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Conflict of Interest

The authors declare that they have no competing interests.

Dietary Intake of Polyphenols and the Risk of Breast Cancer: a Case-Control Study

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ABSTRACT

Despite mounting evidence that dietary polyphenols might have a protective role against the risk of breast cancer (BC), few studies have assessed the relationship between intake of polyphenol classes and subclasses with BC. Thus, we examined the relationship between dietary polyphenol classes and individual polyphenol subclasses and the risk of BC. Overall, 134 newly diagnosed BC patients and 267 healthy hospitalized controls were studied. Dietary intake was assessed using a validated 168-item food frequency questionnaire (FFQ). To estimate dietary intake of polyphenols, polyphenol content (flavonoids, lignans, stilbenes and phenolic acids) of 80 food items were derived from an updated version of the phenol explorer database containing information on the effects of food processing on polyphenol content. The dietary polyphenol intake was calculated by matching the subjects' food consumption data with our polyphenol content database. Multivariate logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Controls had higher intake of total polyphenol (marginally significant; $p = 0.07$), hydroxycinnamic acid (marginally significant; $p = 0.05$) and lignan ($p = 0.01$). After adjusting for potential confounders, high consumption of lignans (highest vs. lowest tertile: OR, 0.51; 95% CI, 0.26–0.97; p for trend = 0.04) associated with decreased risk of BC. There was no significant relationship between intake of other polyphenols and risk of BC. Our findings suggest that high lignan intake is associated with a reduced risk of BC.

Keywords: Breast cancer; Polyphenols; Flavonoids; Lignans

INTRODUCTION

Cancer, as the most deadly disease, has become a major threat to human life around the world [1]. Cancer is a hereditary disorder that develops through multistep carcinogenesis with the involvement of different physiological systems in the human body, including cell signaling and apoptosis, therefore making it highly difficult to treat [2]. The evidence has shown that the different types of cancers are caused by a change in the structure and function

of deoxyribonucleic acid (DNA), vascular endothelial growth factor (VEGF), topoisomerase I & II, mitotic spindle microtubules, histone deacetylases, receptor tyrosine kinases, topoisomerases, CYP26A1 enzyme, etc. [3,4]. Breast cancer (BC) is the most common cancer in women and the second most diagnosed cancer after lung cancer in many societies [5,6]. The prevalence of BC in developed countries is higher than in developing countries, which can be related to many factors such as aging, lifestyle changes, migration to urban communities, etc. [7]. The World Health Organization reports that annually 1.7 million cases are diagnosed and 515,000 die from BC worldwide [6]. Although Iran is a country with a low incidence of BC in the world (25 per 100,000) [8], the incidence of this malignancy has increased over the past decade in this country and affects Iranian women about 10 years earlier than Western countries [9]. Epidemiological studies have suggested that dietary factors play a crucial role in BC [10,11], and diets high in fruits and vegetables are associated with a decreased risk of BC [12,13]. Polyphenols are bioactive and antioxidant compounds existing in plant-based food such as fruits, vegetables, whole grains, and beverages such as tea and coffee [14]. Based on their chemical structure, dietary polyphenols can be categorized into 4 major classes, namely, flavonoids, stilbenes, phenolic acids, and lignans [14]. In recent decades, experimental studies have shown potential anti-carcinogenic action of polyphenols including anti-proliferative, inhibition of angiogenesis, and stimulation of apoptosis against BC [15,16]. On the other hand, some studies have shown that polyphenol-rich foods may play a protective role against BC [17]. Nevertheless, results from previous studies are rather inconsistent and controversial. In addition, the majority of studies have investigated the association of some classes of polyphenols, such as flavonoids, and the risk of BC, while other classes of polyphenols including phenolic acids have been less studied and most of them conducted in Western and developed societies [18-20]. There is a lack of published data on the topic of the relationship between dietary polyphenol classes and individual polyphenol subclasses in the Middle-East region, especially Iran as a developing country. Therefore, to further explore the role of polyphenols in BC, we examined the association of dietary polyphenol classes and individual polyphenol subclasses and the risk of BC among Iranian women.

