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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

An Estrogen-Related Dietary Pattern and Postmenopausal Breast Cancer Risk in a Cohort of Women with a Family History of Breast Cancer

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Abstract

Background: The results of previous studies on diet and postmenopausal breast cancer risk have been inconclusive, but there is some evidence that dietary patterns developed to correlate with estrogen levels are associated with breast cancer. We aimed to examine the association of a previously developed estrogen-related dietary pattern (ERDP) with postmenopausal breast cancer in the Sister Study.

Methods: The ERDP was calculated from food frequency questionnaire responses among Sister Study participants without a personal history of cancer and who contributed postmenopausal person-time at risk. Cox proportional hazards models were used to estimate HRs and 95% confidence intervals for the association between the ERDP and postmenopausal breast cancer.

Results: With more than 261,959 person-years of follow-up and 1,968 incident cases, the ERDP was not associated with total, invasive, estrogen receptor (ER)-positive or ER-negative subtypes of breast cancer. Results were robust to various sensitivity analyses.

Conclusions: The results do not support previous studies observing a positive association between a proestrogenic dietary pattern and postmenopausal breast cancer risk. Null results may be partially explained by high levels of other breast cancer risk factors within the study population, such as a family history of breast cancer.

Impact: An estrogen-related dietary pattern may not be a strong predictor of breast cancer risk in all populations. Future studies of diet and breast cancer should evaluate the potential for effect modification by family history and consider differences in dietary assessment tools when comparing results across study populations. *Cancer Epidemiol Biomarkers Prev; 27(10); 1223–6. ©2018 AACR.*

Introduction

Estrogen is an established risk factor for postmenopausal breast cancer and has been suggested to partially mediate associations between lifestyle factors such as adiposity and breast cancer (1). Dietary factors can influence estrogen metabolism (2); however, studies of diet and breast cancer have been inconclusive. Dietary patterns developed to reflect estrogen exposure have been associated with breast cancer in some populations (3, 4), but not all (5). One such pattern, the estrogen-related dietary pattern (ERDP; ref. 4), was developed in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial to identify food groups that explained the largest variation in levels of unconjugated estradiol and the ratio of 2- and 16-hydroxylated estrogen metabolites, which have been associated with breast cancer risk (6). The ERDP was positively associated with total, invasive, and estrogen receptor (ER)-positive postmenopausal breast cancer in the PLCO (4). We aimed to examine the generalizability of the ERDP by examining its association with total, invasive, and ER subtypes of breast cancer in a separate study of postmenopausal women.

Materials and Methods

The Sister Study, described elsewhere (7), is a prospective cohort of 50,884 women ages 35 to 74 years recruited between 2003 and 2009, all with a sister who was diagnosed with breast cancer, followed up through August 2015 (data release 5.0.1). In the current analysis, participants were excluded if they had a personal history of cancer (n = 2,757), did not contribute any postmenopausal person-time at risk (n = 8,014), reported an extreme caloric intake (<500 or >5,000 kcal/day; n = 1,162), had an extreme body mass index (BMI; <15 or >50 kg/m^2; n = 68), or had missing covariate data (n = 958), bringing the analytic sample to 37,925.

Scoring of the ERDP has been described elsewhere (4). Briefly, the ERDP was calculated by summing across the weighted intakes of 11 previously identified food groups (shown in Table 1) using usual intakes over the past 12 months as measured by a 110 item block food frequency questionnaire (FFQ). Breast cancer cases were ascertained via self-report and confirmed with medical records. Because the positive predictive value of self-reported breast cancer was 99%, self-reports were used when records were not available.

Cox proportional hazards models were used to estimate HRs and 95% CIs for the association between the ERDP and postmenopausal breast cancer. The ERDP was evaluated as a

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Table 1. Population characteristics across quartiles of the ERDP score, Sister Study, 2003–2009

