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Original Contribution

Postmenopausal Breast Cancer Risk and Dietary Patterns in the E3N-EPIC Prospective Cohort Study

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Since evidence relating diet to breast cancer risk is not sufficiently consistent to elaborate preventive proposals, the authors examined the association between dietary patterns and breast cancer risk in a large French cohort study. The analyses included 2,381 postmenopausal invasive breast cancer cases diagnosed during a median 9.7-year follow-up period (1993–2005) among 65,374 women from the E3N-EPIC cohort. Scores for dietary patterns were obtained by factor analysis, and breast cancer hazard ratios were estimated by Cox proportional hazards regression for the highest quartile of dietary pattern score versus the lowest. Two dietary patterns were identified: "alcohol/Western" (essentially meat products, French fries, appetizers, rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, alcoholic beverages, cakes, mayonnaise, and butter/cream) and "healthy/Mediterranean" (essentially vegetables, fruits, seafood, olive oil, and sunflower oil). The first pattern was positively associated with breast cancer risk (hazard ratio = 1.20, 95% confidence interval (CI): 1.03, 1.38; $P = 0.007$ for linear trend), especially when tumors were estrogen receptor-positive/progesterone receptor-positive. The "healthy/Mediterranean" pattern was negatively associated with breast cancer risk (hazard ratio = 0.85, 95% CI: 0.75, 0.95; $P = 0.003$ for linear trend), especially when tumors were estrogen receptor-positive/progesterone receptor-negative. Adherence to a diet comprising mostly fruits, vegetables, fish, and olive/sunflower oil, along with avoidance of Western-type foods, may contribute to a substantial reduction in postmenopausal breast cancer risk.

breast neoplasms; cohort studies; diet; diet, Mediterranean; factor analysis, statistical; postmenopause

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

Breast cancer incidence varies widely between countries, suggesting the influence of environmental factors. The Japanese have traditionally been at low risk of breast cancer (1), but breast cancer incidence in Japan has recently increased (2) concomitantly with major changes in traditional habits, especially diet (3). Indeed, during the past 50 years in Japan, the proportion of energy obtained from fat increased until it represented up to 25% of total energy, and the consumption of dairy products increased 10-fold (4). Thus, the increasing incidence of breast cancer in Japan can be attributed at least partly to the adoption of a Western diet, which is notably characterized by higher intakes of meat, dairy products, and saturated fat, and decreased consumption of traditional Japanese foods such as seafood products (3). However, to date, evidence for associations between breast cancer risk and specific foods or nutrients has been limited, except for alcohol (5).

The recent approach to dietary patterns (6) classifies subjects according to dietary behavior and facilitates public health recommendations; in contrast, the nutrient/food approach permits better assessment of biologic mechanisms involved (7). Several epidemiologic studies have investigated the association between dietary pattern and breast cancer risk (8). A significant inverse relation has been described between breast cancer risk and a "prudent" (9, 10) or "healthy" (11) dietary pattern and specific regional patterns (12–14), in contrast to positive associations with a ‘‘drinker’’ (15) or ‘‘Western’’ pattern (11, 12, 16). However, the World Cancer Research Fund concluded that the evidence was not sufficient to draw firm conclusions (5). Thus, further large-scale prospective studies are needed to strengthen the observed associations.

We investigated the association between dietary pattern and risk of postmenopausal invasive breast cancer, considering potential interactions with known risk factors for breast cancer.

MATERIALS AND METHODS

The E3N cohort

The E3N [Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l’Education Nationale] Study is a prospective cohort study that was initiated in 1990 to investigate factors associated with the most common types of cancer (17). It involves 98,995 women living in France who were born between 1925 and 1950 and are covered by a national health insurance plan for teachers and coworkers. Participants complete biennial self-administered follow-up questionnaires on health status, medical history, and lifestyle. All subjects signed an informed consent form at study entry, and the study protocol was approved by the French National Commission for Computed Data and Individual Freedom.