MATERIALS AND METHODS

Participants

This hospital-based case-control study was conducted at the 2 referral hospitals, Tehran (capital of Iran), between September 2015 and February 2016. We recruited 136 women aged ≥ 30 years and newly diagnosed (< 6 months) with histologically confirmed BC. The control group consisted of 272 women of similar age who were admitted to the same hospital for a wide spectrum of non-neoplastic diseases that were unrelated to smoking, alcohol abuse, and long-term diet modification. Controls were matched to cases on age (within 5 years). Data on cases and controls were collected at the same time and interviewed in the same setting using standardized procedures. Less than 8% of subjects approached for the interview refused to participate. Seven participants were excluded from the analysis because their reported energy intakes were outside of the ± 3 standard deviation (SD) from the mean energy intakes of the population ($n = 5$ controls, 2 cases). Finally, 134 cases and 267 controls remained in the final analysis. All protocols and procedures of the current study were approved by the Shahid Beheshti Ethics Committee (IR.SBMU.RETECH.REC.1398.640). Written informed consent was obtained from all patients.

Assessment of dietary intake

Participants' dietary intake during the year prior to diagnosis for cases or interview for controls was assessed in a personal interview using a valid and reliable semi-quantitative 168 food item food frequency questionnaire (FFQ) [21]. Participants were asked to specify their consumption frequency for each food item on a daily, weekly, monthly, or yearly basis. Intakes were then converted to daily frequencies and a manual for household measures was used to convert intake frequencies to daily grams of food intake [22]. The energy and nutrient content of foods was calculated by the U.S. Department of Agriculture (USDA) food composition table. For some traditional Iranian food items that are not included in the USDA database (e.g., traditional bread), the Iranian food composition table was used. Due to Iranian cultural beliefs, alcohol consumption was not asked and, therefore, was unavailable for the analysis.

Polyphenol assessment

To estimate dietary intake of polyphenols, polyphenol content (flavonoids, lignans, stilbenes and phenolic acids) of 80 food items (including fruits, vegetables, bread and grains, legume and soybean, nuts and seeds, oils, tea and coffee) were derived from an updated version of the phenol explorer database (www.phenol-explorer.eu) containing information on the effects of food processing on polyphenol content [23]. This database contains more than 35,000 content values, for 500 different polyphenols, in over 400 foods. The intake of polyphenols was calculated by multiplying the polyphenol content by the daily consumption of each food. The polyphenol subclasses consisted of five group for flavonoids (anthocyanin, flavones, flavonols, flavanols, flavanones) and two group for phenolic acids (hydroxybenzoic acids and hydroxycinnamic acid).

Assessment of other data

For all participants, the required information about socio-demographic, lifestyle, and clinical information including age (years), menopausal status (pre-menopause, post-menopause), education (illiterate, less than a high school diploma, high school diploma, and more), cancer family history (yes, no), breast cancer family history (yes, no), bra-wearing (day [yes, no], night [yes, no]), marital status (single, married, divorced, widowed), smoking (yes, no), supplement intake (including calcium, iron, zinc, selenium, B complex, vitamin C, folic acid, vitamin A, β carotene, vitamin E, vitamin D, multivitamins-minerals, omega-3 fatty acids, and probiotics; yes, no; If yes, the complementary information about dose and frequency), and anti-inflammatory drug use (yes, no) were collected by general questionnaires. Weight was measured to the nearest 0.5 kg using a digital scale (Seca, Hamburg, Germany) with the participant wearing lightweight clothing and no shoes. Height was measured to the nearest 0.5 cm using by tape meter fixed to a wall. Body mass index (BMI) was then calculated by dividing weight (kg) by the square of height (meter). Furthermore, waist circumference (at the level midway between the lowest rib margin and the iliac) and hip circumference (at the widest point over the buttocks) were measured both to the nearest 0.5 cm using a non-stretchable tape-measure. Subsequently, the waist-hip ratio was calculated. Also, physical activity assessed with a valid and reliable questionnaire [24].

