RESEARCH ARTICLE

Dietary Phytochemical Index and the Risk of Breast Cancer: A Case Control Study in a Population of Iranian Women

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Abstract

In this study we assessed the dietary phytochemical index in relation to the risk of breast cancer in women. This case-control study was conducted on 100 incident breast cancer cases and 175 healthy controls. Data regarding socio-demographic factors, medical history, medications, and anthropometric measurements were collected. Dietary data were obtained using a validated food frequency questionnaire and a energy-adjusted dietary phytochemical index (PI) was calculated. The odds ratios of breast cancer were assessed across energy-adjusted PI quartile categories. The mean age of participants was 46.2±8.9 and 45.9±9.4 years in cases and controls, respectively. The mean PI across quartile categories was 13.9±2.6, 21.1±1.8, 26.7±2.1, 41.6±10.2 in the first, second, third and fourth quartiles, respectively. After adjustment for all potential confounders, the risk of breast cancer in the forth quartile of dietary PI was significantly decreased (OR=0.08, 95%CI=0.01-0.84). Higher intake of phytochemical-rich foods is associated with lower risk of breast cancer.

Keywords: Breast cancer - diet - phytochemical-rich foods - phytochemical index

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Introduction

Results from several sources provide strong evidences that diet is a main modifiable factor related to the risk of breast cancer (Holmes et al., 2004; Michels et al., 2007). Although inconsistencies exist across studies that have investigated the association between plant-based diets and some of the foods including fruit and vegetables, whole grains, legumes and nuts and incidence of breast cancer, however many *in vitro* and experimental studies have shown that phytochemicals in whole plant foods have chemopreventive properties (Smith-Warner et al., 2001; van Gils et al., 2005; Lee et al., 2011; Aune et al., 2012). These bioactive compounds are vary widely in chemical structure and function and are including phenolic compounds, phytoestergenes, organosulfur compounds, plant sterols, soluble and insoluble fibers, and isothiocyanates (Kris-Etherton et al., 2002). Phytochemicals are becoming increasingly important sources of anticancer compounds which can prevent cancer initiation, promotion, and progression by direct antioxidant activity, anti-inflammatory potential and modulation of key cellular signaling pathways (Shu et al., 2010; Tan et al., 2011). Phytochemicals could also act as the potent preventive compounds in development of mammary carcinoma through several mechanisms including ability to inhibit aberrant proliferation in initiated and transformed cells, regulate cell-cycle progression, induce cellular apoptosis, increase the formation of antiproliferative estradiol metabolite, and inhibit cell migration and metastasis (Telang at al., 1997; Katdare at al, 2002; Sun et al., 2008).

Based on the health promotional effects of phytochemicals, McCarty proposed a "phytochemical index" (PI), defined as the percent of dietary calories derived from foods rich in phytochemicals, and suggested that PI could be used as an index of total dietary phytochemical content (McCarty, 2004). This index is a simple method for assessment of phytochemical intake that, despite its limitations, could provide important background for diet quality in relation to chronic diseases (Vincent et al., 2010; Bahadoran et al., 2012; 2013; Mirmiran et al., 2012). In this case-control study we aimed to investigate the association between modified dietary phytochemical index and the risk of breast cancer in a population of Iranian women.

Materials and Methods

Study design and population

This study was conducted on the incident breast cancer cases (100 women) and healthy controls (175

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women) participating in a population-based, case-control study in Tehran. Newly diagnosed cases (identified within 5 month of diagnose), aged 30-65 years, with histologically confirmed breast cancer referred to oncology, radiotherapy, chemotherapy or surgery sectors of Shohada-e-Tajrish hospital between April 2010 and July 2010, were requited. Participants with the history of any cancer or cyst (excluding current breast cancer), history of hormone therapy or special diet were excluded from the study. Age-matched controls without any history of cancers or cyst, hormone therapy or special diet, were also recruited from the individuals referred to other sectors of the hospital. Informed written consents were obtained from all participants and the study protocol was approved by the research council of the Research Institute for Nutrition and Food Sciences, Shahid Beheshti University of Medical Sciences.

