30*(3), 815–827.

De Cicco, P., Catani, M. V., Gasperi, V., Sibilano, M., Quaglietta, M., & Savini, I. (2019). Nutrition and breast cancer: A literature review on prevention, treatment and recurrence. *Nutrients*, *11*(7), 1514. https://doi.org/10.3390/nu11071514

Deng, Y., Yan, Z., Shen, R., Wang, M., Huang, Y., Ren, H., Zhang, Y., & Lemos, B. (2020). Microplastics release phthalate esters and cause aggravated adverse effects in the mouse gut. *Environmental International*, *143*, 105916. https://doi.org/10.1016/j.envint.2020.105916

Dhaini, H. R., & Nassif, R. M. (2014). Exposure assessment of endocrine disruptors in bottled drinking water of Lebanon. *Environmental Monitoring And Assessment*, *186*(9), 5655–5662. https://doi.org/10.1007/s10661-014-3810-x

Doolan, D. M., & Froelicher, E. S. (2009). Using an existing data set to answer new research questions: A methodological review. *Research and Theory for Nursing Practice: An International Journal*, *23*(3), 203–215. https://doi.org/10.1891/1541-

6577.23.3.203

Doolan, D. M., Winters, J., & Nouredini, S. (2017). Answering research questions using an existing data set. *Medical Research Archives*. *5*(9). https://doi.org/10.18103/mra.v5i9.1526

Dwyer, J., Picciano, M. F., & Raiten, D. J. (2003). Estimation of usual intakes: What We Eat in America--NHANES. *Journal of Nutrition*, *133*(2). https://doi.org/10.1093/jn/133.2.609S

Environmental Protection Agency. (2015). *Phthalates*. Retrieved from https://www.epa.gov/sites/production/files/2015-05/documents/biomonitoring-phthalates.pdf

Etikan, I., Abubakar, S., & Alkassim, R. (2017). Frequency measures of epidemiological studies. *Biometrics & Biostatistics International Journal*. 2017;5(1):20-23. https://doi.org/10.15406/bbij.2017.05.00124

Eysteinsdottir, T., Gunnarsdottir, I., Thorsdottir, I., Harris, T., Launer, L. J., Gudnason, V., & Steingrimsdottir, L. (2011). Validity of retrospective diet history: assessing recall of midlife diet using food frequency questionnaire in later life. *Journal of Nutrition, Health & Aging*, *15*(10), 809–814. https://doi.org/10.1007/s12603-011-0067-8

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39, 175-191. https://doi.org/10.3758/BF03193146

Felix, A. S., Bower, J. K., Pfeiffer, R. M., Raman, S. V., Cohn, D. E., & Sherman, M. E. (2017). High cardiovascular disease mortality after endometrial cancer diagnosis: Results from the surveillance, epidemiology, and end results (SEER) database. *International Journal of Cancer*, *140*(3), 555–564. https://doi.org/10.1002/ijc.30470

Fénichel, P., & Chevalier, N. (2019). Is testicular germ cell cancer estrogen dependent? The role of endocrine disrupting chemicals. *Endocrinology*. 2019 Dec 1;160(12):2981-2989. https://doi.org/10.1210/en.2019-00486

Fink, B. N., Steck, S. E., Wolff, M. S., Britton, J. A., Kabat, G. C., Schroeder, J. C., Teitelbaum, S. L., Neugut, A. I., & Gammon, M. D. (2006). Dietary Flavonoid Intake and Breast Cancer Risk among Women on Long Island. *American Journal of Epidemiology*, (5), 514. https://doi.org/10.1093/aje/kwk033

Fisher, R. A. (1926). The arrangement of field experiments. *Journal of the Ministry of Agriculture of Great Britain*, 33, 503–513. https://doi.org/10.23637/rothamsted.8v61q

Food and Agriculture Organization of the United Nations. (2018). *Dietary Assessment: A resource guide to method selection and application in low resource settings.* Retrieved from http://www.fao.org/3/i9940en/I9940EN.pdf

Fortner, R. T., Sisti, J., Chai, B., Collins, L. C., Rosner, B., Hankinson, S. E., Tamimi, R. M., & Eliassen, A. H. (2019). Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: Results from the Nurses' Health Studies. *Breast Cancer Research: BCR*, 21(1), 40.

https://doi.org/10.1186/s13058-019-1119-y

Franke, A. A., Lai, J. F., & Halm, B. M. (2014). Absorption, distribution, metabolism, and excretion of isoflavonoids after soy intake. *Archives of Biochemistry and Biophysics*, *559*, 24–28. https://doi.org/10.1016/j.abb.2014.06.007

Freedman, L. S., Commins, J. M., Moler, J. E., Willett, W., Tinker, L. F., Subar, A. F., Spiegelman, D., Rhodes, D., Potischman, N., Neuhouser, M. L., Moshfegh, A. J., Kipnis, V., Arab, L., & Prentice, R. L. (2015). Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for potassium and sodium intake. *American Journal of Epidemiology*, *181*(7), 473–487. https://doi.org/10.1093/aje/kwu325

Freedman, L. S., Midthune, D., Arab, L., Prentice, R. L., Subar, A. F., Willett, W., Neuhouser, M. L., Tinker, L. F., & Kipnis, V. (2018). Combining a food frequency questionnaire with 24-Hour recalls to increase the precision of estimation of usual dietary intakes-evidence from the validation studies pooling project. *American Journal of Epidemiology*, *187*(10), 2227–2232. https://doi.org/10.1093/aje/kwy126

Freedman, L. S., Schatzkin, A., Midthune, D., & Kipnis, V. (2011). Dealing with dietary measurement error in nutritional cohort studies. *Journal of the National Cancer Institute*, 103(14), 1086-1092. https://doi.org/10.1093/jnci/djr189

Fritz, H., Seely, D., Flower, G., Skidmore, B., Fernandes, R., Vadeboncoeur, S., Kennedy, D., Cooley, K., Wong, R., Sagar, S., Sabri, E., & Fergusson, D. (2013). Soy, red clover, and isoflavones and breast cancer: a systematic review. *PLOS*

One, *8*(11), e81968. https://doi.org/10.1371/journal.pone.0081968

Fucic, A., Gamulin, M., Ferencic, Z., Katic, J., Krayer von Krauss, M., Bartonova, A., & Merlo, D. F. (2012). Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain. *Environmental Health: A Global Access Science Source*, *11 Suppl 1*, S8. https://doi.org/10.1186/1476-069X-11-S1-S8

García-Pérez, M. A. (2012). Statistical conclusion validity: some common threats and simple remedies. *Frontiers in Psychology*, *3*, 325. https://doi.org/10.3389/fpsyg.2012.00325

Gelmann, A., Hill, J., & Vehtari, A. (2022). *Regression and other stories*. Cambridge University Press.