Statistical analysis

The Kolmogorov-Smirnoff test was used to evaluate whether or not the distribution of the variables was normal. The mean values of two groups were compared using the Student's t-test and the means of more than two groups were assessed using analysis of variance for normal distribution variables. Also, non-parametric statistics, including the Mann-Whitney

U test or Kruskal-Wallis test were used for variables without normal distribution. Moreover, the χ^2 test was used for comparing categorical variables. Total polyphenols and polyphenols subclasses were categorized into tertiles based on the distribution of the dietary intake of controls. Binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) adjusted for multiple covariates including age, menopausal status, cancer family history, day bra wearing, physical activity (MET-h/day), vitamin D supplement, total energy intake (kcal/day), BMI and total fiber intake (g/day) in different models. Statistical tests were performed using SPSS software (v.21.0; IBM Corp., Armonk, NY, USA). The p values < 0.05 were considered statistically significant.

RESULTS

The distribution of general characteristics of 134 cases and 267 controls are shown in **Table 1**. Compared with controls, cases were older, post-menopause, and were more likely to have cancer family history and bra use across days. Controls were more likely to take vitamin D supplements than cases. Consumption of polyphenols between cases and controls are presented in **Table 2**. According to this table, the median intake of total polyphenol (marginally significant; $p = 0.07$), hydroxycinnamic acid (marginally significant; $p = 0.05$), and lignan ($p = 0.01$) was higher among controls. The ORs and 95% CIs for BC risk and intakes of total polyphenol and subclasses are presented in **Table 3**. After adjusting for potential confounders, only consumption of lignans (highest vs. lowest tertile: OR, 0.51; 95% CI, 0.26–0.97; p for trend = 0.04) was associated with decreased risk of BC. The ORs and 95% CIs between subgroups of flavonoids and phenolic acids and the risk of BC are presented in

Table 1. General characteristics of participants

Variables	Cases (n = 134)	Controls (n = 267)	p value* [‡]
BMI (kg/m ²)	29.5 (7.3)	28.5 (7.7)	NS
Waist circumference (cm) [†]	99.5 ± 14.5	96.4 ± 13.3	NS
Age (yr)	49.5 ± 10.7	47.13 ± 10.1	0.03[‡]
Physical activity (MET-h/day)	32.1 (6.2)	31.47 (6.1)	NS
Daily energy intake(kcal/day)	2,467.8 (890.2)	2,549.6 (1,068.7)	NS
Breast cancer family history (yes)	11 (8.2%)	12 (4.5%)	NS
Night bra wearing (yes)	106 (79.1%)	190 (71.4%)	NS
Day bra-wearing (yes)	122 (91.0%)	217 (81.6%)	0.01
Inflammatory disease history (yes)	15 (10.4%)	35 (13.2%)	NS
Menopausal status			0.04
Pre-menopause	62 (46.3%)	153 (57.3%)	
Post-menopause	72 (53.7%)	114 (42.7%)	
Marital status			NS
Single	9 (6.8%)	16 (6.0%)	
Married	105 (78.9%)	206 (77.4%)	
Divorced	5 (3.8%)	13 (4.9%)	
Widowed	14 (10.5%)	31 (11.7%)	
Educational level			NS
Illiterate	13 (10.0%)	24 (9.0%)	
Less than a high school diploma	55 (42.3%)	134 (50.4%)	
High school diploma and more	62 (47.7%)	108 (40.6%)	
Smoking (present smoker)	4 (3.0%)	9 (3.4%)	NS
Vitamin D supplement (yes)	20 (14.9%)	65 (24.4%)	0.03
Total fiber intake (g/day)	33.5 (18.7)	35.3 (21.9)	0.21

Continuous values are shown as mean ± standard deviation or median (interquartile range). Categorical values are shown as number (%).

NS, non-significant; MET, metabolic equivalent; BMI, body mass index.

*Independent t-test or Mann-Whitney was used for continuous variables; χ^2 test was used for categorical variables. [†]Normal distribution. [‡]Bold p-values are statistically significant.

