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A dietary pattern derived to correlate with estrogens and risk of postmenopausal breast cancer

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Abstract

Circulating estrogens are an established risk factor for breast cancer and some data suggested that diet may influence estrogen levels. Therefore, using a subsample (n=550) of women from a large cohort, we applied reduced rank regression to identify a dietary pattern that is correlated with estradiol and estrone sulfate. We then adapted the pattern to be used with the full cohort (n=67,802) and prospectively assessed its association with postmenopausal breast cancer. The estrogen food pattern, characterized by higher intakes of red meat, legumes, and pizza, but lower intakes of coffee and whole grains, was modestly but significantly correlated with estradiol (r=0.14) and estrone sulfate (r=0.20). During 22 years of follow-up, we ascertained 4,596 incident breast cancer, with 2,938 estrogen receptor positive tumors and 689 estrogen receptor negative tumors. However, after adjusting for potential confounders, we did not observe any association with overall, estrogen receptor positive, or estrogen receptor negative breast cancer. In conclusion, diet pattern appeared to only have modest association with estrogens, and was not associated to postmenopausal breast cancer risk. Although these results were null, it should be repeated in other populations as differences in food intake may yield a dietary pattern with stronger association with estrogens.

Keywords

diet; reduced rank regression; estrogen; breast cancer

Introduction

Serum estrogen is an established risk factor for post-menopausal breast cancer [1]. However, data on the potential influence of food on estrogen levels in post-menopausal women is scarce. There are suggestions that a higher fiber [2] intake and adherence to the

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Mediterranean diet [3] may be associated with lower estradiol levels, while higher milk [4] intake may be associated with higher levels. In the Nurses' Health Study, we previously found that the Alternate Healthy Eating Index (AHEI) was associated with lower levels of estradiol among overweight post-menopausal women [5]. Because the AHEI was not designed to correlate with estrogen, there might be other food combinations that could have stronger associations. Reduced rank regression (RRR) is a statistical procedure that can identify specific foods that would most strongly correlate with biomarkers. This process uses "response variables" (biomarkers), and derives food patterns that are associated with them [6]. The patterns can in turn be used to predict cancer risk. The advantage of this method is that it generates patterns linked to biological pathways of cancer development. This approach has been used to derive dietary patterns that is simultaneously associated to multiple biomarkers for predicting diabetes [7,8] and cardiovascular [9,10] disease. However, it has not been widely used in cancer research. Two studies have used the RRR approach to study breast cancer. One identified a food pattern associated glycemic load but this pattern was not associated with breast cancer [11], and the other identified a pattern associated with fatty acids [12] intake and noted a direct association. However, the response variables used in these two studies were dietary factors and not biomarkers, thus the ability to elucidate the mechanistic link between food and disease remained limited.

In this analysis, we used RRR to identify a dietary pattern that is significantly associated with estradiol and estrone sulfate, and applied this pattern to a large cohort of women and assessed its association with postmenopausal breast cancer. These two estrogens were selected for their established association with breast cancer. We also stratified our analysis by estrogen receptor status hypothesizing that the association may be stronger with estrogen receptor positive tumors.

Methods

Study population

The Nurses' Health Study (NHS) is a cohort study established in 1976 and consists of 121,700 female nurses aged 30–55 years living in 11 U.S. states at the time [13]. Questionnaires are sent biennially to collect medical, lifestyle, and other health-related information. In 1980, participants completed a 61-item food frequency questionnaire (FFQ). This was expanded to 116 items in 1984 and similar FFQs were sent in 1986, 1990, 1994, 1998, and 2002. For this analysis, we used 1986 as baseline for the cancer analyses because this FFQ was used used to compute the RRR pattern in the subsample of women with estrogen data. After excluding those with a history of cancer (except non-melanoma skin cancer), we included 67,802 women with follow-up from 1986 through 2008. This study was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, MA.

Biomarker subsample and essay

Blood was collected in 1989–1990 in a subsample of women from the Nurses' Health Study [14]. Each willing participant was sent a blood collection kit containing instructions and needed supplies (e.g., blood tubes and needles). Participants made arrangements for blood to be drawn, packaged in an enclosed cool pack, and sent to the laboratory by overnight courier. Almost all the samples arrived within 26 hr of the blood draw. Upon their arrival at the laboratory, the whole blood samples were centrifuged and aliquotted and stored at −130°C or colder. The lifestyles and dietary intakes of women who returned a blood sample were in general similar to those who did not provide a blood sample. The women in this analysis were controls for previous nested case-control studies in breast cancer [15] and

wrist factures (n=550). Estradiol and estrone sulfate levels were measured using radioimmunoassay and intra-assay coefficients of variation were less than 15%.

