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ABSTRACT There is growing evidence that dietary antioxidants may have favourable effects in reducing cancer risk. In a case–control study we investigated the association of dietary total antioxidant capacity (TAC) and risk of breast cancer. Sociodemographic data, medical history and anthropometric measurements were collected from 275 women (100 breast cancer cases & 175 controls). Participants' usual dietary intake was measured using a validated semi-quantitative food frequency questionnaire and their dietary TAC was estimated. An inverse, but non-significant, association was observed between dietary TAC and breast cancer risk. Multiple logistic regression models based on TAC of individual food groups showed that consumption of fruits and vegetables with higher TAC (μmolTE/100 g) was associated with a significantly decreased risk of breast cancer. Our study supports a protective effect of dietary antioxidants in relation to breast cancer risk. Food selection based on TAC of foods may be an

effective strategy to modify the risk of cancer.

Capacité antioxydante totale de l'alimentation et risque de cancer du sein : étude cas-témoins

RÉSUMÉ Des données de plus en plus nombreuses indiquent que les antioxydants alimentaires ont des effets favorables sur la réduction du risque de cancer. Dans une étude cas-témoins, nous avons étudié l'association entre la capacité antioxydante totale de l'alimentaire et le risque de cancer du sein. Les données sociodémographiques, les antécédents médicaux et les mesures anthropométriques ont été recueillis auprès de 275 femmes (100 cas de cancer du sein et 175 cas témoins). L'apport alimentaire habituel des participantes a été mesuré à l'aide d'un questionnaire semi-quantitatif validé sur la fréquence de consommation de l'alimentaire, puis la capacité antioxydante totale de l'alimentaire a été estimée. Une association inverse, mais non significative, a été observée entre la capacité antioxydante totale de l'alimentaire et le risque de cancer du sein. Des modèles de régression logistique multiple reposant sur la capacité antioxydante totale des groupes d'aliments individuels ont démontré que la consommation de fruits et de légumes ayant une capacité antioxydante totale plus élevée (µmolTE/100 g) était associée à un risque significativement moindre de cancer du sein. Notre étude confirme l'effet protecteur des antioxydants alimentaires contre le risque de cancer du sein. La sélection des aliments à partir de leur capacité antioxydante totale peut être une stratégie efficace pour modifier le risque de cancer.

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Introduction

Breast cancer is the most common cancer among women in both developed and developing countries and annually more than 1 million new cases are diagnosed worldwide (1,2). In Iranian women breast cancer also is the most common cancer, with an incidence of 22 per 100 000 (3). The known risk factors contributing to breast cancer include not only genetic factors, family

history and reproductive factors but also potentially modifiable diet-related factors such as body mass index (BMI) and lifestyle, eating patterns and dietary intakes (4–7).

Dietary antioxidants have been reported to protect against oxidative damage and related chronic disease (8,9), but the preventive effects of dietary antioxidants on the risk of breast cancer have not been clarified and the results of epidemiological studies in this regard are limited and inconsistent (10,11). Since the evaluation of a single antioxidant component may not reflect the total antioxidant power of diets and other possible interactions or synergetic effects of antioxidants, the concept of dietary total antioxidant capacity (TAC) was recently developed as a novel and relevant tool for assessment of the beneficial effects of dietary antioxidants (12,13). The TAC of foods describes the ability of food antioxidants to scavenge free radicals and is measured using oxygen radical absorbance capacity assay (14). Dietary TAC has been positively associated with plasma TAC and has also been related to higher diet quality, based on common indexes such as the so-called Mediterranean diet and healthy eating index scores (13,15). Previously we reported that dietary TAC was related to all aspect of the metabolic syndrome and, more interestingly, higher dietary TAC could prevent subsequent weight and abdominal fat gain in adults (16). In the current study, we aimed to study whether dietary TAC was associated with a risk of breast cancer in women.