Ghanavati, M., Clark, C. C. T., Bahrami, A., Teymoori, F., Movahed, M., Sohrab, G., & Hejazi, E. (2021). Dietary intake of polyphenols and total antioxidant capacity and risk of prostate cancer: A case-control study in Iranian men. *European Journal of Cancer Care*, *30*(2), e13364. https://doi.org/10.1111/ecc.13364

Giudice, A., Barbieri, A., Bimonte, S., Cascella, M., Cuomo, A., Crispo, A., D'Arena, G., Galdiero, M., Della Pepa, M. E., Botti, G., Caraglia, M., Capunzo, M., Arra, C., & Montella, M. (2019). Dissecting the prevention of estrogen-dependent breast carcinogenesis through Nrf2-dependent and independent mechanisms. *OncoTargets and Therapy*, *12*, 4937–4953. https://doi.org/10.2147/OTT.S183192

Godos, J., Zappalà, G., Bernardini, S., Giambini, I., Bes-Rastrollo, M., & Martinez-

Gonzalez, M. (2017). Adherence to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of observational studies. *International Journal of Food Sciences and Nutrition*, 68(2), 138-148. https://doi.org/10.1080/09637486.2016.1221900

Gray, J. M., Rasanayagam, S., Engel, C., & Rizzo, J. (2017). State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environmental Health : A Global Access Science Source*, 16(1), 94. https://doi.org/10.1186/s12940-017-0287-4

Guart, A., Bono-Blay, F., Borrell, A., & Lacorte, S. (2014). Effect of bottling and storage on the migration of plastic constituents in Spanish bottled waters. *Food Chemistry*, 2014; 156: 73 DOI: 10.1016/j.foodchem.2014.01.075

Guinter, M. A., Sandler, D. P., McLain, A. C., Merchant, A. T., & Steck, S. E. (2018). An estrogen-related dietary pattern and postmenopausal breast cancer risk in a cohort of women with a Family History of Breast Cancer. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *27*(10), 1223–1226. https://doi.org/10.1158/1055-9965.EPI-18-0514

Harris, H. R., Bergkvist, L., & Wolk, A. (2015). An estrogen-associated dietary pattern and breast cancer risk in the Swedish mammography cohort. *International Journal of Cancer*, *137*(9), 2149–2154. https://doi.org/10.1002/ijc.29586

Hashemipour, M., Kelishadi, R., Amin, M. M., & Ebrahim, K. (2018). Is there any association between phthalate exposure and precocious puberty in girls?

Environmental Science and Pollution Research International, *25*(14), 13589–13596. https://doi.org/10.1007/s11356-018-1567-4

Henderson, B. E., Ross, R., & Bernstein, L. (1988). Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation Award lecture. *Cancer Research*, 48, 246-253. Retrieved from http://cancerres.aacrjournals.org/content/48/2/246.full.pdf

Herichova, I., Reis, R., Hasakova, K., Vician, M., & Zeman, M. (2019). Sex-dependent regulation of estrogen receptor beta in human colorectal cancer tissue and its relationship with clock genes and VEGF-A expression. *Physiological Research*, *68*(Suppl 3), S297–S305. https://doi.org/10.33549/physiolres.934352

Hilz, R., & Wagner, M. (2018). Marital status, partnership and health behaviour: Findings from the German Ageing Survey (DEAS). *Comparative Population Studies-Zeitschrift für Bevölkerungswissenschaft*, *43*, 65-97. https://doi.org/10.12765/CPoS-2018-08

Hirano, M., Yamada, M., Tanaka, T., Koue, T., Saito, T., Higashimori, M., Ochiai, H., Yamamoto, J., Yaguchi, S., Mita, S., Hara, K., & EFPIA Japan Technical Committee PK/PD Task Force. (2021). Surveys/research exploring Japanese phase I studies in global drug development: Are they necessary prior to joining global clinical trials?. *Clinical Pharmacology in Drug Development*, 10: 1410-1418. https://doi.org/10.1002/cpdd.1044

House, J. S., Kessler, R. C., & Herzog, A. R. (1990). Age, socioeconomic status, and health. *Milbank Quarterly*, 383-411. https://doi.org/10.2307/3350111

Huang, Q., Braffett, B. H., Simmens, S. J., Young, H. A., & Ogden, C. L. (2020). Dietary polyphenol intake in US Adults and 10-Year Trends: 2007-2016. *Journal of the Academy of Nutrition and Dietetics*, *120*(11), 1821–1833. https://doi.org/10.1016/j.jand.2020.06.016

Hwang, K.-A., Kang, N.-H., Yi, B.-R., Lee, H.-R., Park, M.-A., & Choi, K.-C. (2012). Genistein, a soy phytoestrogen, prevents the growth of BG-1 ovarian cancer cells induced by 17 beta-estradiol or bisphenol A via the inhibition of cell cycle progression. *International Journal of Oncology*, *42*(2), 733–740. https://doi-org.ezp.waldenulibrary.org/10.3892/ijo.2012.1719

Iino, C., Shimoyama, T., Iino, K., Yokoyama, Y., Chinda, D., Sakurab, H., Fukuda, S., & Nakaji, S. (2019). Daidzein intake is associated with equol producing status through an increase in the intestinal bacteria responsible for equol production. *Nutrients*. 2019; 11(2):433. https://doi.org/10.3390/nu11020433

Jadhav, U., Saxena, M., O'Neill, N. K., Saadatpour, A., Yuan, G. C., Herbert, Z., Murata, K., & Shivdasani, R. A. (2017). Dynamic reorganization of chromatin accessibility signatures during dedifferentiation of secretory precursors into Lgr5+ intestinal stem cells. *Cell Stem Cell* 21, 65–77. https://doi.org/10.1016/j.stem.2017.05.001

Jafer, M., Ibrahim, H., & Taufiq-Yap, Y. H. (2018). Environmental and health effect of xenoestrogen and oestrogen found in food chain and its relation with cancers. *Biochemical & Cellular Archives*, *18*(2).