Dietary assessment

Self-administered semi-quantitative FFQs were designed to assess average food intake over the preceding year. A standard portion size and nine possible consumption frequency categories, from “never, or <1/month” to “6+ times per day” were given for each food. Total energy and nutrient intake was calculated by using the sum from all foods. Previous validation studies revealed reasonably good correlations between food intake and energy-adjusted nutrients assessed by the FFQ and multiple food records completed over the preceding year [16,17].

Case ascertainment

Incident breast cancer was ascertained between 1986 and 2006. In each biennial questionnaire, participants self-report any diagnosis of breast cancer in the previous 2 years. We then sought permission to obtain medical records to confirm the diagnosis. 99% of self-reported cases were confirmed by medical records. We also included 1% of cases confirmed by the participants. Estrogen and progesterone receptor status was obtained from pathology reports and each receptor was classified as positive, negative, or uncertain. Deaths were reported by the postal service, family members, or by searching the National Death Index. In this study, we included only postmenopausal breast cancer cases to reduce potential etiologic heterogeneity.

Covariate ascertainment

Body mass index (BMI) was calculated from weight reported on each biennial questionnaire and height reported on the first questionnaire. Smoking, history of hypertension, aspirin use, multivitamin intake, menopausal status and use of postmenopausal hormone therapy, history of benign breast disease, parity, and age at first birth were assessed every 2 years. Family history of breast cancer was assessed six times during follow-up. Leisure-time physical activity was measured with validated questions on 10 common activities every 2 years [18].

Derivation of dietary pattern

To account for laboratory drift because biomarkers were not assayed all at the same time, the biomarkers were adjusted by dividing the original value with a ratio that is calculated by dividing the geometric mean of the batch by the mean of all batches [19]. To derive a pattern using RRR, we used average diet intake collected by a validated FFQ in 1986 and 1990 to reduce within subject variation. Then we grouped foods into 37 groups and applied RRR to 550 women who had both estradiol and estrone sulfate (ES) data [6]. RRR produces a linear function of food groups that explains variations in the response variables, which in this case was estradiol and estrone sulfate. The first factor (i.e. pattern) derived from RRR was retained as it had the strongest correlation with the two estrogens. Because the RRR factor score cannot be directly computed for women without estradiol and ES values, we generated a simplified pattern using stepwise linear regressions with the RRR factor score as outcome and food groups as predictors. Food groups were retained to form a simplified pattern if the p-value of the coefficient in the stepwise regression model was less than 0.1. Simplified pattern scores were calculated for all postmenopausal women in the cohort by summing the retained standardized food group items for each FFQ collected in 1986, 1990, 1994, 1998, 2002, and 2006.

Statistical analysis

We used Cox proportional hazard models to assess the association between the simplified pattern score and risk of breast cancer between 1986 and 2008 (n=67,802 at baseline). To reduce random within-person variation and to best represent long-term dietary intake, we calculated cumulative averages of the scores from our repeated FFQs [20]. We adjusted for age, energy intake (quintiles), multivitamin use (yes/no), alcohol intake (4 categories), weight change since age 18 (7 categories), BMI (5 categories), BMI at age 18 (4 categories), family history (yes/no), history of benign breast disease (yes/no), physical activity in METs (quintiles), and age at menopause and post-menopausal hormone use (11 categories). We also examined associations separately by estrogen receptor status.

Results

Estradiol and estrone sulfate were moderately correlated (r=0.57, p<0.0001). The first RRR pattern was modestly but significantly correlated with estradiol (r=0.22, p<0.0001) and ES (r=0.24, p<0.0001). This pattern explained 6.5 % of variation in estradiol and 5.7% variation in estrone sulfate. Stepwise linear regression retained a simplified pattern (i.e. “estrogen food pattern”) characterized by higher intake of red meat, legumes, and pizza, but lower intakes of coffee and whole grains, with a correlation coefficient of 0.69 (p<0.0001) with the original RRR pattern score. The estrogen food pattern was weakly but significantly correlated with estradiol (r=0.14, p<0.0001) and ES (r=0.20, p<0.0001) (table 1). Partial correlation adjusting for BMI only slightly attenuated the correlation coefficients, and they remained statistically significant. In a sensitivity analysis, we included estrone into the RRR procedure but that did not improve the correlation between the resulting pattern and the three estrogens, therefore we did not include estrone sulfate in the RRR procedure in this analysis. Among women who provided blood samples, changes in food group intakes were similar across quintiles of estradiol and estrone sulfate (table 2).

