STARS

University of Central Florida
STARS

Honors Undergraduate Theses

UCF Theses and Dissertations

2021

Association Between Plasma Genistein and Health-Related Quality of Life in Breast Cancer Survivors

Tran Pham
University of Central Florida

 Part of the Cell Biology Commons, and the Dietetics and Clinical Nutrition Commons
Find similar works at: https://stars.library.ucf.edu/honorstheses
University of Central Florida Libraries http://library.ucf.edu

This Open Access is brought to you for free and open access by the UCF Theses and Dissertations at STARS. It has been accepted for inclusion in Honors Undergraduate Theses by an authorized administrator of STARS. For more information, please contact STARS@ucf.edu.

Recommended Citation

Pham, Tran, "Association Between Plasma Genistein and Health-Related Quality of Life in Breast Cancer Survivors" (2021). *Honors Undergraduate Theses*. 960.
https://stars.library.ucf.edu/honorstheses/960

www.manaraa.com

ASSOCIATION BETWEEN PLASMA GENISTEIN AND HEALTH-RELATED QUALITY OF LIFE IN BREAST CANCER SURVIVORS

by

TRAN PHAM

University of Central Florida, 2021

A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Health Sciences
in the College of Health Profession and Sciences
and in the Burnett Honors College
at the University of Central Florida
Orlando, FL

Spring Term

2021

Thesis Chair: Eunkyung Lee, PhD, MS, RDN

www.manaraa.com

ABSTRACT

According to the American Cancer Society, breast cancer is the most commonly diagnosed cancer and is the second leading cause of cancer death in American women. Breast cancer screenings and improvement in treatments have resulted in the rising number of survivors in the recent decade. This urged the need for post-diagnosis lifestyle changes to improve breast cancer patients' quality of life. Many studies found soy food, the primary dietary source of phytoestrogens, has a protective effect against breast cancer recurrence and mortality. Dietary phytoestrogens can be classified into two groups: isoflavones and lignans. Daidzein and genistein were identified as the most common isoflavones. Due to their structural similarities to 17- beta estradiol, isoflavones exert agonistic and antagonistic effects. However, limited studies have evaluated the effect of phytoestrogen on health-related quality of life (HRQOL) among cancer survivors. This thesis examined the association between genistein levels and HRQOL and whether these associations are altered by menopausal status using data collected by a research team in South Korea. Women aged 21 to 81 years old, diagnosed with stage I – III primary breast cancer, and received breast cancer surgery at least six months prior were enrolled from five hospitals. Plasma genistein level was measured by orbitrap liquid chromatography-mass spectrometry at the University of Hawaii Cancer Center, Honolulu, Hawaii, U.S.A. HRQOL was self-reported using a validated Korean version of the SF-36 questionnaire. SF-36 has eight domain scores. The scores are summarized into physical (PCS) and mental (MCS) component summary scores, with a higher score indicating better HRQOL. The association between plasma genistein and HRQOL was assessed using a multiple linear regression model adjusting for potential confounders. Stratified analysis was conducted to examine whether menopause status

www.manaraa.com

modified this association. 407 women (mean age: 52.1 ± 8.3) with all available data were included in the analysis. The mean blood genistein concentration was 144.7 nM (range: 1.1-2073.0 nM), and the PCS and MCS scores were 49.5 ± 7.1 and 49.2 ± 9.8, respectively. Analysis for the entire sample showed no significant associations between genistein level and HRQOL score across all domains. Further subgroup analysis by menopausal status revealed that only pre-menopausal women in the highest tertile level of genistein had a higher social function domain score (48.9 vs. 47.2) than those in the lowest tertile with a borderline statistical significance ($p = 0.083$). These findings suggest beneficial effects of genistein may depend on women's menopausal status, but further investigation is necessary.

www.manaraa.com

TABLE OF CONTENTS

www.manaraa.com

INTRODUCTION

Breast cancer is the most diagnosed cancer and is the leading cause of cancer death in women worldwide (Bray et al., 2018). Breast cancer screening before any symptoms and improved treatments have resulted in a better cancer prognosis and contributed to the rising 5-year survival rate of breast cancer. The prolonged survival rate has urged the need for post-diagnosis lifestyle changes to improve breast cancer patients' health-related quality of life (HRQOL). Assessing HRQOL will help better understand the burden of physical and mental problems in breast cancer survivors. Clinicians recognized HRQOL as a powerful tool to measure the implications of treatments and disease burdens. Better breast cancer prognosis and HRQOL have been attributed to lifestyle factors such as healthier dietary habits (Song, Hwang, Moon, Noh, & Lee, 2015).

In breast cancer, estrogen is known to stimulate tumor growth, activate telomerase activity, and promote proliferation and metastasis (Mouridsen, Rose, Brodie, & Smith, 2003). Phytoestrogen has a similar chemical structure to estrogen and exhibits high binding affinity to estrogen receptors on breast cancer cells (Adlercreutz & Mazur, 1997; Dixon, 2004). The majority of dietary phytoestrogens can be classified into two groups: isoflavones and lignans (Valentín-Blasini et al., 2005). Isoflavones can be found in soybeans, while dietary sources of lignans are primarily clover, alfalfa sprouts, and flaxseeds (Kurzer & Xu, 1997) (Valentín-Blasini et al., 2005). Additionally, daidzein and genistein have been identified as the most common isoflavone metabolites and their structures closely resemble 17-β estradiol; due to structural similarities, daidzein and genistein exert agonistic and antagonistic effects against estrogen, depending on the levels of endogenous estrogen and estrogen receptors (Kuiper et al.,

www.manaraa.com

1998; Marzocchella et al., 2011; Yu, Bi, Yu, & Chen, 2016). Many epidemiologic studies correlated isoflavone intake with a lower breast cancer risk (Chen et al., 2014; Song et al., 2015).

The literature shows a significant relationship between dietary patterns with better HRQOL (Kim et al., 2018; Koh et al., 2019; Song et al., 2015). Limited studies have analyzed the relationship between plasma level of phytoestrogen and health outcomes in breast cancer survivors (Nikander et al., 2003). The current cross-sectional study aims to examine the association between plasma levels of phytoestrogen and HRQOL among breast cancer survivors and whether these associations are altered by menopausal status.

www.manaraa.com

LITERATURE REVIEW

Breast Cancer Statistics

Breast cancer is the most commonly diagnosed cancer and is the leading cause of cancer death in women worldwide (Bray et al., 2018). According to the American Cancer Society, breast cancer is the second leading cause of death in US women, and about 1 in 38 women will die from breast cancer (American Cancer Society, 2020). The 5-year survival rate for breast cancer diagnosed from 2009 to 2015 is 90%. The 5-year relative survival rates for localized breast cancer is about 99%, regional is about 86%, and distant is about 27% (Siegel, Miller, & Jemal, 2020). In Korea, the 5-year survival rate for breast cancer diagnosed from 2008 to 2012 is 91.3% (Jung et al., 2015). The high relative 5-year survival rate for early-stage breast cancer can be attributed to earlier detection and improved treatments.