		ERDP quartile (score range)			
		1st (−8.2344 to −0.4442)	2nd (−0.4441 to −0.0584)	3rd (−0.0583 to 0.3467)	4th (0.3468 to 4.6661)
n		9,481	9,482	9,481	9,481
Breast cancer cases	Total	520	474	484	490
	Invasive	393	368	350	373
	Invasive ER^+	308	268	250	272
	Invasive ER^-	47	46	52	56
ERDP score (mean ± SD)		−0.90 ± 0.48	−0.24 ± 0.11	0.13 ± 0.12	0.82 ± 0.47
Age (mean ± SD)		58.3 ± 7.3	58.1 ± 7.5	57.2 ± 7.8	56.0 ± 7.6
BMI (kg/m^2; mean ± SD)		27.0 ± 5.5	27.4 ± 5.6	28.0 ± 6.0	28.7 ± 6.6
BMI at age 30 (kg/m^2; mean ± SD)		22.7 ± 3.3	22.7 ± 3.3	23.0 ± 3.5	23.4 ± 4.0
Total caloric intake (kcal/day)		1,601 ± 590	1,439 ± 532	1,527 ± 535	1,908 ± 649
MET-hours/week (mean ± SD)		53.4 ± 31.9	51.1 ± 31.0	49.6 ± 30.9	49.8 ± 31.1
Age at menarche (mean ± SD)		12.6 ± 1.5	12.6 ± 1.5	12.6 ± 1.5	12.7 ± 1.6
Age at menopause (mean ± SD)		50.3 ± 5.8	50.1 ± 5.9	49.9 ± 6.1	49.8 ± 5.9
Number of relatives with family history (mean ± SD)		1.27 ± 0.59	1.28 ± 0.59	1.27 ± 0.58	1.26 ± 0.57
Parity (mean ± SD)		1.95 ± 1.35	2.01 ± 1.35	2.02 ± 1.37	1.96 ± 1.37
Nulliparous (%)		18.2	16.6	17.2	18.6
PHT status (%)					
	Never	44.6	45.8	48.1	52.0
	Former: estrogen + progesterone	24.4	22.7	21.7	19.4
	Former: estrogen only	16.8	17.1	15.7	14.8
	Former: unknown what type	2.3	2.3	2.4	2.4
	Current: estrogen + progesterone	5.2	5.0	5.1	4.6
	Current: estrogen only	6.7	7.1	7.0	6.8
Race/ethnicity (%)					
	White, non-Hispanic	85.6	84.7	85.0	86.4
	Black, non-Hispanic	8.3	8.1	7.9	5.5
	Hispanic	2.8	4.3	4.5	5.2
	Asian	0.9	0.7	0.5	0.3
	Other	2.4	2.2	2.1	2.6
Alcohol (%)					
	Abstainer	17.8	18.6	19.9	21.1
	≤1 drink/day	70.7	69.8	69.5	67.0
	>1 drink/day	11.5	11.6	10.6	11.9
Smoking (%)					
	Current	7.9	7.8	7.5	8.1
	Former	41.8	38.5	35.0	35.1
	Never	50.3	53.7	57.5	56.8
Education (%)					
	<HS	0.9	1.1	1.2	1.2
	HS grad or some college	32.4	35.0	36.2	34.8
	College grad	39.6	39.0	39.7	41.3
	Postgraduate	27.1	24.9	22.9	22.7
Hysterectomy (%)					
	No	65.6	65.5	65.0	66.8
	Yes	34.4	34.5	35.0	33.2
Non-whole/refined grains (oz/day; mean ± SD)		2.32 ± 1.26	2.39 ± 1.23	2.82 ± 1.34	3.94 ± 1.98
Tomatoes (cups/day; mean ± SD)		0.24 ± 0.17	0.23 ± 0.17	0.25 ± 0.19	0.35 ± 0.28
Other vegetables (cups/day; mean ± SD)		0.63 ± 0.51	0.44 ± 0.33	0.40 ± 0.29	0.45 ± 0.31
Cruciferous vegetables (cups/day; mean ± SD)		0.23 ± 0.27	0.20 ± 0.24	0.22 ± 0.25	0.29 ± 0.41
Cheese (cups/day; mean ± SD)		0.26 ± 0.21	0.28 ± 0.21	0.36 ± 0.24	0.66 ± 0.41
Yogurt (cups/day; mean ± SD)		0.23 ± 0.28	0.10 ± 0.14	0.08 ± 0.12	0.06 ± 0.11
Fish/shellfish high in ω-3 fatty acids (oz/day; mean ± SD)		0.18 ± 0.23	0.14 ± 0.17	0.13 ± 0.17	0.15 ± 0.22
Fish/shellfish low in ω-3 fatty acids (oz/day; mean ± SD)		0.58 ± 0.63	0.40 ± 0.36	0.38 ± 0.34	0.42 ± 0.41
Franks and luncheon meats (oz/day; mean ± SD)		0.37 ± 0.32	0.41 ± 0.33	0.51 ± 0.37	0.78 ± 0.59
Nuts and seeds (oz/day; mean ± SD)		2.11 ± 2.26	1.31 ± 1.33	1.14 ± 1.17	1.20 ± 1.20
Coffee (cups/day; mean ± SD)		2.19 ± 1.68	1.58 ± 1.40	1.19 ± 1.28	1.02 ± 1.25

Abbreviations: HS, high school; MET, metabolic equivalent of task; PHT, postmenopausal hormone therapy.

continuous score (ranging from −8.32 to 4.67) and using quartiles, with the first quartile as the referent group representing diets hypothesized to have the lowest estrogenic risk. Multivariable models included age, total energy intake, BMI at baseline, BMI at age 30, postmenopausal hormone therapy (PHT) use, race/ethnicity, alcohol consumption, number of family members with a history of breast cancer, age at menarche, age at menopause, parity, and hysterectomy. Sensitivity analyses included: restricting to non-Hispanic whites, excluding participants with ≤ 1 year of follow-up, and excluding participants with more than one full family member diagnosed with breast cancer.