Dietary assessment

Dietary data were collected via a self-administered diet history questionnaire assessing consumption of 208 foods and beverages. It included quantitative questions, using a booklet of photographs with portion sizes and frequency of food group consumption, and qualitative questions on food groups. Both questionnaire and booklet were validated and tested for reproducibility after 1 year (18, 19).

The dietary questionnaire was sent between June 1993 and July 1995 to the responders to the previous questionnaire. Women who completed a valid dietary questionnaire represent the French component of the European Prospective Investigation into Cancer and Nutrition (EPIC) (20).

Analytic cohort

In this study of postmenopausal breast cancer, follow-up began on the return date of the dietary questionnaire for women who were already postmenopausal at that time, or the date of menopause if this occurred later. Women contributed person-time until the date of cancer diagnosis, the date of the last completed questionnaire, or the date on which the last available follow-up questionnaire was mailed (July 2005), whichever occurred first.

Among the 74,524 women with available dietary data, we excluded 1,490 women with extreme values (1% on both sides) for the ratio between energy intake and energy requirement (21, 22). We also excluded women with cancer other than basal cell carcinoma or in situ breast lobular carcinoma before the start of follow-up (n = 5,361); those who did not answer the second questionnaire (n = 795); those who had never menstruated (n = 21); and those who had not reached menopause at the time of the last follow-up questionnaire (n = 1,483). Thus, 65,374 women contributed to the analyses, accruing 568,084 person-years of follow-up.

Determining cases

Cases were defined as cases of first primary invasive postmenopausal breast cancer (*International Classification of Diseases for Oncology* codes C50.0–C50.6 and C50.8–C50.9). We classified breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status and by histologic type (ductal, including mixed ductal-lobular; lobular; or other, including tubular carcinomas). Women with in situ breast cancer were censored as noncases at the date of diagnosis. Each questionnaire asked about cancer occurrence, and we subsequently collected pathology reports. Pathology reports were obtained for 94% of declared breast cancer cases; 98% of them confirmed the diagnosis; and 88% of confirmed breast cancers were invasive. Among the 65,374 women studied, 2,381 developed postmenopausal invasive breast cancer during a median follow-up period of 9.7 years. Cases with missing data for hormone receptor status (n = 532) or histologic type (n = 173) were excluded from corresponding analyses.

Dietary patterns

Dietary patterns were produced from principal-components analysis based on 57 predefined food groups (Appendix Table), using the SAS ‘‘Proc Factor’’ procedure (SAS Institute Inc., Cary, North Carolina). This factor analysis forms linear combinations of the original food groups, thereby grouping together correlated variables. Coefficients defining these linear combinations are called factor loadings. A positive factor loading means that the food group is positively associated with the factor, whereas a negative loading reflects an inverse association with the factor. For interpreting the data, we considered foods with a loading coefficient under −0.25 or over 0.25. We rotated factors by orthogonal transformation using the SAS ‘‘Varimax’’ option to maximize the independence (orthogonality) of retained factors and obtain a simpler structure for easier interpretation (15, 23). In determining the number of factors to retain, we considered eigenvalues greater than 1.25 (as in the article by Slattery et al. (24)), the scree test (25, 26) (with values being retained at the break point between components with large eigenvalues and those with small eigenvalues on the scree plot), and the interpretability of the factors. For each subject, we calculated the factor score for each pattern by summing observed consumption from all food groups, weighted by the food group factor loadings. The factor score measures the conformity of a woman’s diet to the given pattern. Labeling was descriptive, based on foods most strongly associated with the dietary patterns.