Socio-demographic, anthropometrics and physical activity

Data regarding socio-demographic factors including age, educational level, occupation, ethics, life aria, alcohol and tobacco use, medical history of disease, familial history of breast cancer or other cancers, history of hormone therapy, medications and supplements, oral contraceptives, age at menarche, marital status, number of full pregnancies, menopause status and other lifestyle-related factors were collected by trained interviewers. Weight was measured to the nearest 100g using digital scales, while the subjects were minimally clothed, without shoes. Height was measured to the nearest 0.5 cm, in a standing position without shoes, using a tape meter. Body mass index was calculated as weight (kg) divided by square of the height (m^2). Physical activity level was assessed using the validated questionnaire to obtain frequency and time spent on light, moderate, hard and very hard intensity activities according to the list of common activities of daily life over the past year. Physical activity levels were expressed as metabolic equivalent hours per week (METs h/wk).

Dietary assessment and phytochemical index calculation

Dietary data were collected using a validated semi-quantitative food frequency questionnaire (FFQ) with 168 food items. This FFQ was developed for dietary assessment of the participants of the Tehran Lipid and Glucose Study (TLGS); the validity and reliability of the FFQ were previously assessed in a random sample, by comparing the data from two FFQs completed 1 y apart and comparing the data from the FFQs and 12 dietary recalls, respectively (Mirmiran et al., 2010). Trained dietitians asked participants to designate their intake frequency for each food item consumed during the past year on a daily, weekly, or monthly basis. Portion sizes of consumed foods reported in household measures were then converted to grams. Mean daily intakes of energy and nutrient for each individual were calculated using the Food Composition Table.

The dietary phytochemical index was calculated based on the modified method previously developed by McCarty (McCarty, 2004); [PI=(phytochemical-rich foods g/d/ total food intake g/d)×100]. Foods included in the phytochemical-rich category were fruits and vegetables, legumes, whole grains, nuts, soy products, olives and olive oil, and additionally, tea, coffee and spices. Potatoes were not considered as vegetables because they are often consumed as a starch component rather than as vegetables. Natural fruit and vegetable juices as well as tomato sauces were included in the fruit and vegetable groups because these are also considered as rich sources of phytochemicals.

Statistical analysis

Differences in general characteristics between the cases and controls were compared using by the analysis of variance for continuous variables and the chi-square test for categorical variables. Energy-adjusted dietary PI was calculated as [(dietary PI×1000)/energy intake], and was assigned as quartiles based on their 25^{th}-50^{th}-75^{th} percentile values. Means for age, weight, BMI, physical activity, energy intake, energy density of diet, and intakes of phytochemical-rich food groups across quartiles of PI were determined by using the general linear model with adjustment for age, and energy intake.

The odds ratio of breast cancer in each quartile of dietary PI was determined by multivariable logistic regression models with adjustment for potential confounding variables. The following potential confounders were included in the final multivariate logistic regression models: age (y); BMI (kg/m^2); educational level (y); occupation (housekeeper/ employee/ retired); use of alcohol and tobacco (yes/no); age at menarche (y); marital status (not married, married, divorced, widow); age at firs pregnancy (y); number of full pregnancy; menopause status (yes/no); family history of breast cancer (yes/no); use of OCP (yes/no); use of bra (<12h, >12h); life satisfaction (yes/no/partly); physical activity (MET-h/week); energy intake (kcal/d); energy density of diet (kcal/100g foods).

To assess the overall trends of odds ratios across increasing quartiles of PI, the median PI of each quartile was used as a continuous variable in logistic regression models. Statistical analysis was performed using SPSS (Version 16.0; Chicago, IL). A p value<0.05 was used as the statistical evaluation tool.