The breast cancer incidence rate has been increasing in high-income countries; the incidence rate is higher in North America and is relatively lower in Asia (DeSantis et al., 2015) (Morey et al., 2019). In a study analyzing trends and patterns of breast cancer among Asian population found that Korean women living in the US had double the incidence rate as those living in Korea. They also found that Chinese women living in Singapore had five times higher incidence rate than those residing in rural China (Youlden, Cramb, Yip, & Baade, 2014).

Importance of Health-Related Quality of Life Among Breast Cancer Survivors

In the past decade, improvements in breast cancer survival rates urged the need to emphasize post-diagnosis lifestyle changes, diet, and HRQOL. Health professionals recognize HRQOL as a powerful instrument to measure the impact of chronic diseases and help clinicians

www.manaraa.com

determine the impact of their interventions on patients (Guyatt, Feeny, & Patrick, 1993). HRQOL instruments can either be self-administered, administered electronically, or conducted by trained interviewers. HRQOL instruments are made up of items or questions grouped into domains; domains may include measurements of physical and emotional functioning (Guyatt et al., 1993).

The SF-36 is a short-form health survey with 36 questions used to assess the HRQOL. It has an eight-scale profile of score as well as a physical and mental component. The eight-scale profile scores were selected from the 40 concepts of the Medical Outcomes Study (MOS) and the chosen items represent concepts most affected by disease and treatment (Ware, 2000). The standard form of SF-36 was made available in 1990; the standard form eliminated one-fourth of the words in the developmental MOS version of the 36 items and reflected improvements in wording, formatting, and scoring (Ware, 2000). Eight-scale profiles of SF-36 include physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The eight-domain scores are calculated using developers' manual. The scores from the eight domains are presented into two summaries, the physical component summary (PCS) and the mental component summary (MCS) score. The PCS score includes physical functioning, role-physical, bodily pain, and general health. The MCS score includes social functioning, role-emotional, vitality, and mental health (Ware, 2000). A higher score in each item indicates better functioning and can be correlated to better HRQOL. The SF-36 health survey has been useful in comparing the relative burden of more than 130 diseases and comparing various treatment plans (Ware, 2000).

www.manaraa.com

Health-Related Quality of Life Scores Among Breast Cancer Survivors

Being diagnosed and living with breast cancer is stressful for many survivors and may negatively affect their quality of life (Cui et al., 2004) (Ganz et al., 1996). It is crucial to understand factors impacting HRQOL to preserve health and well-being. About 24.5% of cancer survivors reported poor physical HRQOL, and 10.1% reported poor mental HRQOL compared with 10.2%, and 5.9% of adults without cancer reported poor physical and mental HRQOL, respectively (Kathryn E. Weaver et al., 2012). In a population-based study comparing patient-reported HRQOL of recently diagnosed breast cancer patients with normative data, participants reported clinically meaningful poorer global health status, social functioning and higher levels of fatigue and anxiety (Høyer et al., 2011). A cross-sectional study using data from the Women's Health Initiative-Observational Study found breast cancer survivors reported worse physical functioning, greater role limitations due to physical health, more pain, less vitality, better social functioning, less sleep disturbance, and more depressive symptoms than women without a history of breast cancer (Paskett et al., 2008). Studying HRQOL is essential to understanding the steps to reducing the breast cancer burden on survivors (K. E. Weaver et al., 2012).

Diet and Health-Related Quality of Life

Studies have demonstrated that the migration of women from a low-risk population to high-risk population causes an increase in breast cancer risk in successive generations, suggesting that changes to Western lifestyle such as dietary patterns may increase the risk of breast cancer (Ziegler et al., 1993). A meta-analysis of 35 studies suggested soy isoflavone's

www.manaraa.com

protective effects against breast cancer risk among pre-and post-menopausal women in Asian countries, including Korea (Chen et al., 2014). Their study reported that in stratified analysis among regions, soy isoflavones had a protective effect against breast cancer risk in women in Asian countries and no statistically significant association was reported in Western countries.

In a 12-week randomized control trial study of the effects of high-dose isoflavone on quality of life (QOL), a significant improvement in QOL was found in women taking isoflavones (Basaria et al., 2009). Several epidemiologic studies found adherence to healthy dietary patterns and guidelines for cancer survivorships was associated with better HRQOL domain scores (Kim et al., 2018; Koh et al., 2019; Song et al., 2015).

Biomechanisms of Phytoestrogen versus Estrogen

Many researchers have proposed phytoestrogen's role in cancer cell differentiation, inhibition of angiogenesis, induction of cancer cell differentiation, inhibition of tyrosine kinase and DNA topoisomerase activities, and antioxidant effects (Kurzer & Xu, 1997). In vivo and in vitro studies have suggested that phytoestrogens may play a significant role in preventing many chronic diseases such as breast cancer, osteoporosis, and other heart diseases (Kurzer & Xu, 1997). Dai et al. analyzed the association between urinary phytoestrogen excretion and breast cancer risk and found that high urinary excretion of phytoestrogen was associated with decreased breast cancer risk (Dai et al., 2003).

Estrogens are hormones that play an essential role in female sexual and reproductive development (Hamilton, Hewitt, Arao, & Korach, 2017). The biological effects of estrogen are mediated through its binding on estrogen receptors on cells. Endogenous estrogens have been

www.manaraa.com

shown to play a role in the pathogenesis of breast cancer and other hormone-dependent diseases (Nelson & Bulun, 2001). Therapeutic interventions of estrogen-dependent disorders typically target the functions of estrogen receptors (Hamilton et al., 2017).

Phytoestrogens are naturally occurring plant-derivatives with molecular weights and structures being very similar to estrogen (Adlercreutz & Mazur, 1997). They exert both weak estrogenic and anti-estrogenic effects due to their similar chemical structure to endogenous estrogen and their high binding affinity to estrogen receptors (Adlercreutz & Mazur, 1997; Dai et al., 2003; Dixon, 2004). Due to these factors, many scientists have postulated that phytoestrogens may have connection to sex hormones and play a role in sex hormone metabolism (Adlercreutz & Mazur, 1997). The majority of dietary phytoestrogens can be classified into two groups: isoflavones and lignans (Valentín-Blasini et al., 2005). Significant dietary sources of isoflavones can be found in soybeans, while lignans are primarily found in clover, alfalfa sprouts, and flaxseeds (Kurzer & Xu, 1997) (Valentín-Blasini et al., 2005).