Statistical analysis

We used Cox proportional hazards regression with age as the underlying time metric for estimating hazard ratios and 95% confidence intervals. Control for potential confounders was ensured by adjustment for a number of factors (see tables for definitions): age, educational level, geographic area at baseline, body mass index (weight (kg)/height $(m)^2$), height, family history of breast cancer in first- or second-degree relatives, age at menarche, age at first full-term pregnancy combined with number of livebirths, menopausal hormone therapy, personal history of benign breast disease or lobular carcinoma in situ at baseline, use of oral contraceptives at baseline, lifetime duration of breastfeeding, frequency of Papanicolaou (Pap) testing at baseline (as an indicator of compliance with gynecologic screening), physical activity at baseline, smoking status at baseline, energy intake (excluding alcohol), current use of phytoestrogen supplements, and current use of vitamin/mineral supplements. P for linear trend was estimated in models into which quartiles of factor scores were entered as an ordinal variable. Potential interactions either suggested in the literature or related to plausible underlying mechanisms were tested. We thus considered energy intake, use of menopausal hormone therapy, physical activity, body mass index, and smoking status in models including an interaction term (potential effect modifier × factor score with ordinal values corresponding to quartiles). Specific types of breast cancer were studied in separate Cox models, and tests of homogeneity for the association between each dietary pattern and risk of different types of breast cancer were based on Wald chi-square statistics (27): For each dietary pattern, the coefficients and their standard errors estimated from the Cox models were used to compute test statistics with degrees of freedom equal to the number of subtypes of breast cancer minus 1. All covariates had fewer than 5% of values missing; therefore, missing values were replaced by the modal value in subjects with complete data (all were qualitative variables). All statistical tests were 2-sided, and significance was set at the 0.05 level. Analyses were performed using SAS software, version 9.1.

RESULTS

Description of dietary patterns

Factor analysis identified 2 main dietary patterns, which accounted for 10% of the variance in consumption of the 57 food and beverage items (Table 1). Pattern 1 was positively correlated with consumption of processed meat and meat products (ham, offal), French fries, appetizers, sandwiches, rice/pasta, potatoes, pulses, pizza/pies, canned fish, eggs, crustaceans, alcoholic beverages, cakes, mayonnaise, and butter/cream and was thus termed "alcohol/Western." Pattern 2 was characterized by a high intake of vegetables and fruits, fish and crustaceans, olives, and sunflower oil. It was labeled "healthy/Mediterranean" because of its Mediterranean traits (fish, fruits, vegetables, olive oil), as well as its healthy traits (use of sunflower oil was highly advocated in the 1990s).

Increasing scores of the "alcohol/Western" pattern were associated with younger age, decreasing prevalence of nulliparity, decreasing duration of breastfeeding, increasing prevalence of overweight, greater height, a higher proportion of relatives with a history of breast cancer, a higher proportion of oral contraceptive use, biennial Pap smears, and a higher prevalence of current smoking. Increasing scores of the "healthy/Mediterranean" pattern were associated with older age, higher education, a higher prevalence of overweight, a higher proportion of personal history of benign breast disease, increasing use of menopausal hormone therapy, increasing duration of breastfeeding, an increasing proportion of annual Pap smears, higher levels of physical activity, and an increasing proportion of former smokers. Energy intake and alcohol use also increased with increasing score, but to a lesser extent than for the alcohol/Western pattern (Table 2).

Table 1. Factor Loadings[a] for Dietary Patterns Identified by Factor Analysis (n = 65,374) in the E3N-EPIC Cohort, France, 1993–2005

Food Group	"Alcohol/ Western" Pattern	"Healthy/ Mediterranean" Pattern
Fruits		0.34
Raw vegetables		0.70
Cooked vegetables		0.66
Potatoes	0.33	
Pulses	0.29	
Rice, pasta, semolina	0.39	
French fries	0.48	
Appetizers	0.45	
Pizza, pies	0.39	
Sandwiches	0.32	
Cakes	0.36	
Processed meat[b]	0.59	
Ham	0.31	
Offal	0.29	
Eggs	0.36	
Canned fish	0.37	
Crustaceans	0.32	0.30
Fish		0.51
Mayonnaise	0.39	
Butter, cream	0.31	
Olive oil		0.46
Sunflower oil		0.26
High-alcohol beverages	0.37	
Wine	0.26	

Abbreviations: E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition.