Methods

Study design and population

This was a hospital-based, case–control study conducted among Iranian women. A sample of 100 women with a primary diagnosis of breast cancer were recruited consecutively from January to July 2010 and were frequency-matched to 175 controls by age (5-year intervals). Cases with histologically confirmed breast cancer (maximum duration of 5 months from diagnosis to interview) were recruited from among women aged 30–65 years who referred to the oncology, radiotherapy, chemotherapy or surgery departments of Shohada-e-Tajrish hospital in Tehran, Islamic Republic of Iran. Participants with a history of any cancer or cyst (excluding current breast cancer) and a history of hormone therapy or special diets were excluded from the study. Age-matched controls without any history of cancers or cysts, acute or chronic diseases affecting nutritional status or hormone therapy or special diet were recruited from among individuals referring to outpatient clinics of the hospital, including the departments of gynaecology and dermatology, from April to July 2010.

Written informed consent was 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.

Sociodemographic, anthropometrics and physical activity

Trained interviewers collected data regarding sociodemographic factors including age, educational level, occupation, ethnic group, residential area, alcohol and tobacco use, medical history of disease, family history of breast cancer or other cancers, history of hormone therapy, medications and supplements, oral contraceptives, age at menarche, marital status, number of full-term pregnancies, menopause status and other lifestyle-related factors. Weight was measured to the nearest 100 g using digital scales, while the subjects were minimally clothed without shoes; height was measured to the nearest 0.5 cm using a tape meter, with subjects in a standing position without shoes. BMI was calculated as weight (kg) divided by square of the height (m2). Physical activity level was assessed using a validated questionnaire to obtain the frequency and time spent on light, moderate, vigorous and very vigorous intensity activities according to the list of common activities of daily life over the previous year. Physical activity levels were expressed as metabolic equivalent hours per week (METs h/week) (17).

Dietary assessment

A validated semi-quantitative food frequency questionnaire (FFQ) with 168 food items was used to estimate the usual dietary intake of participants during the past year. The validity and reliability of this FFQ, developed for dietary assessment of participants in the Tehran Lipid and Glucose Study, was previously assessed in a random sample, by comparing both the data from 2 FFQs completed 1 year apart and the data from the FFQs and 12 dietary recalls respectively (18). The mean energy-adjusted correlation coefficients for overall nutrient intake between the dietary recall and the second FFQ were 0.44 and 0.37 in participants aged ≤ 35 and > 35 years respectively. The mean energy-adjusted reliability coefficients varied from 0.48 and 0.68 in participants aged ≤ 35 and > 35 years; the mean reliability in women was 0.60 (18). Trained dieticians asked participants to designate their intake frequency for each food item consumed during the previous year on a daily, weekly or monthly basis. Portion sizes of consumed foods reported in household measures were then converted to grammes. Mean daily intakes of energy and nutrient for each individual were calculated using the food composition table. Dietary TAC was estimated based on the oxygen radical absorbance capacity of selected foods reported by the nutrient data laboratory of the United States Department of Agriculture, and expressed as μmol of Trolox equivalents per 100 g of foods (μmolTE/100 g) (19).

Statistical analysis

Whole diet TAC as well as TAC for individual food groups was assigned as quartiles based on their 25th, 50th and 75th percentile values. Differences in general characteristics across quartiles of dietary TAC were compared using analysis of variance for continuous variables and the chi-squared test for categorical variables. Mean dietary intakes of participants were compared across quartile categories of dietary TAC using the general linear model with adjustment for age (years, continuous) and energy intakes (kcal/day). The odds ratio (OR) and 95% confidence interval (CI) of breast cancer in each quartile of total TAC as well as TAC for different food groups 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 (years); BMI (kg/m2);

educational level (years); occupation (housekeeper, employee, retired); age at menarche (years); marital status (not married, married, divorced, widowed); age at first pregnancy (years); number of full pregnancies; menopause status (yes/no); family history of breast cancer (yes/no); use of oral contraceptive pills (yes/no); life satisfaction (yes/no/partly); physical activity (METs h/week); energy intake (kcal/day); and energy density of diet (kcal/100 g foods).