Daidzein and genistein have been identified as the most common isoflavones and their structures closely resemble 17-β estradiol; due to structural similarities, isoflavones exert agonistic and antagonist effect, depending on the levels of endogenous estrogen and estrogen receptors (Kuiper et al., 1998; Marzocchella et al., 2011; Yu et al., 2016). Many studies also found an increase in soy foods consumption had protective effects against breast cancer risk.

www.manaraa.com

RESEARCH PURPOSE

Objective

This cross-sectional study aims to examine the association between genistein levels and HRQOL and whether these associations are altered by menopausal status using data collected by a research team in South Korea.

Hypothesis

H1: Participants with higher plasma genistein level will have higher HRQOL scores.

H2: A greater association between higher plasma genistein level and higher HRQOL will be observed among postmenopausal women

www.manaraa.com

METHODS

Study Population

Data from this study was obtained from the Seoul National University (SNU) Breast Cancer Study. Female breast cancer survivors were recruited into the study between September 2012 to May 2019 from 9 large hospitals in South Korea. A total of 961 patients between 21-81 years old who have been diagnosed with primary breast cancer were enrolled in the study. Among the study enrollees, participants were excluded if their cancer stage was 0 or IV according to the American Joint Committee on Cancer (AJCC) criteria, had breast cancer surgery within six months of enrollment, if their plasma phytoestrogen was not measured or their SF-36 HRQOL assessment was missing (n = 86). As a result, 407 participants were included in the current analysis. As this study was approved by the Institutional Review Boards at the participating institutions in South Korea, and individual participants have provided written informed consent at enrollment, this thesis is exempt from the additional review at the University of Central Florida.

Collection of Demographic and Clinical Factors

A trained research nurse asked participants about demographic, socioeconomic, and lifestyle factors at enrollment. Demographic questionnaires were used to collect information about age, education level (high school or less/ high school graduate/ college or more), and marital status (married or cohabiting/ unmarried, divorced, or widowed). Participants were asked about the use of supplementation (yes/no), type, dose, and duration of supplement use, smoking status (never/ former/ current), dose and duration of smoking, and frequency of smoking.

www.manaraa.com

Anthropometric data (height and weight) were collected at enrollment to determine body mass index (BMI). Height and weight at the time of diagnosis were used if participants' anthropometric data at enrollment were missing.

Medical records collected relevant clinical information. Time since surgery, other cancers prior to breast cancer diagnosis, date of primary breast cancer diagnosis, AJCC stage at diagnosis, tumor size, date of surgery, menopausal status, menopausal age, height, and weight at diagnosis were gathered from medical records.

Measurement of Plasma Phytoestrogens

Blood samples were collected at enrollment and were transferred to the laboratory within 24 hours. Blood samples were centrifuged and stored at -70° C until measurement. Plasma phytoestrogen levels were measured by orbitrap liquid chromatography-mass spectrometry (LC/MS) at the University of Hawaii Cancer Center, Honolulu, Hawaii, U.S (Li & Franke, 2015). The inter-assay coefficient of variation (CV) value was 14.6%.

Assessment of Health-Related Quality of Life

Participants completed a validated Korean version of the SF-36 health survey version 2.0 to evaluate their HRQOL eight domains. The eight domains included physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The eight domains are presented into two summaries, physical component summary (PCS) and mental component summary (MCS) (Ware, 2000). The PCS score includes physical functioning, role-physical, bodily pain, and general health, while the MCS score includes social

www.manaraa.com

functioning, role-emotional, vitality, and mental health. The higher score of all domains indicates better HRQOL.

Statistical Analysis

Participants' demographic characteristics according to plasma genistein levels were described in Table 1. In Table 2, mean PCS and MCS were analyzed according to participants' demographic characteristics. Plasma phytoestrogen levels were categorized into tertiles for study participants (T1, T2, and T3). The association between HRQOL and plasma phytoestrogen was estimated using the least squares mean (LS mean) and 95% confidence intervals (CIs) from a generalized linear model (GLM). All models have been adjusted for age at diagnosis (years; continuous), BMI (kg/m^2) at diagnosis, smoking status (never; current, or past smoker), marital status (married/cohabitation or unmarried/divorced/widowed), education level (high school or less, high graduated, college or more), breast cancer stage at diagnosis (I, II, III), menopausal status (premenopausal and post-menopausal) at diagnosis, supplement use (yes, no), and time since surgery (6 months – 1 year, 1 - <2 years, 2 - <5 year, or ≥ 5 years). To test for trends, the median value of HRQOL was calculated for each tertile of plasma phytoestrogen level. A stratified analysis was conducted to analyze the association by menopausal status at study enrollment. All analysis of data was done using the SAS statistical software, ver. 9.4. Statistical significance was defined as P-value < 0.05 in a two-sided statistical test.

www.manaraa.com

RESULTS

Demographic Factors

Participants' demographic characteristics according to plasma genistein levels are presented in Table 1. The sample consisted of 407 participants with a mean age at the time of study consent was 52.1 ± 8.3, and the mean body mass index (BMI) was 23.9 ± 3.2 kg/m^2. The average plasma genistein level was144.9 ± 203.6 nM (range: 1.07 to 2073). At the time of study enrollment, 85.5% of the participants were postmenopausal women, 76.4% of women were high school graduate or above, and 68.8% of women had progesterone receptor-positive (PR+) breast cancer. Women aged 50 or older were more likely to have a higher plasma genistein; 53.5% in the age group 60+, 38.6% in the age group 50 - <60, 22.9% in 40 - <50, and 10% were in 20 - <40 were found in T3 ($p < 0.001$). Women with lower education level were more likely to have higher plasma genistein; 44.8 % of the women who have not graduated from high school, 30.7 % of those who have graduated from high school, and 32% of those who have attended some college were found in T3. 42.5% of women with PR- breast cancer and 30.0% of PR+ breast cancer was found in T2 ($p = 0.041$).

Mean Health-Related Quality of Life Summary Scores

Mean PCS and MCS scores were analyzed according to participants' demographic characteristics (Table 2). The mean PCS and MCS scores among all study participants were scores were scores 49.5 ± 7.1 and 49.2 ± 9.8, respectively. Women in age groups 50 - <60 and 60+ years were found to have lower mean PCS score ($p = 0.045$). The mean PCS score was 50.7 for women in age group 20 - <40, 50.8 for age group 40 - <50, 48.8 for age group 50 – <60, and

www.manaraa.com

48.7 for women in age group 60+. Women who reported they were current alcohol consumers had higher mean PCS score. Women who were never alcohol drinkers had a mean PCS score of 49.0, those who were former alcohol drinker have a mean score of 49.2, and current alcohol users have a score of 51.3 ($p = 0.036$). Women who received chemotherapy as treatment reported both lower PCS score ($p = 0.007$) and MCS score ($p = 0.004$). Those who did not receive chemotherapy for their breast cancer treatment had a mean PCS and MCS score of 51.3 and 51.8, respectively. Those who received chemotherapy had a mean PCS and MCS score of 49.0 and 48.4, respectively. Current smokers reported significantly lower MCS score than those who have never smoked or former smokers. The mean MCS score for current smokers was 34.0, 49.7 for those who have never smoked, and 47.5 for former smokers ($p < 0.001$).