[a] For both patterns, food groups with factor loadings of less than ±0.25 (soup, tea, coffee, chicory, chocolate beverages, juices, soft drinks—regular, soft drinks—light, mineral water, tap water, low-alcohol beverages, white bread, whole-grain bread, crisp bread, breakfast cereals, biscuits, sweets, croissant-like/Danish pastries, dairy-based sweet puddings, high-fat dairy products, low-fat dairy products, canned fruits, meat, poultry and rabbit, cheese, margarine, vegetable oil (except olive oil and sunflower oil), other fats, manufactured salad dressing, salad dressing—light, chocolate, added sugar and artificial sweeteners) were omitted for simplicity.

[b] Except cooked ham.

Table 2. Characteristics of Postmenopausal Women at Baseline, by Quartile of Dietary Pattern Score (n = 65,374), in the E3N-EPIC Cohort, France, 1993–2005[a]

	Quartile of "Alcohol/Western" Pattern Score				Quartile of "Healthy/Mediterranean" Pattern Score			
	1	2	3	4	1	2	3	4
Age, years	55.1 (6.8)	53.5 (6.6)	52.2 (6.3)	51.2 (6.0)	52.4 (6.8)	53.0 (6.7)	53.3 (6.6)	53.3 (6.4)
<12 years of education, %	11.8	10.9	10.5	11.8	12.2	11.3	10.7	10.8
Age at menarche, years	12.8 (1.4)	12.8 (1.4)	12.8 (1.4)	12.8 (1.4)	12.9 (1.4)	12.8 (1.4)	12.8 (1.4)	12.6 (1.4)
Age at first full-term pregnancy and no. of livebirths, %								
Nulliparous	14.2	12.0	10.7	9.5	12.3	11.1	11.4	11.7
<30 years and 1–2 births	48.4	50.2	50.2	51.4	48.3	50.0	50.5	51.4
<30 years and ≥3 births	27.4	27.5	28.1	28.8	27.5	28.3	28.2	27.8
≥30 years and ≥1 birth	10.0	10.3	11.0	10.3	11.9	10.7	10.0	9.1
Body mass index[b], %								
<18.5	5.0	3.3	3.1	2.5	5.5	3.5	2.7	2.3
≥18.5 and <25	76.5	76.9	76.3	71.0	78.1	77.9	75.6	69.2
≥25	18.5	19.8	20.6	26.5	16.4	18.6	21.7	28.5
Height, cm	160.6 (5.6)	161.1 (5.6)	161.7 (5.6)	162.2 (5.6)	161.2 (5.7)	161.3 (5.6)	161.4 (5.6)	161.7 (5.6)
Family history of breast cancer in first- or second-degree relative, %	22.6	23.3	23.6	24.4	23.3	23.1	23.8	23.8
Menopausal hormone therapy, %	49.7	50.9	51.7	49.8	46.6	51.3	51.5	52
Personal history of benign breast disease[c] or lobular carcinoma in situ, %	28.2	29.6	29.9	29.1	28.4	28.7	29.6	30
Ever use of oral contraceptives, %	51.2	57.7	63.2	68.1	59.9	59.5	59.8	60.6
Lifetime duration of breastfeeding, months[d]	3.7 (5.8)	3.5 (5.2)	3.3 (5.1)	3.1 (4.9)	3.2 (5.0)	3.4 (5.1)	3.5 (5.3)	3.6 (5.6)
Frequency of Papanicolaou testing, %								
Never	3.4	2.7	2.5	2.7	3.8	2.8	2.6	2.2
Irregularly	12.1	11.6	10.6	11.5	13.2	11.8	10.9	10.1
Every 4–5 years	3.7	3.0	3.1	3.4	3.4	3.2	3.2	3.4
Every 2–3 years	24.7	26.2	26.9	27.6	26.8	26.8	26.3	25.4
Every year	56.1	56.4	56.9	54.8	52.7	55.4	57.1	59.0
Physical activity (metabolic equivalents/week), %								
<29.0	32.4	33.1	33.2	32.5	36.0	33.4	31.2	30.7
29.0–46.7	34.2	35.3	35.5	34.9	35.4	35.6	34.8	34.2
>46.7	33.3	31.6	31.3	32.6	28.7	31.0	34.0	35.1
Alcohol consumption, g/day	5.6 (8.3)	9.1 (11.1)	12.0 (13.3)	18.2 (18.8)	10.5 (13.8)	10.8 (13.6)	11.3 (13.8)	12.1 (15.3)
Smoking status, %								
Never smoker	61.4	57.8	54.7	51.7	58.9	58.1	55.9	52.8
Former smoker	28.3	29.7	30.7	31.0	26.9	29.2	30.7	32.9
Current smoker	10.3	12.5	14.6	17.3	14.2	12.7	13.3	14.4
Energy intake (excluding alcohol), kcal/day	1,662.2 (410.5)	1,933.3 (407.6)	2,175.2 (424.9)	2,594.4 (513.5)	1,974.9 (555.1)	2,024.6 (527.1)	2,097.4 (534.2)	2,255.3 (574.4)