Table 2. Intake of total polyphenol and subclasses between cases and controls

Polyphenols	Cases (n = 134)	Controls (n = 267)	p value ^{*,†}
Total polyphenol (mg/day)	2,079.31 (976.19)	2,193.83 (1,069.87)	0.07
Total flavonoids (mg/day)	725.22 (561.25)	733.23 (471.13)	0.15
Flavonol (mg/day)	591.57 (544.62)	595.13 (399.05)	0.13
Flavan-3-ol (mg/day)	80.10 (50.10)	83.29 (49.72)	0.17
Flavone (mg/day)	3.29 (3.44)	3.72 (3.35)	0.28
Flavanones (mg/day)	63.34 (28.84)	63.09 (41.93)	0.22
Total phenolic acid (mg/day)	232.22 (155.48)	236.72 (141.56)	0.21
Hydroxybenzoic acid (mg/day)	134.06 (101.94)	133.36 (90.68)	0.41
Hydroxycinnamic acid (mg/day)	86.14 (55.44)	91.70 (61.48)	0.05
Lignan (mg/day)	8.93 (3.98)	9.33 (6.31)	0.01[†]
Stilbenes (mg/day)	0.16 (0.10)	0.11 (0.12)	0.28

Values are shown as median (interquartile range).

NS, non-significant.

*Mann-Whitney test was used. [†]Bold p-values are statistically significant.

Table 3. Association between dietary intake of polyphenols and the risk of breast cancer

Polyphenols	T1	T2	T3	p for trend [†]
Total polyphenols (mg/day)	< 1,814.91	1,814.91–2,474.72	> 2,474.72	
Cases/controls	48/88	44/89	42/90	
Age-adjusted model	Ref. (1.00)	0.86 (0.51–1.44)	0.79 (0.47–1.32)	0.37
Multi-adjusted model*	Ref. (1.00)	0.86 (0.51–1.47)	0.68 (0.39–1.19)	0.18
Flavonoids (mg/day)	< 579.18	579.18–954.94	> 954.94	
Cases/controls	57/101	35/87	42/79	
Age-adjusted model	Ref. (1.00)	0.73 (0.43–1.22)	0.92 (0.55–1.52)	0.68
Multi-adjusted model	Ref. (1.00)	0.82 (0.47–1.41)	1.11 (0.64–1.92)	0.61
Phenolic acids (mg/day)	< 187.76	187.76–284.83	> 284.83	
Cases/controls	53/101	44/85	37/81	
Age-adjusted model	Ref. (1.00)	0.97 (0.59–1.59)	0.85 (0.50–1.43)	0.56
Multi-adjusted model	Ref. (1.00)	1.32 (0.76–2.28)	1.11 (0.61–2.02)	0.72
Lignans (mg/day)	< 7.61	7.61–10.76	> 10.76	
Cases/controls	56/88	50/89	28/90	
Age-adjusted model	Ref. (1.00)	0.82 (0.50–1.34)	0.48 (0.28–0.84)	0.01
Multi-adjusted model	Ref. (1.00)	0.81 (0.48–1.36)	0.51 (0.26–0.97)	0.04[†]
Stilbenes (mg/day)	< 0.12	0.12–0.23	> 0.23	
Cases/controls	36/98	54/80	45/89	
Age-adjusted model	Ref. (1.00)	1.16 (0.66–2.04)	0.43 (0.27–0.83)	0.01
Multi-adjusted model	Ref. (1.00)	0.83 (0.37–1.93)	0.62 (0.26–1.53)	0.31

Logistic regression models were used to obtain the odds ratio of breast cancer risk, with 95% confidence intervals in tertile of dietary total and subclasses of polyphenols intake.

*Additionally adjusted menopausal status, cancer family history, day bra-wearing, physical activity (MET-h/day), vitamin D supplement, total energy intake (kcal/day), body mass index and total fiber intake (g/day). [†]Bold p-values are statistically significant.

Table 4. As shown, there was no significant relationship between intakes of flavonoids and phenolic acids subgroup and risk of BC.

DISCUSSION

In the present study, higher lignan intake was associated with a reduced risk of BC. There was no significant association between flavonoids and phenolic acids subclasses including flavones, flavanols, flavonols, flavanones, anthocyanins, hydroxybenzoic acids and hydroxycinnamic acids with the risk of BC. In consistent with our results, an inverse association of lignans with BC risk has previously been reported [25–27]. However, no inverse relationship has been reported in some other studies [28–30]. The results of a meta-analysis showed that there was no association between plant lignan intake and overall

Table 4. The OR (95%CI) of dietary intake of flavonoid and phenolic acid subclasses for breast cancer