In the main cohort, we ascertained 4596 incident breast cancer over 22 years of follow-up, with clear classification of 2938 estrogen receptor positive tumors and 689 estrogen receptor negative tumors. Women with high estrogen food pattern score had higher BMI, consumed more calories, but less likely to smoke, consumed less folate, and physically less active (table 3).

Multivariate analysis showed no association between the estrogen food pattern score and total breast cancer, ER+ or ER− tumors (table 4). Results stratified by progesterone receptor status did not differ. There was no effect modification by BMI. Adding estrone to RRR did not improve the correlation between the pattern and estrogens and the derived pattern remained null for breast cancer (total, ER+ and ER−).

Discussion

This is the first study that derived a dietary pattern specifically correlated with estrogen levels. The dietary pattern derived with this method had modest association with estradiol and estrone sulfate but was not associated with post-menopausal breast cancer. Data on the association between dietary patterns and estrogen levels are scarce. In this cohort, a higher Alternate Healthy Eating Index (AHEI) was associated with lower concentrations of estradiol [5] and in a small 6-month intervention study, the Mediterranean diet resulted in lower levels of estradiol without any appreciable difference in weight change compared with the typical diet group [3]. Although the AHEI was associated with a lower risk of ER- breast cancer [21], this subtype is unlikely to be strongly influenced by estrogen levels. Therefore, although lower estrogen was observed with higher AHEI score, the components of AHEI likely influenced breast cancer risk through other mechanisms.

RRR overcomes the weak association between single foods and biomarker levels by being able to derive a dietary pattern that is correlated with multiple biomarkers. Although the RRR procedure has been applied to breast cancer in two studies, results were mixed and the response variables were dietary factors [11,12]. A dietary pattern associated with fatty acid intake, characterized by low intake of bread, fruit juices, but high intake of processed meat, fish, and fats was associated with fatty acids intake, was associated with higher risk of breast cancer [12]. On the other hand, a diet correlated with glycemic load, characterized by higher intakes of sweets, refined grains, and salty snacks, had no association with breast cancer [11]. The strength of association between RRR patterns and breast cancer depends on the correlation between the RRR patterns and biomarkers, as well as the strength of association between biomarkers and breast cancer. Although we observed a significant association between the dietary pattern and estrogens, the correlation may be was insufficiently strong to have represented a change in a magnitude that would influence breast cancer risk.

This study included a substantial sample to identify food groups correlated with estrogen, and a large number of cases to separately examine ER+ and ER− tumors. We had detailed information on potential confounders but since lifestyle factors were self-reported, some level of measurement error was inevitable. The sample size for the estrogens was substantial, but that does not guarantee that the distribution would sufficiently reflect the distribution of these biomarkers in the main cohort.

In conclusion, although a diet pattern characterized by higher intakes of red meat, legumes, and pizza, but lower intakes of coffee and whole grains was modestly associated with estradiol and ES, it was not associated with postmenopausal breast cancer risk. Although we did not identify a dietary pattern with strong association with estrogens, other populations may consume different foods in different amounts that may find otherwise. Therefore, the association between food groups and estrogen levels and their relationship with breast cancer should be explored in other populations.

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Table 1

Pearson correlation coefficients (p value) for the estrogen food pattern and its components, and RRR pattern score, estradiol, and estrone sulfate (n=550).

	RRR pattern score	Estradiol	Estrone sulfate
Estrogen food pattern score	0.68 (p<0.0001)	0.14 (p<0.0001)	0.20 (p<0.0001)
Red meat	0.35 (p<0.00010	0.07 (p=0.06)	0.07 (p=0.12)
Coffee	−0.33 (p<0.0001)	−0.09 (p=0.01)	−0.10 (p=0.02)
Legumes	0.29 (p<0.0001)	0.05 (p=0.20)	0.11 (p=0.008)
Whole grains	−0.20 (p<0.0001)	−0.04 (p=0.22)	−0.07 (p=0.12)
pizza	0.37 (p<0.0001)	0.08 (p=0.03)	0.11 (p=0.01)

Table 2

Mean dietary characteristics (average of 1986 and 1990 FFQ) (standard error) according to quintiles of estrogen levels