Stratified Analysis by Menopausal Status

Table 3 shows the analysis between plasma genistein level and HRQOL in all women. Table 4 and 5 show further subgroup analysis by menopausal status. Results from these tables revealed a positive borderline significant relationship between plasma genistein level and social functioning domain score among pre-menopausal women. Premenopausal women in T3 had an average social functioning domain score of 48.86 while women in T1 had an average score of 47.24 ($p = 0.083$).

www.manaraa.com

DISCUSSION

In this study, we analyzed the association between plasma genistein and HRQOL in Korean breast cancer survivors. The majority of study participants were premenopausal women and graduated high school. Women above 50 years old or those who did not graduate from higher school had higher level of plasma genistein. The average plasma genistein level was 144.9 ± 203.6 nM (range: 1.07 to 2073). A study comparing plasma and urinary phytoestrogens in healthy Japanese and Finnish women observed higher level of phytoestrogen in Japanese women and the mean genistein level in healthy Japanese women was 406.8 nM (Uehar, Arai, Watanabe, & Adlercreutz, 2000). Another study found Japanese men and women had higher concentration of circulating phytoestrogen than individuals in the UK (Morton, Arisaka, Miyake, Morgan, & Evans, 2002). These findings may help explain what factors may contribute to a lower breast cancer incidence rate in Asian population than those in Western populations. One significant factor may be dietary patterns and behaviors.

We found that women aged 50 and above reported lower PCS scores. This may be due to a decrease of physical well-being that comes with old age. In general, older women with breast cancer tend to be impacted more by the physical changes (Høyer et al., 2011). Women who are current smokers at the time of the study reported lower MCS score than former smokers or those who have never smoked. Similar to our study, several studies examining HRQOL among breast cancer survivors and women without breast cancer found statistically significant lower mental health current smokers than in nonsmokers (Avis et al., 2020; Han, Robinson, Jensen, Smith, & Yabroff, 2021). This finding highlights the importance of modifiable health behaviors in understanding HRQOL in breast cancer survivors.

www.manaraa.com

Our analysis showed no significant relationship between plasma genistein level and HRQOL. However, we were able to find a positive borderline significant relationship between social functioning domain and plasma genistein level was found in premenopausal women. Younger women tend to have more severe anxiety and depression symptoms (Høyer et al., 2011). This could partly be due to some younger patients are unable to cope with the diagnosis of cancer in their early life and this may impact their mental health. We originally hypothesized that postmenopausal women with higher plasma genistein would have better HRQOL because of a decreased estrogen production by ovaries and endogenous genistein may act in the body to cope with the fluctuating hormone levels. Since most study participants were post-menopausal women, they may experience impaired HRQOL due to many factors such as old age and menopausal symptoms. Several studies found phytoestrogen supplementation was linked to improved quality of life (QOL) and improvements in menopausal symptoms in women (Basaria et al., 2009; D'Anna et al., 2007; Davinelli et al., 2017). A 12-week randomized control trial studying the effects of high-dose isoflavones and QOL found a significant improvement in QOL in women taking isoflavones (Basaria et al., 2009). In another 12-month randomized control study, those who received phytoestrogen genistein had a 56.4% reduction in hot flushes than control group (D'Anna et al., 2007).

In a cross-sectional study among 3,770 Japanese women aged 18 to 20 years old found women consuming the traditional Japanese diet characterized by high intake of rice, miso soup, and soy products and low intake of bread and confectionaries had lower prevalence of functional constipation (Okubo et al., 2007).

www.manaraa.com

Strengths and Limitations

One advantage to our study is the direct measurement of plasma genistein, which is more objective than the use of a food frequency questionnaire and limiting the possibility of a recall bias. In a study looking at dietary intake and plasma concentration and urinary excretion of phytoestrogens found measurements of plasma phytoestrogen levels are useful biomarkers of isoflavone intakes (Arai et al., 2000). A Plasma genistein measurement is more representative of the bioavailability, absorption, and metabolism of phytoestrogen in the body and reflect the dietary intake of soy foods.

This study has a number of limitations. While plasma genistein may be a more objective measure it could only reflect the short-term soy intake. Circulating endogenous estrogen levels could affect the body's genistein function, but the level of endogenous estrogen was not measured. Since we only included one type of phytoestrogen in our analysis, we cannot determine how other types of phytoestrogen may affect plasma genistein level. Due to the nature of the cross-sectional study design, we were unable to establish a causal relationship between plasma genistein and HRQOL score. While SF-36 is a non-disease-specific and versatile questionnaire to measure HRQOL, it may not reflect specific symptoms impairing quality of life in women with breast cancer. Other breast cancer or menopausal specific questionnaires may be more appropriate in measuring HRQOL. Lastly, other comorbidities were not recorded at study enrollment and may have affected the analysis.

www.manaraa.com

CONCLUSIONS

The objective of this cross-sectional study was to examine the association between plasma genistein and HRQOL among breast cancer survivors. The results of this study showed that plasma genistein score has a positive borderline significant relationship with social-functioning domain score. The implication of this study is to urge future research to analyze the association between plasma levels of all phytoestrogens in combination with endogenous estrogen and HRQOL. Exploring factors that may improve HRQOL may help health professionals choose interventions that will lead to better patient overall outcome.