Jang, W. Y., Kim, M.-Y., & Cho, J. Y. (2022). Antioxidant, anti-inflammatory, anti-

menopausal, and anti-cancer effects of lignans and their metabolites. *International Journal of Molecular Sciences*, *23*(24). https://doi.org/10.3390/ijms232415482

Jeddi, M. Z., Rastkari, N., Ahmadkhaniha, R., & Yunesian, M. (2016). Endocrine disruptor phthalates in bottled water: daily exposure and health risk assessment in pregnant and lactating women. *Environmental Monitoring and Assessment*, *188*(9). https://doi.org/10.1007/s10661-016-5502-1

Kabagambe, E. K., Baylin, A., Allan, D. A., Siles, X., Spiegelman, D., & Campos, H. (2001). Application of the method of triads to evaluate the performance of food frequency questionnaires and biomarkers as indicators of long-term dietary intake. *American Journal of Epidemiology*, *154*(12). 1126–1135. https://doi.org/10.1093/aje/154.12.1126

Kahlert, J., Gribsholt, S. B., Gammelager, H., Dekkers, O. M., & Luta, G. (2017). Control of confounding in the analysis phase - An overview for clinicians. *Clinical Epidemiology*, *9*, 195–204. https://doi.org/10.2147/CLEP.S129886

Katchy, A., Pinto, C., Jonsson, P., Nguyen-Vu, T., Pandelova, M., Riu, A., Schramm, K. W., Samarov, D., Gustafsson, J. Å., Bondesson, M., & Williams, C. (2014). Coexposure to phytoestrogens and bisphenol A mimics estrogenic effects in an additive manner. *Toxicological Sciences*, (1), 21. https://doi.org/10.1093/toxsci/kft271

Kato, I., Tominaga, S., & Terao, C. (1989). An epidemiological study on marital status and cancer incidence. *Japanese Journal of Cancer Research*, *80*(4), 306-311. https://doi.org/10.1111/j.1349-7006.1989.tb02311.x

Kirkpatrick, S. I., Baranowski, T., Subar, A. F., Tooze, J. A., & Frongillo, E. A. (2019). Best practices for conducting and interpreting studies to validate self-report dietary assessment methods. *Journal of Academy of Nutrition and Dietetics*, *119*(11), 1801-1816. https://doi.org/10.1016/j.jand.2019.06.010

Koch, H. M., Lorber, M., Christensen, K. L., Pälmke, C., Koslitz, S., & Brüning, T. (2013). Identifying sources of phthalate exposure with human biomonitoring: results of a 48h fasting study with urine collection and personal activity patterns. *International Journal of Hygiene and Environmental Health*, *216*(6), 672–681. https://doi.org/10.1016/j.ijheh.2012.12.002

Korde, L. A., Wu, A. H., Fears, T., Nomura, A. M. Y., West, D. W., Kolonel, L. N., Pike, M. C., Hoover, R. N., & Ziegler, R. G. (2009). Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiology, Biomarkers & Prevention*, *18*(4), 1050–1059. https://doi.org/10.1158/1055-9965.EPI-08-0405

Kotsopoulos, J., Gronwald, J., Karlan, B., Rosen, B., Huzarski, T., Moller, P., Lynch, H. T., Singer, C. F., Senter, L., Neuhausen, S. L., Tung, N., Eisen, A., Foulkes, W. D., Ainsworth, P., Sun, P., Lubinski, J., & Narod, S. A. (2018). Age-specific ovarian cancer risks among women with a BRCA1 or BRCA2 mutation. *Gynecologic Oncology*, *150*(1), 85–91. https://doi.org/10.1016/j.ygyno.2018.05.011

Kuiper, G. G., Lemmen, J. G., Carlsson, B., Corton, J. C., Safe, S. H., van der Saag, P. T., van der Burg, B., & Gustafsson, J. A. (1998). Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor

beta. *Endocrinology*, *139*(10), 4252–4263. https://doi.org/10.1210/endo.139.10.6216

Kyrø, C., Tjønneland, A., Overvad, K., Olsen, A., & Landberg, R. (2018). Higher whole-grain intake is associated with lower risk of Type 2 diabetes among middle-aged men and eomen: The Danish diet, cancer, and health cohort. *Journal of Nutrition*, *148*(9), 1434–1444. https://doi.org/10.1093/jn/nxy112

LaKind, J. S., & Naiman, D. Q. (2011). Daily intake of bisphenol A and potential sources of exposure: 2005-2006 National Health and Nutrition Examination Survey. *Journal of Exposure Science & Environmental Epidemiology*, *21*(3), 272–279. https://doi.org/10.1038/jes.2010.9

LaKind, J. S., & Naiman, D. Q. (2015). Temporal trends in bisphenol A exposure in the United States from 2003-2012 and factors associated with BPA exposure: Spot samples and urine dilution complicate data interpretation. *Environmental Research*, *142*, 84–95. https://doi.org/10.1016/j.envres.2015.06.013

Lansdowne, L. (2018). *Cancer cells vs normal cells*. Retrieved from https://www.technologynetworks.com/cancer-research/articles/cancer-cells-vs-normal-cells-307366

Lee, G. A., Choi, K. C., & Hwang, K. A. (2018). Treatment with phytoestrogens reversed triclosan and bisphenol A-induced anti-apoptosis in breast cancer cells. *Biomolecules & Therapeutics*, *26*(5), 503–511. https://doi.org/10.4062/biomolther.2017.160

Lepri, S. R., Sartori, D., Semprebon, S. C., Baranoski, A., Coatti, G. C., & Mantovani, M.

S. (2018). Genistein affects expression of cytochrome P450 (CYP450) genes in hepatocellular carcinoma (HEPG2/C3A) cell line. *Drug Metabolism Letters*, *12*(2), 138-144. https://doi.org/10.2174/1872312812666180709150440

Li, A. J., Baldwin, R. L., & Karlan, B. Y. (2003). Estrogen and progesterone receptor subtype expression in normal and malignant ovarian epithelial cell cultures. *American Journal of Obstetrics and Gynecology*, *189*(1), 22–27. https://doi.org/10.1067/mob.2003.328

Li, H., Li, C., An, L., Deng, C., Su, H., Wang, L., Jiang, Z., Zhou, J., Wang, J., Zhang, C., & Jin, F. (2019). Phthalate esters in bottled drinking water and their human exposure in Beijing, China. *Food Additives & Contaminants: Part B: Surveillance Communications*, *12*(1), 1–9. https://doi.org/10.1080/19393210.2018.1495272

Lin, C. Y., Chen, P. C., Hsieh, C. J., Chen, C. Y., Hu, A., Sung, F. C., Lee, H. L., & Su, T. C. (2017). Positive association between urinary concentration of phthalate metabolites and oxidation of DNA and lipid in adolescents and young adults. *Scientific Reports*, *7*, 44318. https://doi.org/10.1038/srep44318

Lite, C., Raja, G., Juliet, M., Sridhar, V., Subhashree, K., Kumar, P., Chakraborty, P., & Arockiaraj, J. (2022). In utero exposure to endocrine-disrupting chemicals, maternal factors and alterations in the epigenetic landscape underlying later-life health effects. *Environmental Toxicology and Pharmacology*, *89*, 103779. https://doi.org/10.1016/j.etap.2021.103779

Lorah, J. (2020). Interpretation of main effects in the presence of non-significant interaction effects. Quantitative Methods for Psychology. 16(1). 33-45.

https://doi.org/10.20982/tqmp.16.1.p033

Luo, Q., Liu, Z. H., Yin, H., Dang, Z., Wu, P. X., Zhu, N. W., Lin, Z., & Liu, Y. (2018). Migration and potential risk of trace phthalates in bottled water: A global situation. *Water Research*, *147*, 362–372. https://doi.org/10.1016/j.watres.2018.10.002

Machado, V. S., & Bicalho, R. C. (2015). The infectious disease epidemiologic triangle of bovine uterine diseases. *Animal Reproduction* , *12*(3), 450–464.