	Estradiol			Estrone sulfate		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Median (pg/mL)	**3.6**	**6.7**	**13.5**	**81**	**184**	**483**
RRR pattern score	−0.31 (0.06)	−0.02 (0.06)	0.34 (0.06)	−0.17 (0.08)	0.02 (0.08)	0.38 (0.08)
Estrogen food pattern score	−0.99 (0.16)	−0.56 (0.16)	0.15 (0.15)	−0.68 (0.23)	0.32 (0.23)	0.37 (0.22)
Energy intake (kcal)	1657 (36)	1811 (34)	1731 (35)	1738 (48)	1790 (43)	1797 (41)
Alcohol (g)	7 (0.8)	7 (1.0)	5 (0.8)	6 (0.8)	4 (0.6)	7 (1.2)
Red meat (servings/d)	0.49 (0.2)	0.50 (0.2)	0.55 (0.2)	0.51 (0.03)	0.52 (0.03)	0.56 (0.03)
Coffee (servings/d)	2.8 (0.14)	2.1 (0.13)	2.1 (0.13)	2.6 (0.16)	2.0 (0.15)	2.1 (0.15)
Legumes (servings/d)	0.36 (0.02)	0.41 (0.02)	0.41 (0.02)	0.39 (0.02)	0.41 (0.03)	0.44 (0.03)
Whole grains (servings/d)	1.3 (0.07)	1.6 (0.09)	1.3 (0.08)	1.4 (0.12)	1.5 (0.11)	1.2 (0.10)
Pizza (servings/d)	0.05 (0.004)	0.06 (0.004)	0.07 (0.005)	0.05 (0.004)	0.05 (0.005)	0.07 (0.006)

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Table 3

Age standardized baseline (1986) characteristics according to quintiles of estrogen food pattern score*

	Q1	Q2	Q3	Q4	Q5
BMI (kg/m^2)	24.4	24.7	25.1	25.3	26.0
Current smoker (%)	24	22	21	20	18
Physical activity (MET/wk)	16	15	14	13	13
Family history (%)	9	9	8	8	8
Energy (kcal/d)	1639	1629	1699	1806	2074
Alcohol intake (g/d)	6	7	6	6	6
Fiber (g/d)**	19	18	18	17	17
Folate (mcg/d)*	432	417	406	391	391
Red meat (servings/d)	0.3	0.4	0.5	0.7	0.9
Legumes (servings/d)	0.3	0.3	0.4	0.4	0.6
Pizza (per 2 slices/d)	0.03	0.05	0.06	0.07	0.12
Coffee (cups/d)	3.9	2.8	2.3	1.9	1.5
Whole grains (servings/d)	2.0	1.2	1.0	0.9	0.8

* P values for trend were all <0.0001 for all lifestyle and intake characteristics

** energy adjusted

Table 4

Relative risk (95% CI) for quintiles of estrogen pattern score and risk of post-menopausal breast cancer

	Q1	Q2	Q3	Q4	Q5	P trend
Total breast cancer						
No. of cases	1028	910	933	885	840	
Age & energy adjusted	1	0.90 (0.82, 0.98)	0.95 (0.87, 1.04)	0.95 (0.87, 1.05)	0.96 (0.87, 1.06)	0.71
Multivariate adjusted*	1	0.88 (0.80, 0.96)	0.93 (0.85, 1.02)	0.94 (0.86, 1.05)	0.95 (0.86, 1.05)	0.47
ER+ tumors						
No. of cases	664	610	588	551	525	
Age & energy adjusted	1	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)	0.94 (0.83, 1.06)	0.37
Multivariate adjusted*	1	0.92 (0.82, 1.03)	0.92 (0.82, 1.03)	0.92 (0.82, 1.03)	0.94 (0.83, 1.07)	0.36
ER− tumors						
No. of cases	132	138	155	137	127	
Age & energy adjusted	1	1.06 (0.84, 1.35)	1.21 (0.96, 1.52)	1.10 (0.86, 1.40)	1.04 (0.81, 1.35)	0.69
Multivariate adjusted*	1	1.04 (0.82, 1.32)	1.18 (0.93, 1.50)	1.08 (0.84, 1.38)	1.03 (0.79, 1.34)	0.73

*adjusted for age (in months), energy intake (quintiles), multivitamin use (yes/no), alcohol intake (4 categories), weight change since age 18 (8 categories), BMI at age 18 (5 categories), family history (yes/no), history of benign breast disease (yes/no), physical activity (5 categories), postmenopausal hormone use (12 categories)

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