Results

The mean age of participant was 46.2±8.9 and 45.9±9.4 y in cases and controls, respectively. The mean of age at menarche significantly was lower and the mean of age at first pregnancy was significantly higher in cases as compared with controls (p<0.01). There were no significant differences in BMI, physical activity, energy intakes, menopause status, educational levels, occupation, marital status and family history of breast cancer between two groups. The use of tobacco and OCP were significantly higher, while life satisfaction was significantly lower in women with diagnosed breast cancer as compared with controls (p<0.05).

The mean of dietary phytochemical index was significantly lower in cases compared with controls (58±1 vs. 61±1, p<0.01). Characteristics of the study participants across quartile categories of dietary PI are shown in Table 1. The range of energy-adjusted PI was <17.7, 17.7-24.1, 24.2-30.5 and >30.5, and the mean of PI was 41±0.1, 58±0.1, 66±0.1 and 76±0.1 in the first, second, third and fourth quartiles, respectively. Participants in the upper PI quartile were older and had lower weight and BMI ($p<0.05$). Dietary intakes of energy, energy density and phytochemical-rich food groups across quartiles of PI are provided in Table 2. Energy intakes and dietary energy density significantly decreased across increasing phytochemical index (p for trend<0.001). A significant increasing trend across PI quartiles were observed for dietary intakes of fruits, vegetables, tea and coffee (p for trend<0.001). The odds ratio and 95%CI of breast cancer across quartiles of energy-adjusted dietary phytochemical index are presented in Table 3. In the first model, after adjustment for age, the risk of breast cancer significantly decreased in the forth quartile as compared to first category of dietary PI (OR=0.21, 95%CI=0.05-0.76). In the second model, after adjustment for age at menarche, age at firs pregnancy, number of full pregnancy, smoking, use of OCP and the use of bra, the risk of breast cancer in the forth quartile of dietary PI significantly decreased more than 80 percent (OR=0.18, 95%CI=0.03-0.87). In the third model, after additional adjustment for body mass index and life satisfaction, decreased the risk of breast cancer in the forth quartile of dietary PI remained significant (OR=0.14, 95%CI=0.21-0.91). In the full model, after additional adjustment for menopause status, family history of breast cancer, physical activity, energy intake, and energy density of the diet, in the forth quartile category of dietary phytochemical index, the risk of breast cancer decreased significantly more than 90 percent (OR=0.08, 95%CI=0.01-0.84).

Table 1. Characteristics of Participants Across Quartile Categories of the Dietary Phytochemical Index

	(n, 274)				
	Q1 (n, 68)	Q2 (n, 69)	Q3 (n, 69)	Q4 (n, 68)	P**
Energy-adjusted dietary PI					
Range	<17.7	17.7-24.1	24.2-30.5	>30.5	
Mean	13.9±2.6	21.1±1.8	26.7±2.1	41.6±10.2	0.01
Case/control	30/38	33/36	21/48	16/52	0.008
Age (y)	43.8±9.3	46.3±9.4	46.7±9.2	47.4±8.8	0.05
Physical activity (MET-h/week)	39.1±0.5	39.5±0.5	37.2±0.5	37.8±0.5	0.04
Weight (kg)	76.2±1.5	72.6±1.6	67.1±1.7	73.1±2.2	0.002
Body mass index (kg/m^2)	30.8±0.5	29.9±0.6	27.6±0.6	28.6±0.7	0.002

*Data are mean±SD unless stated otherwise. **Analysis of variance was used to compare continuous variables and the chi-square test for categorical

Table 2. Dietary Intakes* of Participants Across Quartiles of Energy-adjusted Dietary Phytochemical Index