www.manaraa.com

APPENDIX A: FIGURES

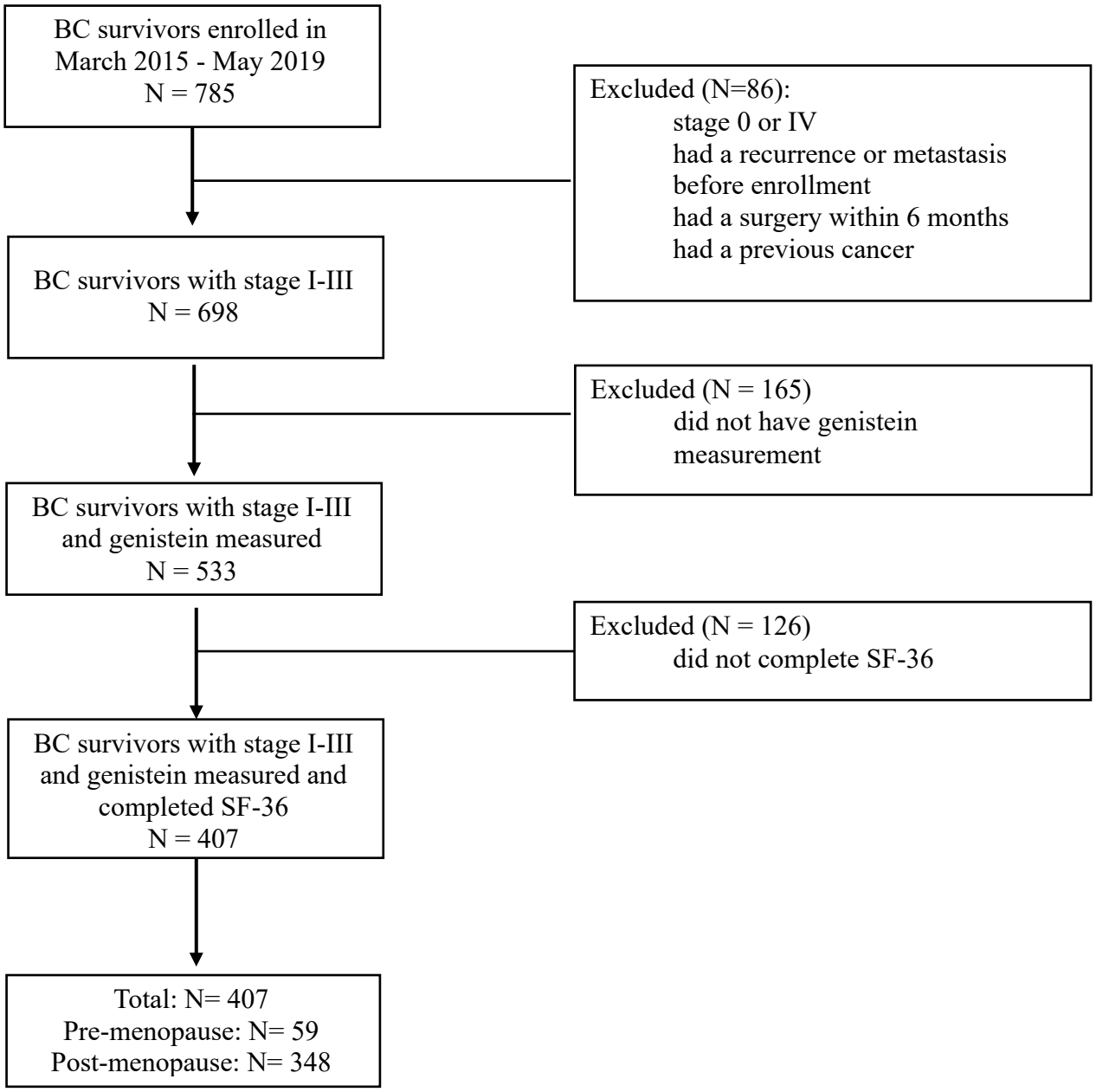

Figure 1 Flow diagram of cohort selection.

www.manaraa.com

APPENDIX B: TABLES

Table 1: Characteristics of study participants according to tertile of plasma genistein

		Total		T1		T2		T3		p-value
Variables	Categories	N	%	N	%	N	%	N	%	
Study Population		407	100	129	31.7	138	33.9	140	34.4	
Age at consent (years)	20 - <40	20	4.9	14	70.0	4	20.0	2	10.0	< .0001
	40 - <50	140	34.4	56	40.0	52	37.1	32	22.9	
	50 - <60	176	43.2	46	26.1	62	35.2	68	38.6	
	60+	71	17.4	13	18.3	20	28.2	38	53.5	
Body mass index (kg/m2)	< 18.5	8	2	4	50.0	3	37.5	1	12.5	0.328
	18.5 - < 23	168	41.3	54	32.1	50	29.8	64	38.1	
	23 - < 25	90	22.1	25	27.8	35	38.9	30	33.3	
	25 - < 30	123	30.2	39	31.7	41	33.3	43	35.0	
	30+	18	4.4	7	38.9	9	50.0	2	11.1	
Menopausal status at diagnosis	Premenopausal	269	66.1	93	34.6	90	33.5	86	32.0	0.176
	Postmenopausal	138	33.9	36	26.1	48	34.8	54	39.1	
Current menopausal status	Premenopausal	59	14.5	26	44.1	19	32.2	14	23.7	0.059
	Postmenopausal	348	85.5	103	29.6	119	34.2	126	36.2	
Education	Less than high school	96	23.6	19	19.8	34	35.4	43	44.8	0.038
	High school graduate	189	46.4	65	34.4	66	34.9	58	30.7	
	Some college or more	122	30	45	36.9	38	31.1	39	32.0	
Marital status	Married or cohabitation	323	79.4	103	31.9	108	33.4	112	34.7	0.601
	Single	17	4.2	8	47.1	5	29.4	4	23.5	
	Divorce or widow	67	16.5	18	26.9	25	37.3	24	35.8	
Smoking	Never	373	91.6	114	30.6	132	35.4	127	34.0	0.261
	Former	24	5.9	10	41.7	5	20.8	9	37.5	

المنارة للاستشارات
www.manaraa.com

	Current	10	2.5	5	50.0	1	10.0	4	40.0	
Alcohol	Never	167	41	42	25.1	64	38.3	61	36.5	0.137
	Former	156	38.3	54	34.6	47	30.1	55	35.3	
	Current	84	20.6	33	39.3	27	32.1	24	28.6	
Dietary supplement use	No	134	32.9	45	33.6	48	35.8	41	30.6	0.528
	Yes	273	67.1	84	30.8	90	33.0	99	36.3	
Family history of breast cancer	No	346	85	108	31.2	119	34.4	119	34.4	0.848
	Yes	61	15	21	34.4	19	31.1	21	34.4	
Cancer Stage	I	204	50.1	56	27.5	65	31.9	83	40.7	0.105
	II	161	39.6	57	35.4	58	36.0	46	28.6	
	III	42	10.3	16	38.1	15	35.7	11	26.2	
Time since surgery (year)	1 - < 2y	170	41.8	59	34.7	53	31.2	58	34.1	0.804
	2 - < 5y	157	38.6	47	29.9	57	36.3	53	33.8	
	5y +	80	19.7	23	28.8	28	35.0	29	36.3	
ER status	No	92	22.6	25	27.2	40	43.5	27	29.3	0.880
	Yes	315	77.4	104	33.0	98	31.1	113	35.9	
PR status	No	127	31.2	33	26.0	54	42.5	40	31.5	0.041
	Yes	280	68.8	96	34.3	84	30.0	100	35.7	
Radiation therapy	No	146	35.9	51	34.9	53	36.3	42	28.8	0.198
	Yes	261	64.1	78	29.9	85	32.6	98	37.5	
Chemotherapy	No	95	23.3	29	30.5	27	28.4	39	41.1	0.253
	Yes	312	76.7	100	32.1	111	35.6	101	32.4	
Endocrine Therapy	No	92	22.6	28	30.4	37	40.2	27	29.3	0.311
	Yes	315	77.4	101	32.1	101	32.1	113	35.9	
HER2 therapy	No	342	84	107	31.3	116	33.9	119	34.8	0.900
	Yes	65	16	22	33.8	22	33.8	21	32.3	
Anti-hormone use	Never	86	21.1	26	30.2	36	41.9	24	27.9	0.179
	Ever	321	78.9	103	32.1	102	31.8	116	36.1	