Manjelievskaia, J., Brown, D., McGlynn, K. A., Anderson, W., Shriver, C. D., & Zhu, K. (2017). Chemotherapy use and survival among young and middle-aged patients with colon cancer. *JAMA Surgery*, *152*(5), 452–459. https://doi.org/10.1001/jamasurg.2016.5050

Marshall, G., & Jonker, L. (2010). A concise guide to... descriptive statistics. *Synergy*, 22–25.

Maskarinec, G., Ju, D., Morimoto, Y., Franke, A. A., & Stanczyk, F. Z. (2017). Soy food intake and biomarkers of breast cancer risk: Possible difference in Asian women? *Nutrition & Cancer*, *69*(1), 146. https://doi.org/10.1080/01635581.2017.1250924

Matthay, E. C., & Glymour, M. M. (2020). A Graphical Catalog of Threats to Validity: Linking social science with epidemiology. *Epidemiology*, *31*(3), 376–384. https://doi.org/10.1097/EDE.0000000000001161

Maxwell, T., Chun, S. Y., Lee, K. S., Kim, S., & Nam, K. S. (2017). The anti-metastatic effects of the phytoestrogen arctigenin on human breast cancer cell lines regardless of the status of ER expression. *International Journal of*

Oncology, *50*(2), 727–735. https://doi.org/10.3892/ijo.2016.3825

Mazzaglia, A., Cincotta, F., Lanza, C. M., Condurso, C., Tripodi, G., Muratore, G., & Verzera, A. (2016). Chemical migration in mineral water packaged in PET bottles and sensory shanges during the shelf-life. *Italian Journal of Food Science*, *28*, 55–58.

McKale, M., & Aishwarya, S. (2019). Epigenetic gene regulation by dietary compounds in cancer prevention. *Advances in Nutrition*, *10*(6), 1012-1028, https://doi.org/10.1093/advances/nmz046

McKeown, N. M., Day, N. E., Welch, A. A., Runswick, S. A., Luben, R. N., Mulligan, A. A., McTaggart, A., & Bingham, S. A. (2001). Use of biological markers to validate self-reported dietary intake in a random sample of the European prospective investigation into cancer United Kingdom Norfolk cohort. *American Journal of Clinical Nutrition 74:* 188–196. https://doi.org/10.1093/ajcn/74.2.188

McMichael-Phillips, D. F., Harding, C., Morton, M., Roberts, S. A., Howell, A., Potten, C. S., & Bundred, N. J. (1998). Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *American Journal of Clinical Nutrition*, *68*(6 Suppl), 1431S–1435S. https://doi.org/10.1093/ajcn/68.6.1431S

McPherson, K., Steel, C. M., & Dixon, J. M. (2000). ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. *British Medical Journal (Clinical Research Ed.)*, *321*(7261), 624-8. https://doi.org/10.1136/bmj.309.6960.1003

Melzer, D., Rice, N. E., Lewis, C., Henley, W. E., & Galloway, T. S. (2010). Association

of urinary bisphenol A concentration with heart disease: Evidence from NHANES 2003/06. *PLOS ONE*, *5*(1), 1–9. https://doi.org/10.1371/journal.pone.0008673

Mense, S. M., Hei, T. K., Ganju, R. K., & Bhat, H. K. (2008). Phytoestrogens and breast cancer prevention: possible mechanisms of action. *Environmental Health Perspectives*, *116*(4), 426–433. https://doi.org/10.1289/ehp.10538

Merrill, R. M. (2013). *Introduction to epidemiology* (6th ed.). Jones & Bartlett.

Momenimovahed, Z., & Salehiniya, H. (2019). Epidemiological characteristics of and risk factors for breast cancer in the world. *Breast Cancer*, *11*, 151–164. https://doi.org/10.2147/BCTT.S176070

Montuori, P., Jover, E., Morgantini, M., Bayona, J. M., & Triassi, M. (2008). Assessing human exposure to phthalic acid and phthalate esters from mineral water stored in polyethylene terephthalate and glass bottles. *Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, *25*(4), 511–518. https://doi.org/10.1080/02652030701551800

Mukund, V., Mukund, D., Sharma, V., Mannarapu, M., & Alam, A. (2017). Genistein: Its role in metabolic diseases and cancer. *Critical Reviews in Oncology/Hematology*, *119*, 13–22. https://doi.org/10.1016/j.critrevonc.2017.09.004

National Cancer Institute [NCI]. (2021). *What is cancer?* Retrieved from https://www.cancer.gov/about-cancer/understanding/what-is-cancer

National Health and Nutrition Examination Survey. (n.d.). *2003-2004 Questionnaire Data - Continuous NHANES.* Retrieved from https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Questionna

ire&CycleBeginYear=2003

National Institute of Environmental Health Sciences. (2023). *Nutrition, Health, and Your Environment.* Retrieved from https://www.niehs.nih.gov/health/topics/nutrition/index.cfm

Nawrocki, J., Dabrowska, A., & Borcz, A. (2002). Investigation of carbonyl compounds in bottled waters from Poland. *Water Research, 36*(19), 4893–4901. https://doi.org/10.1016/s0043-1354(02)00201-4

Nurul-Fadhilah, A., Teo, P. S., & Foo, L. H. (2012). Validity and reproducibility of a food frequency questionnaire (FFQ) for dietary assessment in Malay adolescents in Malaysia. *Asia Pacific Journal of Clinical Nutrition* 21: 97.

Ocké, M., & Kaaks, R. (1997). Biochemical markers as additional measurements in dietary validity studies: application of the method of triads with examples from the European Prospective Investigation into Cancer and Nutrition. *American Journal of Clinical Nutrition, 65(*4 Suppl*)*, 1240S-1245S. https://doi.org/10.1093/ajcn/65.4.1240S

Park, J., Kim, S., Park, M., Kim, Y., Lee, H., Choi, H., & Lim, S. (2017). Relationship between dietary factors and bisphenol a exposure: the second Korean National Environmental Health Survey (KoNEHS 2012–2014). *Annals of Occupational and Environmental Medicine*, (1), 1. https://doi.org/10.1186/s40557-017-0200-1

Parsons, J. K., Pierce, J. P., Mohler, J., Paskett, E., Jung, S. H., Morris, M. J., Small, E., Hahn, O., Humphrey, P., Taylor, J., & Marshall, J. (2018). Men's eating and living (MEAL) study (CALGB 70807 [Alliance]): Recruitment feasibility and

baseline demographics of a randomized trial of diet in men on active surveillance for prostate cancer. *BJU International*, *121*(4), 534–539. https://doi.org/10.1111/bju.13890