To assess the overall trends of ORs across increasing quartiles of TAC, the median of each quartile was used as a continuous variable in logistic regression models. Statistical analysis was performed using SPSS, version 16.0. A P-value

Results

Background data

The mean ages of participants were 46.2 (SD 8.9) years and 45.9 (SD 9.4) years in the case and control groups respectively. The mean of age at menarche was significantly lower and the mean of age at first pregnancy was significantly higher in cases as compared with controls (P T able 1
). There were no significant differences, however, in BMI, physical activity, energy intake, diabetes prevalence, menopause status, educational level, occupation or marital status between the 2 groups (Table 1).

The mean dietary TAC of women with breast cancer was 1564 (SD 452) μmolTE/100 g of foods and this was not statistically different from that of the controls [1584 (SD 600) μmolTE/100 g].

Dietary TAC across quartiles

The characteristics of the total study participants across quartile categories of dietary TAC are shown in Table 2 . There were no significant differences in age, physical activity, weight, BMI and other characteristics of the participants across quartiles of TAC.

Dietary intakes of energy, energy density, dietary TAC and dietary intake of food groups across quartile categories of TAC are shown in Table 3 . Dietary energy intake (kcal/day) decreased significantly across increasing dietary TAC (P for trend

Regression models

The OR and 95% CI of breast cancer across quartiles of dietary TAC are presented in Table 4 . After adjustment for potential confounding variables, a non-significant inverse association was observed between dietary TAC and breast cancer risk. When multiple logistic regression models

were conducted based on TAC of individual food groups, we observed that a higher TAC of fruits and vegetables consumed was accompanied by a significant decreased risk of breast cancer (P for trend 2030 (μmolTE/100 g of fruits) decreased the odds of breast cancer more than 80% (OR 0.16; 95% CI: 0.06–0.44). Women who had a TAC consumption from vegetables > 617 (μmolTE/100 g of vegetables) also had significant lower odds of breast cancer in the 3rd quartile (OR 0.32; 95% CI: 0.15–0.71) and 4th quartile category (OR 0.29; 95% CI: 0.13–0.68). The TAC from other food groups showed no similar effects.

The OR and 95% CI of breast cancer across quartiles of dietary TAC are presented in Table 4. After adjustment for potential confounding variables, a non-significant inverse association was observed between dietary TAC and breast cancer risk. Multiple logistic regression models were also conducted based on TAC of individual food groups; TAC of fruits was not associated with the risk of breast cancer in the first model but after additional adjustment for potential confounders in the second, third and fourth models, we observed that a higher TAC of fruits was accompanied by a significant decreased risk of breast cancer (P for trend 2030 (μmolTE/100 g of fruits) decreased the odds of breast cancer more than 80% (OR 0.16; 95% CI: 0.06–0.44). There was no significant association between TAC of vegetables and breast cancer risk in the first, second and third models; after additional adjustment for menopause status, family history of breast cancer, physical activity, energy intake and energy density of diet. In the fourth model, women who had a TAC consumption from vegetables > 617 (μmolTE/100 g of vegetables) also had significant lower odds of breast cancer in the 3rd quartile (OR 0.32; 95% CI: 0.15–0.71) and 4th quartile category (OR 0.29; 95% CI: 0.13–0.68). The TAC from other food groups showed no similar effects.

Discussion

The most important finding of this study was an inverse non-significant association between dietary TAC and breast cancer risk. Moreover a significantly higher odds of breast cancer was observed with an increased TAC of fruits and vegetables. Previous epidemiological studies have evaluated the association of dietary antioxidants and serum antioxidant levels with breast cancer risk (10,11) but, to our knowledge, dietary TAC in relation to breast cancer risk has not yet been investigated.

There is a common hypothesis that oxidative stress and oxidative products as well as low serum levels of antioxidants and low intake of dietary antioxidants could affect breast cancer risk in women (10,11,20,21). However, the results from prospective and case–control studies are inconsistent and current data do not provide a clear association of antioxidant status and breast cancer risk. In a cohort study, no significant association was observed between breast cancer risk and serum levels of antioxidants—including lycopene, lutein, xanthine, β-cryptoxanthin, α- and β-carotene, retinol, α-tocopherol and selenium—after 9.5 years' follow-up (10). In another prospective study, the median concentrations of β-carotene, lycopene and total carotene were