Results

Population characteristics across quartiles of ERDP are shown in Table 1. The ERDP was not associated with any breast cancer

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Table 2. HRs (95% confidence interval) for the relationship between the ERDP score and postmenopausal breast cancer in the Sister Study, 2003–2015

	ERDP quartiles				Estimate for continuous ERDP score[a]
	1st	2nd	3rd	4th	
Total breast cancer					
No. of cases	520	474	484	490	
Age adjusted	1.00 (ref)	0.92 (0.81–1.04)	0.98 (0.86–1.11)	1.03 (0.91–1.17)	1.01 (0.95–1.08) $P = 0.71$
Age and energy adjusted	1.00 (ref)	0.93 (0.82–1.06)	0.98 (0.87–1.11)	1.01 (0.89–1.14)	1.00 (0.94–1.06) $P = 0.94$
Multivariable adjusted[b]	1.00 (ref)	0.92 (0.81–1.04)	0.96 (0.85–1.09)	0.99 (0.87–1.12)	0.98 (0.92–1.05) $P = 0.61$
Invasive					
No. of cases	393	368	350	373	
Age adjusted	1.00 (ref)	0.95 (0.82–1.09)	0.94 (0.81–1.08)	1.05 (0.91–1.21)	1.01 (0.94–1.09) $P = 0.71$
Age and energy adjusted	1.00 (ref)	0.97 (0.84–1.11)	0.95 (0.82–1.10)	1.01 (0.87–1.16)	0.99 (0.92–1.07) $P = 0.84$
Multivariable adjusted[b]	1.00 (ref)	0.95 (0.82–1.09)	0.92 (0.79–1.06)	0.97 (0.84–1.12)	0.97 (0.90–1.04) $P = 0.37$
Invasive ER+					
No. of cases	308	268	250	272	
Age adjusted	1.00 (ref)	0.88 (0.75–1.04)	0.86 (0.73–1.02)	0.99 (0.84–1.16)	0.98 (0.90–1.07) $P = 0.63$
Age and energy adjusted	1.00 (ref)	0.90 (0.76–1.06)	0.87 (0.74–1.03)	0.94 (0.80–1.11)	0.96 (0.88–1.04) $P = 0.30$
Multivariable adjusted[b]	1.00 (ref)	0.88 (0.75–1.04)	0.85 (0.71–1.00)	0.91 (0.77–1.08)	0.93 (0.86–1.02) $P = 0.11$
Invasive ER−					
No. of cases	47	46	52	56	
Age adjusted	1.00 (ref)	0.99 (0.66–1.49)	1.14 (0.77–1.70)	1.25 (0.85–1.85)	1.16 (0.95–1.41) $P = 0.14$
Age and energy adjusted	1.00 (ref)	1.00 (0.66–1.50)	1.15 (0.77–1.71)	1.23 (0.83–1.82)	1.15 (0.94–1.40) $P = 0.18$
Multivariable adjusted[b]	1.00 (ref)	0.99 (0.66–1.50)	1.14 (0.76–1.69)	1.21 (0.81–1.81)	1.14 (0.93–1.40) $P = 0.20$
Person years accumulated	66,545	66,112	65,100	64,201	

[a]HR corresponds to 1-unit increase in ERDP score.

[b]Includes adjustment for age, TEI, BMI, BMI at age 30, PHT, race/ethnicity, alcohol use, number of family members with a history of breast cancer, age at menarche, age at menopause, parity, and hysterectomy.

outcomes, although the HRs for ER-negative increased slightly with increasing ERDP (Table 2).

Discussion

Despite having a larger sample size with power to detect smaller associations than in PLCO, our investigation did not support previous studies observing an association between estrogen-based dietary patterns and postmenopausal breast cancer risk (3, 4). In PLCO, participants in the highest ERDP quartile were at 20% increased risk of invasive postmenopausal breast cancer (4). However, when stratified by family history of breast cancer, the association was limited to women without a family history. Null results presented here are in agreement with the stratified results in PLCO, and may be partially explained by the strong presence of family history, although excluding those with the strongest family history did not change results. Evidence for modification by family history in dietary studies of cancer is limited (8).

In addition to the potential for a true null or masking of an association by the ubiquitous familial risk, it is possible that differences in the FFQs used explain the null association. The FFQs used here and in the PLCO cohort to derive the ERDP differ in the number and description of the line items containing relevant foods. It is possible that these differences explain the different distributions of the scores between the two populations. The range of −8.23 to 4.67 in the Sister Study compared with a range of −4.52 to 6.58 in PLCO participants could indicate that participants in the Sister Study were not consuming diets with as much estrogenic potential, or that the FFQ in the Sister Study did not capture as many of the estrogen relevant foods. The lack of agreement between studies investigating dietary estrogenic potential support the need for research that evaluates differences across strata of family history, along with consideration of the impact of differing dietary assessment tools when comparing dietary patterns across study populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.A. Guinter, S.E. Steck

Development of methodology: M.A. Guinter, A.T. Merchant, S.E. Steck

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.P. Sandler

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.P. Sandler, A.C. McLain, A.T. Merchant, S.E. Steck

Writing, review, and/or revision of the manuscript: M.A. Guinter, D.P. Sandler, A.T. Merchant, S.E. Steck

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