	(n, 274)				
	Q1 (n, 68)	Q2 (n, 68)	Q3 (n, 68)	Q4 (n, 68)	P**
Energy-adjusted dietary PI					
Range	<17.7	17.7-24.1	24.2-30.5	>30.5	
Mean	13.9±2.6	21.1±1.8	26.7±2.1	41.6±10.2	0.01
Energy (kcal/d)	3976±59	2837±59	2326±59	1624±59	0.001
Energy density (kcal/100g of foods)	142±2.8	126±2.8	117±2.8	102±2.8	0.001
Fruits (g/d)	224±55	538±33	723±35	823±49	0.001
Vegetables (g/d)	231±58	499±34	632±51	637±37	0.001
Legumes (g/d)	48.2±8.5	45.6±5.1	43.2±5.4	47.0±7.6	0.91
Whole grains (g/d)	188±17.9	158±10.5	137±11.5	126±15.7	0.18
Nuts (g/d)	6.6±2.9	10.9±1.8	15.8±1.8	17.9±2.6	0.08
Soy products (g/d)	4.8±2.9	10.2±1.8	9.9±1.8	5.7±2.6	0.06
Tea and coffee (cup/d)	0.5±0.6	2.8±0.4	3.7±0.4	5.1±0.5	0.001
Spices (g/d)	0.61±0.15	0.65±0.11	0.89±0.11	0.78±0.13	0.34

*Data are adjusted mean±SEM for all dietary intakes, adjusted for age and energy intake. **linear regression model was used to compare the dietary intakes of participants across quartiles of dietary phytochemical index

Table 3. The Odds Ratio and 95%CI* of Breast Cancer Across Quartiles of Energy-adjusted Dietary Phytochemical Index

	(n, 274)				
	Q1 (n, 68)	Q2 (n, 68)	Q3 (n, 68)	Q4 (n, 68)	P**
Model 1[a]	1	0.57 (0.18-1.82)	0.36 (0.10-1.29)	0.21 (0.05-0.76)	0.09
Model 2[b]	1	0.48 (0.10-2.16)	0.27 (0.05-1.41)	0.18 (0.03-0.87)	0.17
Model 3[c]	1	0.45 (0.07-2.67)	0.19 (0.03-1.38)	0.14 (0.21-0.91)	0.15
Model 4[d]	1	0.51 (0.08-3.04)	0.16 (0.02-1.21)	0.08 (0.01-0.84)	0.11

*Multivariable logistic regression models were used with adjustment of potential confounders. **To assess the overall trends of odds ratios across dietary PI quartiles, the median PI for each quartile was used as a continuous variable in logistic regression models. [a]Adjusted for age (y). [b]Additional adjustment for age at menarche (y), age at firs pregnancy (y), number of full pregnancy, smoking (yes/no), use of oral contraceptive (yes/no) and the use of bra (<12 h/>12h). [c]Additional adjustment for body mass index (kg/m^2) and life satisfaction (yes/no/partly). [d]Additional adjustment for menopause status (yes/no), family history of breast cancer (yes/no), physical activity (MET-hours/week), energy intake (kcal/d), and energy density of the diet (kcal/100 g foods)

Discussion

The results from this case-control study, showed that increased energy intakes from phytochemical-rich foods (more than 30% of energy per each 1000 kcal), independent of confounding variables, may be related to decrease the risk of breast cancer. The mean dietary intakes from phytochemical-rich foods was nearly 3 times in participants in the forth quartile of dietary PI; also women in the highest quartile of dietary PI as compared with lower quartile consumed more than 3.6 times fruits (g/d), 2.7 times vegetables and nuts (g/d), and 10 times tea and coffee (cup/d).

Previously the association of each whole plant phytochemical-rich foods such as whole grains, legumes, fruits and vegetables, soy products, nuts and others with the risk of breast cancer have been investigated; but in this study, for the first time, we tried to explain this association in the new frame as dietary phytochemical index. In this study we performed the modified dietary phytochemical index that previously developed with McCarty (2004). In the modified dietary PI, instead of energy intake from phytochemical-rich foods to total energy intake, the ratio of total phytochemical-rich foods as gram per day to total food intakes (g/d) after adjustment for energy intake (kcal/d) was considered; so we could include the dietary intakes of tea, coffee and spices as the main phytochemical-rich foods in the PI to cover the weakness of previous index. This index could provide more comprehensive picture of the overall dietary intakes of phytochemical-rich foods in relation to the risk of disease (Vincent et al., 2010; Bahadoran at al., 2012; Mirmiran et al., 2012).