Patel, S., Homaei, A., Raju, A. B., & Meher, B. R. (2018). Estrogen: The necessary evil for human health, and ways to tame it. *Biomedicine & Pharmacotherapy*, *102*, 403–411. https://doi.org/10.1016/j.biopha.2018.03.078

Paterni, I., Granchi, C., & Minutolo, F. (2017). Risks and benefits related to alimentary exposure to xenoestrogens. *Critical Reviews in Food Science and Nutrition*, *57*(16), 3384–3404. https://doi.org/10.1080/10408398.2015.1126547

Patisaul, H. B., Sullivan, A. W., Radford, M. E., Walker, D. M., Adewale, H. B., Winnik, B., Coughlin, J. L., Buckley, B., & Gore, A. C. (2012). Anxiogenic effects of developmental bisphenol A exposure are associated with gene expression changes in the juvenile rat amygdala and mitigated by soy. *PLOS One*, *7*(9), e43890. https://doi.org/10.1371/journal.pone.0043890

Petursdottir, A. I., & Carr, J. E. (2018). Applying the taxonomy of validity threats from mainstream research design to single-case experiments in applied behavior analysis. *Behavior Analysis in Practice*, *11*(3), 228–240. https://doi.org/10.1007/s40617-018-00294-6

Pike, M. C., & Spicer, D. V. (2000). Hormonal contraception and chemoprevention of female cancers. *Endocrine-Related Cancer*, *7*(2), 73–83. https://doi.org/10.1677/erc.0.0070073

Pons, D. G., Vilanova-Llompart, J., Gaya-Bover, A., Alorda-Clara, M., Oliver, J., Roca,

P., & Sastre-Serra, J. (2019). The phytoestrogen genistein affects inflammatory-related genes expression depending on the ERα/ERβ ratio in breast cancer cells. *International Journal of Food Sciences & Nutrition*, 70(8), 941. https://doi.org/10.1080/09637486.2019.1597025

Pourhoseingholi, M. A., Baghestani, A. R., & Vahedi, M. (2012). How to control confounding effects by statistical analysis. *Gastroenterology and Hepatology From Bed to Bench*, *5*(2), 79–83.

Prins, G. S., Ye, S. H., Birch, L., Zhang, X., Cheong, A., Lin, H., Calderon-Gierszal, E., Groen, J., Hu, W. Y., Ho, S. M., & van Breemen, R. B. (2017). Prostate cancer risk and DNA methylation signatures in aging rats following developmental BPA exposure: A dose-response analysis. *Environmental Health Perspectives*, *125*(7), 077007. https://doi.org/10.1289/EHP1050

Rattanaburee, T., Tanawattanasuntorn, T., Thongpanchang, T., Tipmanee, V., & Graidist, P. (2021). Trans-(-)-kusunokinin: A potential anticancer lignan compound against HER2 in breast cancer cell lines? *Molecules*, *26*(15), 4537. https://doi.org/10.3390/molecules26154537

Rawluszko-Wieczorek, A. A., Marczak, L., Horst, N., Horbacka, K., Krokowicz, P., & Jagodzinski, P. P. (2017). Significance of intratissue estrogen concentration coupled with estrogen receptors levels in colorectal cancer prognosis. *Oncotarget*, *8*(70), 115546–115560. https://doi.org/10.18632/oncotarget.23309

Ressing, M., Blettner, M., & Klug, S. J. (2010). Data analysis of epidemiological studies: part 11 of a series on evaluation of scientific publications. *Deutsches Arzteblatt*

International, *107*(11), 187–192. https://doi.org/10.3238/arztebl.2010.0187

Rod, N. H., Hansen, A. M., Nielsen, J., Schnohr, P., & Gronbaek, M. (2009). Low-risk factor profile, estrogen levels, and breast cancer risk among postmenopausal women. *International Journal of Cancer*, *124*(8), 1935–1940. https://doi.org/10.1002/ijc.24136

Rosinger, A. Y., Herrick, K. A., Wutich, A. Y., Yoder, J. S., & Ogden, C. L. (2018). Disparities in plain, tap and bottled water consumption among US adults: National Health and Nutrition Examination Survey (NHANES) 2007-2014. *Public Health Nutrition*, *21*(8), 1455–1464. https://doi.org/10.1017/S1368980017004050

Ross, P. T., & Bibler Zaidi, N. L. (2019). Limited by our limitations. *Perspectives on Medical Education, 8(4)***,** 261–264. https://doi.org/10.1007/s40037-019-00530-x

Rowland, I., Faughnan, M., Hoey, L., Wähälä, K., Williamson, G., & Cassidy, A. (2003). Bioavailability of phyto-oestrogens. *British Journal of Nutrition, 89 Suppl 1*, S45-S58. https://doi.org/10.1079/BJN2002796

Roy, D., Cai, Q., Felty, Q., & Narayan, S. (2007). Estrogen-induced generation of reactive oxygen and nitrogen species, gene damage and estrogen-dependent cancers. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews*, *10(4),* 235-257. https://doi.org/10.1080/15287390600974924

Russo, G. I., Di Mauro, M., Regis, F., Reale, G., Campisi, D., Marranzano, M., Lo Giudice, A., Solinas, T., Madonia, M., Cimino, S., & Morgia, G. (2018). Association between dietary phytoestrogens intakes and prostate cancer risk in

Sicily. *Aging Male: The Official Journal of the International Society for the Study of the Aging Male*, *21*(1), 48–54. https://doi.org/10.1080/13685538.2017.1365834

Rutkowska, A. Z., Szybiak, A., Serkies, K., & Rachoń, D. (2016). Endocrine disrupting chemicals as potential risk factor for estrogen-dependent cancers. *Polskie Archiwum Medycyny Wewnetrznej*, *126*(7-8), 562–570. https://doi.org/10.20452/pamw.3481

Safe, S. H. (1997). Is there an association between exposure to environmental estrogens and breast cancer? *Environmental Health Perspectives Supplements*, *05 Suppl 3*(Suppl 3), 675. https://doi.org/10.1289/ehp.97105s3675

Sakharkar, P., & Kahaleh, A. (2017). Age and racial/ethnic disparities and burden of prostate cancer: A cross sectional population based study. *Journal of Basic Clinic Pharmacy*, 8, S022-S026.