Abbreviation: T, tertile

www.manaraa.com

Table 2: Characteristics of study participants according to summary component scores

Variable		PCS				MCS			
		N	Mean	Std	p-value	N	Mean	Std	p-value
	Study Population	407	49.5	7.1		407	49.2	9.8	
Genistein	T1	129	49.9	6.8	0.684	129	49.1	9.6	0.973
	T2	138	49.7	7.6		138	49.4	9.8	
	T3	140	49.1	7		140	49.1	10.2	
Age at consent	20 - <40	20	50.7	6.7	0.045	20	47.1	11.2	0.722
	40 -<50	140	50.8	6.7		140	49.5	8.5	
	50 - <60	176	48.8	7.1		176	49.4	10.4	
	60+	71	48.7	7.8		71	48.7	10.6	
Body mass index (kg/m	<18.5	8	49.7	7.6	0.069	8	45.6	12.6	0.698
	18.5 - <23 normal	168	50.2	6.6		168	49.3	10.1	
	23 - <25 normal	90	50.5	7.3		90	49.5	8.8	
	25 - <30	123	48.1	7.6		123	49.4	9.4	
	30+ obesity	18	48.2	6.9		18	46.9	14.1	
Current menopausal status	Premenopausal	59	51.4	6.2	0.034	59	51.2	8.1	0.099
	Postmenopausal	348	49.2	7.2		348	48.9	10.1	
Menopausal status at diagnosis	Premenopausal	269	50.1	6.8	0.028	269	49.1	9.9	0.831
	Postmenopausal	138	48.5	7.7		138	49.4	9.8	
Education	Less than high	96	48	7.7	0.059	96	47.4	10.9	0.064
	High school	189	50.1	6.6		189	49.2	9.9	
	Some college or	122	49.9	7.3		122	50.6	8.7	
Marital status	Married or	323	49.4	7.2	0.695	323	49.5	9.5	0.429
	Single	17	48.9	6.7		17	49.1	9	
	Divorce or widow	67	50.2	6.7		67	47.8	11.7	
Smoking	Never	373	49.6	7.1	0.445	373	49.7	9.5	< .001
	Former	24	49.5	7.2		24	47.5	9.3	
	Current	10	46.7	8.7		10	34	12.7	

المنارة للاستشارات
www.manaraa.com

Alcohol	Never	167	49	7	0.036	167	49.6	9	0.674
	Former	156	49.2	7.5		156	49.1	10.4	
	Current	84	51.3	6.4		84	48.5	10.5	
Dietary supplement use	No	134	49.4	6.6	0.798	134	48.9	10.4	0.695
	Yes	273	49.6	7.4		273	49.3	9.6	
Family history of breast cancer	No	346	49.8	7.1	0.057	346	49.3	9.9	0.846
	Yes	61	47.9	7.2		61	49	9.5	
Cancer stage	I	204	49.8	6.6	0.136	204	49.6	9.3	0.339
	II	161	49.8	7.7		161	49.3	10.4	
	III	42	47.5	7.3		42	47.1	10.2	
Time since surgery (year)	1 -<2y	170	48.7	7.1	0.121	170	49.4	9.7	0.375
	2 - <5y	157	50.3	6.9		157	48.4	9.9	
	5y+	80	49.9	7.4		80	50.3	10	
Radiation therapy	No	146	49	7.3	0.251	146	49.5	9.2	0.663
	Yes	261	49.8	7		261	49.1	10.2	
Chemotherapy	No	95	51.3	6.1	0.007	95	51.8	7.9	0.004
	Yes	312	49	7.3		312	48.4	10.2	
Endocrine therapy	No	92	49.4	7.1	0.828	92	49.5	9.6	0.758
	Yes	315	49.6	7.2		315	49.1	9.9	
HER2 therapy	No	342	49.7	7.1	0.208	342	49.5	9.9	0.203
	Yes	65	48.5	7.5		65	47.8	9.7	
Anti-hormone use	Never	86	49.8	7	0.687	86	49.4	9.8	0.841
	Ever	321	49.5	7.2		321	49.2	9.9	

Abbreviation: PCS, physical component summary; MCS, mental component summary; Std, standard deviation

www.manaraa.com

Table 3: Health-related quality of life scores according to plasma genistein levels in all study participants

	T1	T2	T3	p-value
Physical component summary	47.61 [45.37, 49.85]	47.71 [45.37, 50.05]	47.54 [45.21, 49.87]	0.361
Physical functioning	45.89 [43.46, 48.31]	45.26 [42.73, 47.79]	45.14 [42.62, 47.66]	0.654
Role physical	46.18 [43.34, 49.01]	46.10 [43.13, 49.06]	45.51 [42.56, 48.46]	0.227
Bodily pain	48.30 [45.47, 51.14]	48.59 [45.62, 51.56]	48.56 [45.60, 51.52]	0.966
General health	45.07 [42.27, 47.88]	45.42 [42.49, 48.36]	46.16 [43.24, 49.08]	0.960
Mental component score	44.28 [41.21, 47.36]	43.97 [40.76, 47.19]	44.21 [41.01, 47.42]	0.856
Vitality	46.11 [42.76, 49.47]	46.06 [42.55, 49.57]	45.43 [41.94, 48.93]	0.549
Social functioning	47.07 [44.59, 49.55]	47.49 [44.90, 50.09]	48.07 [45.48, 50.65]	0.198
Role-emotional	44.86 [41.56, 48.16]	44.30 [40.85, 47.76]	43.87 [40.43, 47.31]	0.907
Mental health	42.92 [39.69, 46.15]	42.33 [38.95, 45.71]	42.98 [39.62, 46.35]	0.716

Abbreviation: T, tertile

www.manaraa.com

Table 4: Health-related quality of life scores according to plasma genistein levels in premenopausal women

	T1	T2	T3	p-value
Physical component summary	48.16 [45.70, 50.62]	47.92 [45.27, 50.57]	48.71 [46.11, 51.32]	0.926
Physical functioning	46.73 [43.94, 49.52]	45.87 [42.87, 48.88]	46.35 [43.40, 49.30]	0.647
Role physical	45.92 [42.71, 49.12]	44.98 [41.52, 48.44]	45.73 [42.34, 49.13]	0.312
Bodily pain	48.34 [45.23, 51.46]	47.69 [44.32, 51.05]	49.02 [45.72, 52.33]	0.644
General health	47.44 [44.40, 50.47]	48.52 [45.25, 51.79]	49.46 [46.25, 52.67]	0.298
Mental component score	45.10 [41.46, 48.73]	44.26 [40.34, 48.18]	45.48 [41.63, 49.33]	0.504
Vitality	47.00 [43.16, 50.83]	45.49 [41.35, 49.63]	47.44 [43.38, 51.50]	0.763
Social functioning	47.24 [44.39, 50.09]	47.92 [44.85, 50.99]	48.86 [45.84, 51.87]	0.083
Role-emotional	44.56 [40.75, 48.37]	43.23 [39.11, 47.34]	43.72 [39.68, 47.75]	0.998
Mental health	44.79 [41.08, 48.51]	43.91 [39.90, 47.92]	45.16 [41.22, 49.09]	0.494