Flavonoid and phenolic acid subclasses	T1	T2	T3	p for trend
Flavones (mg/day)	< 2.78	2.78–4.84	> 4.84	
Cases/controls	50/88	42/88	42/91	
Age-adjusted model	Ref. (1.00)	0.87 (0.52–1.46)	0.85 (0.51–1.42)	0.54
Multi-adjusted model*	Ref. (1.00)	0.91 (0.53–1.57)	0.84 (0.48–1.48)	0.56
Flavonols (mg/day)	< 414.25	414.25–763.43	> 763.43	
Cases/controls	51/88	39/91	44/88	
Age-adjusted model	Ref. (1.00)	0.71 (0.42–1.20)	0.82 (0.49–1.36)	0.43
Multi-adjusted model	Ref. (1.00)	0.65 (0.38–1.13)	0.88 (0.51–1.52)	0.67
Flavanols (mg/day)	< 65.13	65.13–98.67	> 98.67	
Cases/controls	54/88	34/89	46/90	
Age-adjusted model	Ref. (1.00)	0.60 (0.35–1.02)	0.77 (0.46–1.27)	0.29
Multi-adjusted model	Ref. (1.00)	0.70 (0.40–1.21)	1.01 (0.56–1.76)	0.99
Flavanones (mg/day)	< 53.45	53.45–73.29	> 73.29	
Cases/controls	43/87	60/90	31/90	
Age-adjusted model	Ref. (1.00)	1.25 (0.76–2.05)	0.67 (0.38–1.17)	0.19
Multi-adjusted model	Ref. (1.00)	1.33 (0.78–2.27)	0.90 (0.49–1.63)	0.73
Anthocyanins (mg/day)	< 23.61	23.61–42.91	> 42.91	
Cases/controls	37/96	50/85	47/86	
Age-adjusted model	Ref. (1.00)	0.84 (0.47–1.49)	0.47 (0.26–0.85)	0.01
Multi-adjusted model	Ref. (1.00)	0.45 (0.23–1.21)	0.54 (0.21–1.32)	0.14
Hydroxybenzoic acid (mg/day)	< 98.05	98.05–172.51	> 172.51	
Cases/controls	56/90	35/89	43/88	
Age-adjusted model	Ref. (1.00)	0.61 (0.36–1.03)	0.77 (0.46–1.27)	0.28
Multi-adjusted model	Ref. (1.00)	0.76 (0.44–1.31)	0.91 (0.52–1.57)	0.73
Hydroxycinnamic acid (mg/day)	< 72.61	72.61–110.58	> 110.58	
Cases/controls	48/90	52/88	34/89	
Age-adjusted model	Ref. (1.00)	1.09 (0.66–1.79)	0.71 (0.42–1.22)	0.24
Multi-adjusted model	Ref. (1.00)	1.33 (0.77–2.31)	1.02 (0.52–1.97)	0.95

Logistic regression models were used to obtain the OR of breast cancer risk, with 95% CIs in tertile of flavonoids and phenolic acids subclasses.

OR, odds ratio; CI, confidence interval.

*Additionally adjusted for menopausal status, cancer family history, day bra wearing, physical activity (MET-h/day), vitamin D supplement, total energy intake (kcal/day), body mass index and total fiber intake (g/d).

risk of BC. When analysis was stratified by menopausal status, a significant reduction was observed in post-menopausal women [31]. The protective effect of lignan against BC in post-menopausal women suggests that dietary lignan has a protective role only at low estradiol levels [31]. Previous studies, mainly from the Asian population, have shown that high consumption of flavonoids, especially isoflavones, is inversely related to the risk of BC [32,33]. Our findings failed to confirm the result of these studies. It may be due to low consumption of isoflavonoids rich foods in Iran. Except for soya, other sources of isoflavones are rarely consumed in Iran. It should be noted that the mean intake of isoflavones in our study is < 1 mg/day (data not shown). However, some studies have not found an association between isoflavones and breast cancer risk [17,34]. It is possible that the association between isoflavones and BC risk is not established through dietary studies, but only through urine excretion measurements [35]. Most previous studies have focused on some specific classes of polyphenols and flavonoids, while the evaluation of other polyphenol subclasses has been less studied [36–38]. Previous studies have reported different levels of polyphenol and polyphenol subclasses consumption [39,40]. The heterogeneity of individual food composition and different dietary patterns in populations makes it relatively difficult to compare polyphenol consumption in different individuals [41]. The findings of European Prospective Investigation into Cancer and Nutrition (EPIC) Study indicate no associations between flavonoid and lignan intake and BC risk. Results after analysis based on menopausal status also remained insignificant [42]. The results of a meta-analysis