significantly lower in women with diagnosed breast cancer, and a non-significant decreased risk of breast cancer was observed in women who had higher serum levels of antioxidants after 20 years' follow-up (11). A prospective cohort of Swedish women found no overall association between dietary intake of ascorbic acid, beta-carotene, retinol or vitamin E and breast cancer incidence, while higher consumption of high ascorbic acid foods had preventive effects but only in overweight women (20). A case–control study on Malaysian women showed that poor antioxidant status, as indicated by low plasma vitamin A, higher levels of malondialdehyde as an indicator of oxidative stress and lower intake of dietary antioxidants including vitamin A, E and selenium, was associated with increased breast cancer risk (21). Recently, Aune et al. conducted a systematic review and meta-analysis of prospective studies of dietary intake of carotenoids and breast cancer risk and reported that only intake of β-carotene was associated with a decreased breast cancer risk (RR 0.95; 95% CI: 0.91–0.99) (22). To our knowledge, studies investigated the association of dietary antioxidant and breast cancer risk are mainly limited to some particular antioxidants including carotenoids, vitamin C, E, A and selenium, while there are various other micronutrients and bioactive phytochemicals with antioxidative activity in foods. Therefore, an assessment of the TAC of the whole diet and food groups in relation to breast cancer risk can lead to more reliable results.

Several mechanisms have been proposed to explain the association between oxidative stress, antioxidant status and breast cancer risk. There is a common hypothesis that oxidative stress is involved in malignant processes in the breast. Increased oxidative stress and over-production of free radicals that induces metabolic and inflammatory processes can lead to DNA damage, initiation of programmed cell death, activation of several proto-oncogenes and mutations of tumour suppressor genes that have critical roles in mammary carcinogenesis (23–25). Some exogenous and endogenous factors have important roles in modifying these oxidative damage. Enzymatic (thioredoxin reductase, superoxide dismutase, catalase and gluthathione peroxidase) and non-enzymatic (glutathione, antioxidant vitamins and minerals, flavonoids) antioxidant defence systems, as well as higher levels of plasma TAC, were found to be associated with reduced risk of breast cancer (26–28). Since intakes of antioxidants and antioxidant-rich foods are directly related to the status of the antioxidant defence system, dietary intake of antioxidants may be considered as a main dietary factor that could modify the risk of breast cancer.

Studies show that the Mediterranean diet and other Mediterranean-type dietary patterns rich in fruits, vegetables, olive oil, legumes, whole grains, fish and low-fat dairy products have higher antioxidant load and are related to higher TAC (29,30); these dietary patterns are also considered as protective against the development of cancer (31). Modifying antioxidant intake by selecting foods based on their TAC could lead to a decreased risk of chronic diseases such as cancer (32,33). So, beyond the common recommendations regarding adherence to Mediterranean-style dietary patterns, selection of food items with a higher antioxidant load should also be recommended.

The small sample size and the case–control design can be considered as weaknesses of this study. However, there were some strengths of this study, including the use of a validated semi-quantitative FFQ for assessment of dietary intake, using multiple logistic regression models with adjustment of several confounding variables, and considering dietary TAC instead of single dietary antioxidants in relation to breast cancer risk.

Based on the findings from this study and other previous investigations, diets high in antioxidant-rich foods especially fruits and vegetables, whole grains, nuts, legumes and other plant-based foods is recommended to reduce the risk of cancer. Among the various food groups, higher TAC levels have been reported in nuts (especially walnuts, pistachio and almonds), fruits (plums, blackberries blueberries, oranges, dates, figs, apples and grapes) and vegetables (broccoli, cabbage, potato, beet, spinach, lettuce and onion) and dried fruits (dried pears) (19). In this study, other than dietary TAC, we examined the association of antioxidant capacity of food groups including fruits, vegetables and legumes with breast cancer risk. Independent of other dietary factors and potential confounders, consumption of fruits and vegetables with higher antioxidant capacity had higher protective effects to decrease the odds of breast cancer. These findings suggested that food selection based on the TAC of foods may be an effective strategy to increase antioxidant intake and hence to modify the risk of cancer.

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