Abbreviations: E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition.
[a] Data are presented as mean values with standard deviations in parentheses, unless otherwise indicated.
[b] Weight (kg)/height (m)^2.
[c] Including fibrocystic breast disease, mastosis, and fibroadenoma.
[d] Among parous women (n = 57,776).

Table 3. Hazard Ratios for Invasive Postmenopausal Breast Cancer, by Quartile of Score for the Alcohol/Western Dietary Pattern (n = 65,374), Among Women in the E3N-EPIC Cohort, France, 1993–2005

	Quartile of "Alcohol/Western" Pattern Score							P for Linear Trend
	1 (HR = 1)[a]	2		3		4		
		HR	95% CI	HR	95% CI	HR	95% CI	
Total								
No. of cases	574		583		620		604	
Age-adjusted model	1.00	1.08	0.96, 1.21	1.22	1.08, 1.36	1.26	1.12, 1.41	<0.0001
Multivariable model[b]	1.00	1.05	0.93, 1.19	1.17	1.03, 1.33	1.20	1.03, 1.38	0.007
ER+/PR+								
No. of cases	259		257		276		292	
Age-adjusted model	1.00	1.07	0.90, 1.27	1.22	1.03, 1.45	1.38	1.17, 1.64	<0.001
Multivariable model[b]	1.00	1.03	0.86, 1.24	1.18	0.97, 1.43	1.33	1.07, 1.65	0.005
ER−/PR−								
No. of cases	79		72		80		68	
Age-adjusted model	1.00	0.94	0.68, 1.30	1.09	0.79, 1.49	0.96	0.69, 1.33	0.96
Multivariable model[b]	1.00	0.95	0.68, 1.32	1.05	0.74, 1.49	0.84	0.56, 1.27	0.56
ER−/PR+								
No. of cases	18		16		13		15	
Age-adjusted model	1.00	0.90	0.46, 1.77	0.75	0.37, 1.54	0.90	0.45, 1.80	0.65
Multivariable model[b]	1.00	0.83	0.41, 1.68	0.64	0.29, 1.42	0.75	0.32, 1.79	0.42
ER+/PR−								
No. of cases	92		106		101		105	
Age-adjusted model	1.00	1.22	0.92, 1.61	1.22	0.92, 1.62	1.33	1.00, 1.77	0.06
Multivariable model[b]	1.00	1.23	0.92, 1.65	1.24	0.91, 1.71	1.38	0.97, 1.97	0.09

Abbreviations: CI, confidence interval; E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

[a] Reference category.

[b] Adjusted HR from Cox proportional hazards regression. HRs were adjusted for age (years; time scale), educational level (<12 or ≥12 years of schooling), region at baseline (7 categories), body mass index (weight (kg)/height (m)^2; <18.5, ≥18.5 and <25, or ≥25, as a time-dependent variable), height (cm; continuous), family history of breast cancer in a first- or second-degree relative (yes or no), age at menarche (years; continuous), age at first full-term pregnancy combined with number of livebirths (nulliparous, <30 years and 1–2 births, <30 years and ≥3 births, or ≥30 years and ≥1 birth), menopausal hormone therapy initiated before the previous year (yes or no; time-dependent variable), personal history of benign breast disease (fibrocystic breast disease, mastosis, or adenoma) or lobular carcinoma in situ (yes or no) at baseline, use of oral contraceptives at baseline (yes or no), lifetime duration of breastfeeding (0, <7, ≥7 and <12, or ≥12 months), frequency of Papanicolaou testing at baseline as an indicator of adherence to gynecologic screening (never, irregularly, every 4–5 years, every 2–3 years, or every year), physical activity (metabolic equivalents/week, in tertiles), smoking status at baseline (never, former, or current smoker), energy intake excluding alcohol (kcal/day, in quartiles), current use of phytoestrogen supplements (yes or no; time-dependent variable), and current use of vitamin/mineral supplements (yes or no; time-dependent variable).