Despite the protective effects of whole plant foods against the risk of breast cancer remain unclear (Nicodemus at al., 2001; Egeberg et al., 2009 Masala at al., 2012), in the recent years, there have been growing evidences that phytochemicals and natural bioactive components in plant foods could have preventive effects in the incidence and development of different type of cancers (Loo et al., 2003; Saracino et al., 2007); moreover there is new approach to phytochemicals as standard complementary treatment of cancers (Sak et al., 2012).

The plant foods which are considered in the phytochemical index might have potential to slow or prevent the appearance of any types of the cancer through their bioactive compounds, particularly, soluble and insoluble fibers, lignans, sterols and stanols, carotenoids, chlorophyll, flavonoids, indole, isothiocyanates, phytoestergenes, polyphenolic compounds, protease inhibitors, sulfides, terpens and their bioactive metabolites (Potter et al., 1996; Miller et al., 2012). Based on the previous investigations, higher dietary phytochemical index is accompanied with higher intake of total fiber, total carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein, and xanthine), vitamin E, vitamin C, other antioxidants and phytochemicals (Mirmiran et al., 2012; Vincent et al., 2010). All of these bioactive components have well known properties in the prevention of some types of cancers especially breast cancer. Dietary fiber is one of these protective compounds that ecological data as well as prospective and clinical studies are in agreement about its beneficial effects; recently, results from European Prospective Investigation into Cancer and Nutrition (EPIC) showed that diets rich in dietary fiber and, particularly, fiber from vegetables may be associated with a small reduction in risk of breast cancer (Ferrari et al., 2013). Meta-analysis of the previous evidences from prospective studies also confirms the protective role of dietary fiber against breast cancer (Aune et al., 2012). Based on the results from a recent meta-analysis of prospective studies, dietary carotenoids, especially, β-carotene strongly associated with reduced breast cancer risk (Aune et al., 2012). Intakes of α-carotene, β-carotene, and lutein/zeaxanthin also were inversely associated with the risk of negative estrogen receptor (ER-) breast cancer (Zhang et al., 2012). Based on the results of new meta-analysis of epidemiologic studies, dietary intakes of flavonols, flavones and flavan-3-ols is associated with a decreased risk of breast cancer, especially among post-menopausal women (Hui et al., 2013). Other dietary phytochemicals including soy isoflavones, isothiocyanates, green tea catechins also have preventive effects against incidence of breast cancer (Sartippour et al., 2001; Fowke et al., 2003; Dong et al., 2011).

Anticarcinogenic properties of these phytochemicals are attributed to inhibiting phase I enzymes, induction of phase II enzymes, scavenge DNA reactive agents, suppress the abnormal proliferation of early and pre-neoplastic lesions, and inhibit certain properties of the cancer cell (Waladkhani et al., 1998); other mechanisms involved in the preventive effects of phytochemicals against cancer are regulation of steroid hormone and estrogen metabolism, inhibition of cell adhesion and invasion, induction of tumor suppress gene expression, cell cycle arrest and apoptosis, and modulation of some important signal transduction pathways (Liu et al., 2004).

Although small sample size and case-control setting were considered as weakness of the current study, but use of a validated semi-quantitative FFQ for assessment of dietary intake, using multiple logistic regression models with adjustment of several confounding variables, were the strengths of this study.

In conclusion, we investigated an inverse association between dietary phytochemical index and the risk of breast cancer, independent of potential confounding variables. More intakes from phytochemical-rich foods including whole grains, fruits and vegetables, legumes, nuts, spices, tea and coffee, synergistically, could have preventive properties against breast cancer in women.

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