Abbreviation: T, tertile

www.manaraa.com

Table 5: Health-related quality of life scores according to plasma genistein levels in post-menopausal women

	T1	T2	T3	p-value
Physical component summary	45.76 [41.01, 50.51]	47.05 [42.50, 51.60]	45.20 [40.67, 49.73]	0.220
Physical functioning	42.69 [37.74, 47.64]	43.19 [38.45, 47.93]	41.99 [37.27, 46.72]	0.992
Role physical	45.33 [39.73, 50.93]	47.65 [42.29, 53.01]	45.29 [39.95, 50.64]	0.484
Bodily pain	45.71 [39.76, 51.67]	48.48 [42.77, 54.18]	46.18 [40.50, 51.86]	0.592
General health	40.69 [34.63, 46.75]	39.79 [33.99, 45.59]	39.49 [33.71, 45.27]	0.357
Mental component score	39.60 [34.04, 45.16]	41.04 [35.71, 46.36]	39.83 [34.52, 45.14]	0.470
Vitality	40.16 [33.72, 46.60]	44.72 [38.55, 50.89]	40.49 [34.35, 46.64]	0.127
Social functioning	46.05 [41.10, 51.00]	45.46 [40.71, 50.20]	45.12 [40.40, 49.85]	0.851
Role-emotional	43.33 [36.95, 49.70]	45.22 [39.12, 51.33]	43.70 [37.62, 49.79]	0.813
Mental health	35.69 [29.55, 41.84]	36.43 [30.55, 42.32]	35.91 [30.05, 41.77]	0.708

Abbreviation: T, tertile

www.manaraa.com

REFERENCES

Adlercreutz, H., & Mazur, W. (1997). Phyto-oestrogens and Western diseases. Annals of Medicine, 29(2), 95-120. doi:Doi 10.3109/07853899709113696

American Cancer Society. (2020). How Common Is Breast Cancer?: Breast Cancer Statistics. Retrieved from https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html

Arai, Y., Uehara, M., Sato, Y., Kimira, M., Eboshida, A., Adlercreutz, H., & Watanabe, S. (2000). Comparison of Isoflavones Among Dietary Intake, Plasma Concentration and Urinary Excretion for Accurate Estimation of Phytoestrogen Intake. Journal of Epidemiology, 10(2), 127-135. doi:10.2188/jea.10.127

Avis, N. E., Levine, B., Goyal, N., Crawford, S. L., Hess, R., Colvin, A., . . . Greendale, G. A. (2020). Health-related quality of life among breast cancer survivors and noncancer controls over 10 years: Pink SWAN. Cancer, 126(10), 2296-2304. doi:https://doi.org/10.1002/cncr.32757

Basaria, S., Wisniewski, A., Dupree, K., Bruno, T., Song, M. Y., Yao, F., . . . Dobs, A. S. (2009). Effect of high-dose isoflavones on cognition, quality of life, androgens, and lipoprotein in post-menopausal women. J Endocrinol Invest, 32(2), 150-155. doi:10.1007/BF03345705

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

المنارة للاستشارات

www.manaraa.com

Chen, M., Rao, Y., Zheng, Y., Wei, S., Li, Y., Guo, T., & Yin, P. (2014). Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: a meta-analysis of epidemiological studies. PLoS One, 9(2), e89288. doi:10.1371/journal.pone.0089288

Cui, Y., Shu, X.-O., Gao, Y., Cai, H., Wen, W., Ruan, Z.-X., . . . Zheng, W. (2004). The Long-Term Impact of Medical and Socio-Demographic Factors on the Quality of Life of Breast Cancer Survivors Among Chinese Women. Breast Cancer Research and Treatment, 87(2), 135-147. doi:10.1023/B:BREA.0000041620.76871.97

D'Anna, R., Cannata, M. L., Atteritano, M., Cancellieri, F., Corrado, F., Baviera, G., . . . Squadrito, F. (2007). Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause, 14(4), 648-655. doi:10.1097/01.gme.0000248708.60698.98

Dai, Q., Franke, A. A., Yu, H., Shu, X. O., Jin, F., Hebert, J. R., . . . Zheng, W. (2003). Urinary phytoestrogen excretion and breast cancer risk: evaluating potential effect modifiers endogenous estrogens and anthropometrics. Cancer Epidemiol Biomarkers Prev, 12(6), 497-502. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12814993 https://cebp.aacrjournals.org/content/cebp/12/6/497.full.pdf

Davinelli, S., Scapagnini, G., Marzatico, F., Nobile, V., Ferrara, N., & Corbi, G. (2017). Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. Maturitas, 96, 77-83. doi:10.1016/j.maturitas.2016.11.016

www.manaraa.com

DeSantis, C. E., Bray, F., Ferlay, J., Lortet-Tieulent, J., Anderson, B. O., & Jemal, A. (2015). International Variation in Female Breast Cancer Incidence and Mortality Rates. Cancer Epidemiol Biomarkers Prev, 24(10), 1495-1506. doi:10.1158/1055-9965.EPI-15-0535

Dixon, R. A. (2004). PHYTOESTROGENS. Annual Review of Plant Biology, 55(1), 225-261. doi:10.1146/annurev.arplant.55.031903.141729

Ganz, P. A., Coscarelli, A., Fred, C., Kahn, B., Polinsky, M. L., & Petersen, L. (1996). Breast cancer survivors: psychosocial concerns and quality of life. Breast Cancer Res Treat, 38(2), 183-199. doi:10.1007/BF01806673

Guyatt, G. H., Feeny, D. H., & Patrick, D. L. (1993). Measuring Health-Related Quality of Life. Annals of Internal Medicine, 118(8), 622-629. doi:10.7326/0003-4819-118-8-199304150-00009

Hamilton, K. J., Hewitt, S. C., Arao, Y., & Korach, K. S. (2017). Estrogen Hormone Biology. Curr Top Dev Biol, 125, 109-146. doi:10.1016/bs.ctdb.2016.12.005

Han, X., Robinson, L. A., Jensen, R. E., Smith, T. G., & Yabroff, K. R. (2021). Factors Associated With Health-Related Quality of Life Among Cancer Survivors in the United States. JNCI cancer spectrum, 5(1), pkaa123-pkaa123. doi:10.1093/jncics/pkaa123