Santana, J., Giraudi, C., Marengo, E., Robotti, E., Pires, S., Nunes, I., & Gaspar, E. M. (2014). Preliminary toxicological assessment of phthalate esters from drinking water consumed in Portugal. *Environmental Science and Pollution Research International*, *21*(2), 1380–1390. https://doi.org/10.1007/s11356-013-2020-3

Sauvant, M. P., Pepin, D., & Bohatier, J. (1995). Chemical and in vitro toxicological evaluations of water packaged in polyvinyl chloride and polyethylene terephthalate bottles. *Food Additives and Contaminants*, *12*(4), 567–584. https://doi.org/10.1080/02652039509374345

Sax, L. (2010). Polyethylene terephthalate may yield endocrine disruptors. *Environmental Health Perspectives*, 118(4), 445–448.

https://doi.org/10.1289/ehp.0901253

Schatzkin, A., Kipnis, V., Carroll, R. J., Midthune, D., Subar, A. F., Bingham, S., Schoeller, D. A., Troiano, R. P., & Freedman, L. S. (2003). A comparison of a food frequency questionnaire with a 24-hour recall for use in an epidemiological cohort study: Results from the biomarker-based Observing Protein and Energy Nutrition (OPEN) study. *International Journal of Epidemiology*, *32*(6), 1054-1062. https://doi.org/10.1093/ije/dyg264

Schettler, T. (2006). Human exposure to phthalates via consumer products. *International Journal of Andrology*, *29*(1), 134–139. https://doi.org/10.1111/j.1365-2605.2005.00567.x

Schmidt, S., Degen, G. H., Seibel, J., Hertrampf, T., Vollmer, G., & Diel, P. (2006). Hormonal activity of combinations of genistein, bisphenol A and 17beta-estradiol in the female Wistar rat. *Archives of Toxicology*, *80*(12), 839–845. https://doi.org/10.1007/s00204-006-0102-4

Selcuklu, S. D., Donoghue, M. T., Rehmet, K., de Souza Gomes, M., Fort, A., Kovvuru, P., Muniyappa, M. K., Kerin, M. J., Enright, A. J., & Spillane, C. (2012). MicroRNA-9 inhibition of cell proliferation and identification of novel miR-9 targets by transcriptome profiling in breast cancer cells. *Journal of Biological Chemistry*, *287*(35), 29516–29528. https://doi.org/10.1074/jbc.M111.335943

Semba, R. D., Rahman, N., Du, S., Ramsing, R., Sullivan, V., Nussbaumer, E., Love, D., & Bloem, M. W. (2021). Patterns of legume purchases and consumption in the United States. *Frontiers in Nutrition*, *8*, 732237.

https://doi.org/10.3389/fnut.2021.732237

Setchell, K. D., Zimmer-Nechemias, L., Cai, J., & Heubi, J. E. (1998). Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. *American Journal of Clinical Nutrition*, *68*(6 Suppl), 1453S–1461S. https://doi.org/10.1093/ajcn/68.6.1453S

Setia, M. S. (2016). Methodology series module 3: Cross-sectional studies. *Indian Journal of Dermatology*, 61(3), 261–264. http://doi.org/10.4103/0019-5154.182410

Shan, Z., Rehm, C. D., Rogers, G., Ruan, M., Wang, D. D., Hu, F. B., Mozaffarian, D., Zhang, F. F., & Bhupathiraju, S. N. (2019). Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999-2016. *Journal of the American Medical Association*, *322*(12), 1178–1187. https://doi.org/10.1001/jama.2019.13771

Shim, J. S., Oh, K., & Kim, H. C. (2014). Dietary assessment methods in epidemiologic studies. *Epidemiology and Health*, *36*, e2014009. https://doi.org/10.4178/epih/e2014009

Shivappa, N., Niclis, C., Coquet, J. B., Román, M. D., Hébert, J. R., & Diaz, M. D. P. (2018). Increased inflammatory potential of diet is associated with increased odds of prostate cancer in Argentinian men. *Cancer Causes & Control : CCC*, *29*(9), 803–813. https://doi.org/10.1007/s10552-018-1056-6

Shu, X. O., Jin, F., Dai, Q., Wen, W., Potter, J. D., Kushi, L. H., Ruan, Z., Gao, Y. T., & Zheng, W. (2001). Soyfood intake during adolescence and subsequent risk of

breast cancer among Chinese women. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *10*(5), 483–488.

Song, K., Atkinson, C., Frankenfeld, C., Jokela, T., Wähälä, K., Thomas, W., & Lampe, J. (2006). Prevalence of daidzein-metabolizing phenotypes differs between Caucasian and Korean American women and girls, *Journal of Nutrition*, *136*(5), 1347–1351, https://doi.org/10.1093/jn/136.5.1347

Sopik, V., Sun, P., & Narod, S. A. (2017). The prognostic effect of estrogen receptor status differs for younger versus older breast cancer patients. *Breast Cancer Research and Treatment*, *165*(2), 391–402. https://doi.org/10.1007/s10549-017-4333-2

Sorenmo, K. U., Durham, A. C., Radaelli, E., Kristiansen, V., Peña, L., Goldschmidt, M. H., & Stefanovski, D. (2019). The estrogen effect; clinical and histopathological evidence of dichotomous influences in dogs with spontaneous mammary carcinomas. *PLOS One*, *14*(10), 1–24. https://doi.org/10.1371/journal.pone.0224504

Soto, A. M., Fernandez, M. F., Luizzi, M. F., Oles Karasko, A. S., & Sonnenschein, C. (1997). Developing a marker of exposure to xenoestrogen mixtures in human serum. *Environmental Health Perspectives*, *105 Suppl 3(Suppl 3)*, 647–654. https://doi.org/10.1289/ehp.97105s3647

Spagnuolo, C., Russo, G. L., Orhan, I. E., Habtemariam, S., Daglia, M., Sureda, A., Nabavi, S. F., Devi, K. P., Loizzo, M. R., Tundis, R., & Nabavi, S. M. (2015).

Genistein and cancer: Current status, challenges, and future directions. *Advances in Nutrition*, *6*(4), 408–419. https://doi.org/10.3945/an.114.008052

Stewart, B. W., & Wild, C. P. (2014). *World Cancer Report 2014*. WHO Press

Stillwater, B. J., Bull, A. C., Romagnolo, D. F., Neumayer, L. A., Donovan, M. G., & Selmin, O. I. (2020). Bisphenols and risk of breast cancer: A Narrative Review of the Impact of Diet and Bioactive Food Components. *Frontiers in Nutrition*, *7*, 581388. https://doi.org/10.3389/fnut.2020.581388

Sullivan, L. M. (2012). *Essentials of Biostatistics in Public Health*. Jones & Bartlett Learning.

Szklo, M., & Nieto, F. J. (2014). *Epidemiology – Beyond Basics*. Jones & Bartlett Learning.