showed an inverse association between flavonols and flavones and the risk of BC. However, no significant association was found for other flavonoid subclasses or total flavonoids [43]. These discrepancies in the reported results may be explained by various reasons. One of the main reasons could be the variety of polyphenols measurement methods and possible measurement errors [14]. Differences in polyphenol content during processing such as canning, storing, freezing, and cooking can be another reason [44]. On the other hand, the amount, type and source of polyphenols might be different in diverse countries. For example, dietary intake of polyphenols may be higher in Asia and countries that adherence the Mediterranean diet [45,46]. Most intrinsic polyphenols are thought to damage BC metastasis through inhibiting of matrix metalloproteinase expression, intervention with the VEGF signaling pathway, modulation of epithelial-mesenchymal transition regulator, inhibition of nuclear factor kappa B, and mammalian target of rapamycin expression, and other associated mechanisms. Consumption of natural polyphenols has been shown to affect endogenous metabolites and complex biological metabolic pathways in the body [16]. On the other hand, women tend to start menopausal hormone therapy (MHT) during menopause, which can continue for several years [47]. MHT involves the use of estrogen alone or in combination with progesterone, which is more commonly used in western countries [48]. Estrogen is recognized as a factor that induces the progression of BC [49]. Studies have also shown that the risk of BC for estrogen and progesterone together was higher than for estrogen alone, especially if progesterone use was daily rather than intermittent [47]. Epidemiological studies have demonstrated that there is a link between soy consumption as an isoflavones-rich food and the menopausal symptoms such as hot flashes [50]. Indeed, isoflavones can mimic the effects of estrogen by binding to estrogen receptors and relieve menopausal symptoms. [51]. Despite the beneficial effects of isoflavones, there is still no consensus on their use instead of MHT [52]. A meta-analysis of 51 randomized controlled trials showed that both MHT and soy isoflavones interventions are effective for the reduction of menopausal hot flashes. However, using indirect comparison, a significant difference between the effects of MHT and soy isoflavones on hot flashes was observed [53]. Due to Iranian cultural beliefs, alcohol consumption was not asked and, therefore, was unavailable for the analysis. But a study found BC risk was reduced in women who did not drink alcohol but consumed polyphenols. Whereas, BC risk was increased in heavy alcohol drinkers [54]. Polyphenols have been shown to inhibit the proliferation and transformation of cancer cells by scavenging free radicals, regulating nitric oxide production, and affecting signal transduction pathways (such as mitogen-activated protein kinase) [55].

Our study has some advantages. We estimated dietary intakes using a FFQ developed for assessing Iranian dietary intake. Validity and reliability of the FFQ was qualified in a previous study [21]. Also, use of new patient cases, using hospital controls and administering FFQs by trained interviewers were other strengths of our study. In contrast, several limitations are also intrinsic in the present study. The diversity of polyphenols compounds is complex and the use of FFQs may lead to measurement errors. Recall bias is a limitation in any dietary research using a questionnaire to quantify dietary intake, because it depends on the individual's memory and there is a possibility of over or under reporting by individuals. Additionally, the selection bias is difficult to avoid in case-control studies. However, these problems were ameliorated by using new patient cases through hospital controls and implementation FFQs by trained interviewers in a hospital setting. Moreover, the present study is a case-control study with a small sample size that unable to investigate the long-term effects of risk factors on the occurrence of BC. A cohort or longitudinal study will be required to evaluate the association between the risk factors such as diet and the risk of chronic diseases.

CONCLUSION

The present study showed that the high intake of lignans was related to the decreased risk of BC. As shown in previous studies, our findings confirm that a polyphenol-rich diet may reduce the risk of breast cancer but to understand the interactions between diet and health, an assessment of the diet with all its complexity of foods would be required. This complexity illustrates the exposure to food bio-actives and their impacts on human health.

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