Høyer, M., Johansson, B., Nordin, K., Bergkvist, L., Ahlgren, J., Lidin-Lindqvist, A., . . . Lampic, C. (2011). Health-related quality of life among women with breast cancer – a population-based study. Acta Oncologica, 50(7), 1015-1026. doi:10.3109/0284186X.2011.577446

www.manaraa.com

Jung, K. W., Won, Y. J., Kong, H. J., Oh, C. M., Cho, H., Lee, D. H., & Lee, K. H. (2015). Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat, 47(2), 127-141. doi:10.4143/crt.2015.060

Kim, N. H., Song, S., Jung, S. Y., Lee, E., Kim, Z., Moon, H. G., . . . Lee, J. E. (2018). Dietary pattern and health-related quality of life among breast cancer survivors. BMC Womens Health, 18(1), 65. doi:10.1186/s12905-018-0555-7

Koh, D., Song, S., Moon, S. E., Jung, S. Y., Lee, E. S., Kim, Z., . . . Lee, J. E. (2019). Adherence to the American Cancer Society Guidelines for Cancer Survivors and Health-Related Quality of Life among Breast Cancer Survivors. Nutrients, 11(12). doi:10.3390/nu11122924

Kuiper, G. G., Lemmen, J. G., Carlsson, B., Corton, J. C., Safe, S. H., van der Saag, P. T., . . . Gustafsson, J. A. (1998). Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology, 139(10), 4252-4263. doi:10.1210/endo.139.10.6216

Kurzer, M. S., & Xu, X. (1997). Dietary phytoestrogens. Annu Rev Nutr, 17, 353-381. doi:10.1146/annurev.nutr.17.1.353

Li, X., & Franke, A. A. (2015). Improved profiling of estrogen metabolites by orbitrap LC/MS. Steroids, 99(Pt A), 84-90. doi:10.1016/j.steroids.2014.12.005

Marzocchella, L., Fantini, M., Benvenuto, M., Masuelli, L., Tresoldi, I., Modesti, A., & Bei, R. (2011). Dietary flavonoids: molecular mechanisms of action as anti- inflammatory agents. Recent Pat Inflamm Allergy Drug Discov, 5(3), 200-220. doi:10.2174/187221311797264937

www.manaraa.com

Morey, B. N., Gee, G. C., von Ehrenstein, O. S., Shariff-Marco, S., Canchola, A. J., Yang, J., . . . Gomez, S. L. (2019). Higher Breast Cancer Risk Among Immigrant Asian American Women Than Among US-Born Asian American Women. Prev Chronic Dis, 16, E20. doi:10.5888/pcd16.180221

Morton, M. S., Arisaka, O., Miyake, N., Morgan, L. D., & Evans, B. A. (2002). Phytoestrogen concentrations in serum from Japanese men and women over forty years of age. J Nutr, 132(10), 3168-3171. doi:10.1093/jn/131.10.3168

Mouridsen, H. T., Rose, C., Brodie, A. H., & Smith, I. E. (2003). Challenges in the endocrine management of breast cancer. Breast, 12 Suppl 2, S2-19. doi:10.1016/s0960-9776(03)80158-3

Nelson, L. R., & Bulun, S. E. (2001). Estrogen production and action. Journal of the American Academy of Dermatology, 45(3, Supplement), S116-S124. doi:https://doi.org/10.1067/mjd.2001.117432

Nikander, E., Kilkkinen, A., Metsä-Heikkilä, M., Adlercreutz, H., Pietinen, P., Tiitinen, A., & Ylikorkala, O. (2003). A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstetrics & Gynecology, 101(6), 1213-1220. doi:https://doi.org/10.1016/S0029-7844(03)00232-1

Okubo, H., Sasaki, S., Murakami, K., Kim, M. K., Takahashi, Y., Hosoi, Y., & Itabashi, M. (2007). Dietary patterns associated with functional constipation among Japanese women aged 18 to 20 years: a cross-sectional study. J Nutr Sci Vitaminol (Tokyo), 53(3), 232-238. doi:10.3177/jnsv.53.232

www.manaraa.com

Paskett, E. D., Alfano, C. M., Davidson, M. A., Andersen, B. L., Naughton, M. J., Sherman, A., . . . Hays, J. (2008). Breast cancer survivors' health-related quality of life : racial differences and comparisons with noncancer controls. Cancer, 113(11), 3222-3230. doi:10.1002/cncr.23891

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. CA Cancer J Clin, 70(1), 7-30. doi:10.3322/caac.21590

Song, S., Hwang, E., Moon, H. G., Noh, D. Y., & Lee, J. E. (2015). Adherence to Guidelines for Cancer Survivors and Health-Related Quality of Life among Korean Breast Cancer Survivors. Nutrients, 7(12), 10307-10319. doi:10.3390/nu7125532

Uehar, M., Arai, Y., Watanabe, S., & Adlercreutz, H. (2000). Comparison of plasma and urinary phytoestrogens in Japanese and Finnish women by time-resolved fluoroimmunoassay. Biofactors, 12(1-4), 217-225. doi:10.1002/biof.5520120134

Valentín-Blasini, L., Sadowski, M. A., Walden, D., Caltabiano, L., Needham, L. L., & Barr, D. B. (2005). Urinary phytoestrogen concentrations in the U.S. population (1999–2000). Journal of Exposure Science & Environmental Epidemiology, 15(6), 509-523. doi:10.1038/sj.jea.7500429

Ware, J. E. J. (2000). SF-36 Health Survey Update. Spine, 25(24), 3130-3139. Retrieved from https://journals.lww.com/spinejournal/Fulltext/2000/12150/SF_36_Health_Survey_Update.8.aspx

Weaver, K. E., Forsythe, L. P., Reeve, B. B., Alfano, C. M., Rodriguez, J. L., Sabatino, S. A., . . . Rowland, J. H. (2012). Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey.

www.manaraa.com

Cancer Epidemiol Biomarkers Prev, 21(11), 2108-2117. doi:10.1158/1055-9965.Epi-12-0740

Weaver, K. E., Forsythe, L. P., Reeve, B. B., Alfano, C. M., Rodriguez, J. L., Sabatino, S. A., . . . Rowland, J. H. (2012). Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 21(11), 2108-2117. doi:10.1158/1055-9965.EPI-12-0740

Youlden, D. R., Cramb, S. M., Yip, C. H., & Baade, P. D. (2014). Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer biology & medicine, 11(2), 101-115. doi:10.7497/j.issn.2095-3941.2014.02.005

Yu, J., Bi, X., Yu, B., & Chen, D. (2016). Isoflavones: Anti-Inflammatory Benefit and Possible Caveats. Nutrients, 8(6). doi:10.3390/nu8060361

Ziegler, R. G., Hoover, R. N., Pike, M. C., Hildesheim, A., Nomura, A. M. Y., West, D. W., . . . Hyer, M. B. (1993). Migration Patterns and Breast Cancer Risk in Asian-American Women. JNCI: Journal of the National Cancer Institute, 85(22), 1819-1827. doi:10.1093/jnci/85.22.1819

www.manaraa.com