Tan, M. M., Ho, W. K., Yoon, S. Y., Mariapun, S., Hasan, S. N., Lee, D. S., Hassan, T., Lee, S. Y., Phuah, S. Y., Sivanandan, K., Ng, P. P., Rajaram, N., Jaganathan, M., Jamaris, S., Islam, T., Rahmat, K., Fadzli, F., Vijayananthan, A., Rajadurai, P., … Teo, S. H. (2018). A case-control study of breast cancer risk factors in 7,663 women in Malaysia. *PLOS One*, *13*(9), e0203469. https://doi.org/10.1371/journal.pone.0203469

Tang, L., Platek, M. E., Yao, S., Till, C., Goodman, P. J., Tangen, C. M., Wu, Y., Platz, E. A., Neuhouser, M. L., Stanczyk, F. Z., Reichardt, J. K. V., Santella, R. M., Hsing, A., Figg, W. D., Lippman, S. M., Thompson, I. M., & Ambrosone, C. B. (2018). Associations between polymorphisms in genes related to estrogen metabolism and function and prostate cancer risk: Results from the prostate

cancer prevention trial. *Carcinogenesis*, *39*(2), 125–133. https://doi.org/10.1093/carcin/bgx144

Trabert, B., Brinton, L. A., Anderson, G. L., Pfeiffer, R. M., Falk, R. T., Strickler, H. D., Sliesoraitis, S., Kuller, L. H., Gass, M. L., Fuhrman, B. J., Xu, X., & Wentzensen, N. (2016). Circulating estrogens and postmenopausal ovarian cancer risk in the women's health initiative observational study. *Cancer Epidemiology, Biomarkers & Prevention: A publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *25*(4), 648–656. https://doi.org/10.1158/1055-9965.EPI-15-1272-T

Trinh, Q. D. (2018). Understanding the impact and challenges of secondary data analysis. *Urologic Oncology*, *36*(4), 163–164. https://doi.org/10.1016/j.urolonc.2017.11.003

Ugai, T., Sasamoto, N., Lee, H. Y., Ando, M., Song, M., Tamimi, R., Kawachi, I., Campbell, P., Giovannucci, E., Weiderpass, E., Rebbeck, T., & Ogino, S. (2022). Is early-onset cancer an emerging global epidemic? Current evidence and future implications. *Nature Reviews. Clinical Oncology, 19(10)*, 656–673. https://doi.org/10.1038/s41571-022-00672-8

Ulm, M., Ramesh, A. V., McNamara, K. M., Ponnusamy, S., Sasano, H., & Narayanan, R. (2019). Therapeutic advances in hormone-dependent cancers: Focus on prostate, breast and ovarian cancers. *Endocrine Connections*, *8*(2), R10–R26. https://doi.org/10.1530/EC-18-0425

U.S. Census Bureau. (2020). *QuickFacts United States*. Retrieved from

https://www.census.gov/quickfacts/fact/table/US/PST040221

U.S. Department of Agriculture. (2015). *2015-2020 Dietary guidelines for Americans (8th ed.)*. US Department of Health and Human Services and US Department of Agriculture. Retrieved from https://health.gov/our-work/food-nutrition/2015-2020-dietaryguidelines

Va, P., Dodd, K. W., Zhao, L., Thompson-Paul, A. M., Mercado, C. I., Terry, A. L., Jackson, S. L., Wang, C. Y., Loria, C. M., Moshfegh, A. J., Rhodes, D. G., & Cogswell, M. E. (2019). Evaluation of measurement error in 24-hour dietary recall for assessing sodium and potassium intake among US adults - National Health and Nutrition Examination Survey (NHANES), 2014. *American Journal of Clinical Nutrition*, *109*(6), 1672–1682. https://doi.org/10.1093/ajcn/nqz044

Valentín-Blasini, L., Blount, B. C., Caudill, S. P., & Needham, L. L. (2003). Urinary and serum concentrations of seven phytoestrogens in a human reference population subset. *Journal of Exposure Analysis and Environmental Epidemiology*, *13*(4), 276–282. https://doi.org/10.1038/sj.jea.7500278

Vergne, S., Sauvant, P., Lamothe, V., Chantre, P., Asselineau, J., Perez, P., Durand, M., Moore, N., & Bennetau-Pelissero, C. (2009). Influence of ethnic origin (Asian v. Caucasian) and background diet on the bioavailability of dietary isoflavones. *British Journal of Nutrition, 102*(11), 1642-1653. https://doi.org/10.1017/S0007114509990833

Vieux, F., Maillot, M., Rehm, C. D., Barrios, P., & Drewnowski, A. (2020). Trends in tap and bottled water consumption among children and adults in the United States:

Analyses of NHANES 2011-16 data. *Nutrition Journal*, *19*(1), 1. https://doi.org/10.1186/s12937-020-0523-6

Viggiani, M., Polimeno, L., Di Leo, A., & Barone, M. (2019). Phytoestrogens: Dietary intake, bioavailability, and protective mechanisms against colorectal neoproliferative lesions. *Nutrients*. 2019; 11(8):1709. https://doi.org/10.3390/nu11081709

Wada, K., Nakamura, K., Tamai, Y., Tsuji, M., Kawachi, T., Hori, A., Takeyama, N., Tanabashi, S., Matsushita, S., Tokimitsu, N., & Nagata, C. (2013). Soy isoflavone intake and breast cancer risk in Japan: from the Takayama study. *International Journal of Cancer*, *133*(4), 952–960. https://doi.org/10.1002/ijc.28088

Wagner, M., & Oehlmann, J. (2009). Endocrine disruptors in bottled mineral water: Total estrogenic burden and migration from plastic bottles. *Environmental Science and Pollution Research International*, *16*(3), 278–286. https://doi.org/10.1007/s11356-009-0107-7

Wagner, W. (2017). *Using IBM SPSS Statistics for Research Methods and Social Science Statistics*. SAGE Publications.

Walden University. (2016). *What is a logistic regression?* Retrieved from https://www.youtube.com/watch?v=Jx1gnW-w1e8

Wang, J., Jenkins, S., & Lamartiniere, C. A. (2014). Cell proliferation and apoptosis in rat mammary glands following combinational exposure to bisphenol A and genistein. *BMC Cancer*, *14*, 379. https://doi.org/10.1186/1471-2407-14-379

Wang, T., Liu, B., Guan, Y., Gong, M., Zhang, W., Pan, J., Liu, Y., Liang, R., Yuan, Y.,

& Ye, L. (2018). Melatonin inhibits the proliferation of breast cancer cells induced by bisphenol A via targeting estrogen receptor-related pathways. *Thoracic Cancer*, *9*(3), 368–375. https://doi.org/10.1111/1759-7714.12587

Watson, C., Koong, L., Jeng, Y., & Vinas, R. (2019). Xenoestrogen interference with nongenomic signaling actions of physiological estrogens in endocrine cancer cells. *Steroids*, *142*, 84-93. https://doi.org/10.1016/j.steroids.2018.06.014

Whitley, E., & Ball, J. (2002). Statistics review 4: Sample size calculations. *Critical Care (London, England)*, *6*(4), 335-341. https://doi.org/10.1186/cc1521

Willett, W. (2013). *Nutritional Epidemiology*. Oxford University Press.

Willett, W., & Lenart, E. (1998). Reproducibility and validity of food-frequency questionnaires. *In Nutritional Epidemiology*. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199754038.003.0006

Williams, G. P., & Darbre, P. D. (2019). Low-dose environmental endocrine disruptors, increase aromatase activity, estradiol biosynthesis and cell proliferation in human breast cells. *Molecular and Cellular Endocrinology*, *486*, 55–64. https://doi.org/10.1016/j.mce.2019.02.016

World Health Organization. (2022). *Cancer*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/cancer

Wu, A., Franke, A., Wilkens, L., Tseng, C., Conroy, S., Li, Y., Polfus, L., De Rouen, M., Caberto, C., Haiman, C., Stram, D., Marchand, L., & Cheng, I. (2021). Urinary phthalate exposures and risk of breast cancer: The multiethnic cohort study.

Breast Cancer Research. 23(1), 44. https://doi.org/10.1186/s13058-021-01419-6

Wu, A., Wan, P., Hankin, J., Tseng, C., Yu, M., & Pike, M. (2002). Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis*, *23*(9), 1491–1496. https://doi.org/10.1093/carcin/23.9.1491

Xu, X., Zhou, G., Lei, K., LeBlanc, G. A., & An, L. (2019). Phthalate Esters and Their Potential Risk in PET Bottled Water Stored under Common Conditions. *International Journal of Environmental Research and Public Health*, *17*(1), 141. https://doi.org/10.3390/ijerph17010141

Xu, Z.-X., Liu, J., Gu, L.-P., Huang, B., & Pan, X.-J. (2017). Biological effects of xenoestrogens and the functional mechanisms via genomic and nongenomic pathways. *Environmental Reviews*, 25(3), 306–322. https://doi.org/10.1139/er-2016-0075

Yakimchuk, K., Revanna, C., Huang, D., Inzunza, J., & Okret, S. (2018). Suppression of lymphoma growth by the xenoestrogens bisphenol A and genistein. *Endocrine Connections*, *7*(12), 1472-1479. https://doi.org/10.1530/EC-18-0459

Yang, C. Z., Yaniger, S. I., Jordan, V. C., Klein, D. J., & Bittner, G. D. (2011). Most plastic products release estrogenic chemicals: A potential health problem that can be solved. *Environmental Health Perspectives*, *119*(7), 989–996. https://doi.org/10.1289/ehp.1003220

Yang, H., Sukocheva, O. A., Hussey, D. J., & Watson, D. I. (2012). Estrogen, male dominance and esophageal adenocarcinoma: Is there a link? *World Journal of Gastroenterology*, *18*(5), 393–400. https://doi-org./10.3748/wjg.v18.i5.393

Yuan, C., Spiegelman, D., Rimm, E. B., Rosner, B. A., Stampfer, M. J., Barnett, J. B., Chavarro, J. E., Rood, J. C., Harnack, L. J., Sampson, L. K., & Willett, W. C. (2018). Relative validity of nutrient intakes assessed by questionnaire, 24-Hour recalls, and diet records as compared with urinary recovery and plasma concentration biomarkers: Findings for women. *American Journal of Epidemiology*, *187*(5), 1051–1063. https://doi.org/10.1093/aje/kwx328

Yue, W., Yager, J., Wang, J., Jupe, E., & Santen, R. (2013). Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. *Steroids. 78*(2), 161-170. https://doi.org/10.1016/j.steroids.2012.11.001

Zaineddin, A. K., Buck, K., Vrieling, A., Heinz, J., Flesch-Janys, D., Linseisen, J., & Chang-Claude, J. (2012). The association between dietary lignans, phytoestrogen-rich foods, and fiber intake and postmenopausal breast cancer risk: A German case-control study. *Nutrition & Cancer, 64*(5), 652–665. https://doi.org/10.1080/01635581.2012.683227

Zhang, F., Haslam, D., Terry, M., Knight, J., Andrulis, I., Daly, M., Buys, S., & John, E. (2017). Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. *Cancer*, *123*(11), 2070–2079. https://doi.org/10.1002/cncr.30615

Zhang, H. Y., Cui, J., Zhang, Y., Wang, Z. L., Chong, T., & Wang, Z. M. (2016). Isoflavones and prostate cancer: A review of some critical issues. *Chinese Medical Journal*, 129(3), 341–347. https://doi.org/10.4103/0366-6999.174488

Zhang, Q., Feng, H., Qluwakemi, B., Wang, J., Yao, S., Cheng, G., Xu, H., Qiu, H., Zhu,

L., & Yuan, M. (2017). Phytoestrogens and risk of prostate cancer: An updated meta-analysis of epidemiologic studies. *International Journal of Food Sciences and Nutrition*, *68*(1), 28–42. https://doi.org/10.1080/09637486.2016.1216525

Zhang, W., & Xue, J. (2016). Economically motivated food fraud and adulteration in China: An analysis based on 1553 media reports. *Food Control, 67*(2016), 192-198. https://doi.org/10.1111/1750-3841.14279

Zhao, L., Huang, S., Mei, S., Yang, Z., Xu, L., Zhou, N., Yang, Q., Shen, Q., Wang, W., Le, X., Lau, W. B., Lau, B., Wang, X., Yi, T., Zhao, X., Wei, Y., Warner, M., Gustafsson, J. Å., & Zhou, S. (2018). Pharmacological activation of estrogen receptor beta augments innate immunity to suppress cancer metastasis. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(16), E3673–E3681. https://doi.org/10.1073/pnas.1803291115

Zhao, T. T., Jin, F., Li, J. G., Xu, Y. Y., Dong, H. T., Liu, Q., Xing, P., Zhu, G. L., Xu, H., & Miao, Z. F. (2019). Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: A meta-analysis of prospective cohort studies. *Clinical Nutrition (Edinburgh, Scotland)*, *38*(1), 136–145. https://doi.org/10.1016/j.clnu.2017.12.006

Zhu, X., Huang, I. Y., & Manning, L. (2019). The role of media reporting in food safety governance in China: A dairy case study. *Food Control*, *96*, 165–179. https://doi.org/10.1016/j.foodcont.2018.08.027

Ziaei, S., & Halaby, R. (2017). Dietary isoflavones and breast cancer risk. *Medicines*, *4*(2), 18. https://doi.org/10.3390/medicines4020018

Appendix: NHANES Questionnaires

1. Medical Condition (MCQ_C):
    a. MCQ220 - Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?
        i. MCQ230A – What kind of cancer was it?
2. Food Frequency Questionnaire – Raw Questionnaire (FFQRAW_C):
    a. FFQ0056 – Q.56 How often did you eat cooked dried beans (such as baked beans, pintos, kidney, blackeyed peas, lima, lentils, soybeans, or refried beans? (Please don't include bean soups or chili.)
    b. FFQ0096 – Q.96 How often did you eat tofu, soy burgers, or soy meat-substitutes?
3. Bottled Water (DR1TOT_C and DR2TOT_C)
    a. Total bottled water drank yesterday. (gm)