Alcohol/Western pattern and breast cancer risk

The alcohol/Western dietary pattern was positively associated with breast cancer risk (Table 3). The multivariable hazard ratio for the highest quartile versus the lowest was 1.20 (95% confidence interval (CI): 1.03, 1.38; P = 0.007 for linear trend). After adjustment for alcohol intake, the association was not substantially modified, but it was weakened (for quartile 4 vs. quartile 1, multivariable hazard ratio (HR) = 1.14, 95% CI: 0.98, 1.33; P = 0.054 for linear trend).

The association between this pattern and breast cancer risk was statistically significant only for ER-positive (ER+)/PR-positive (PR+) tumors (for quartile 4 vs. quartile 1, multivariable HR = 1.33, 95% CI: 1.07, 1.65; P = 0.005 for linear trend). The test for homogeneity between ER+/PR+ tumors and ER+/PR-negative (PR−) tumors was not statistically significant, while the P value for all ER+ tumors versus ER-negative (ER−) tumors was 0.06.

Associations did not vary significantly across ductal (n = 1,619) and lobular (n = 396) tumors (P for homogeneity = 0.50). The multivariable hazard ratios (quartile 4 vs. quartile 1) were 1.17 (95% CI: 0.98, 1.40; P = 0.06 for linear trend) and 1.36 (95% CI: 0.96, 1.95; P = 0.09 for linear trend) for ductal and lobular tumors, respectively.

Table 4. Hazard Ratios for Invasive Postmenopausal Breast Cancer, by Quartile of Score for the Healthy/Mediterranean Dietary Pattern ($n = 65{,}374$), Among Women in the E3N-EPIC Cohort, France, 1993–2005

	Quartile of "Healthy/Mediterranean" Pattern Score							P for Linear Trend
	1 (HR = 1)[a]	2		3		4		
		HR	95% CI	HR	95% CI	HR	95% CI	
Total								
No. of cases	593	606		594		588		
Age-adjusted model	1.00	0.97	0.87, 1.09	0.94	0.84, 1.05	0.92	0.82, 1.03	0.12
Multivariable model[b]	1.00	0.95	0.85, 1.07	0.90	0.80, 1.01	0.85	0.75, 0.95	0.003
ER+/PR+								
No. of cases	262	273		273		276		
Age-adjusted model	1.00	0.99	0.83, 1.17	0.97	0.82, 1.15	0.97	0.82, 1.15	0.71
Multivariable model[b]	1.00	0.96	0.81, 1.14	0.92	0.78, 1.09	0.88	0.74, 1.05	0.13
ER−/PR−								
No. of cases	76	74		77		72		
Age-adjusted model	1.00	0.93	0.68, 1.28	0.96	0.70, 1.31	0.88	0.64, 1.22	0.50
Multivariable model[b]	1.00	0.90	0.65, 1.24	0.90	0.65, 1.24	0.78	0.56, 1.10	0.17
ER−/PR+								
No. of cases	14	15		14		19		
Age-adjusted model	1.00	1.02	0.49, 2.11	0.94	0.45, 1.96	1.23	0.62, 2.46	0.60
Multivariable model[b]	1.00	1.02	0.49, 2.12	0.92	0.43, 1.94	1.18	0.58, 2.42	0.71
ER+/PR−								
No. of cases	117	117		87		83		
Age-adjusted model	1.00	0.96	0.74, 1.24	0.70	0.53, 0.93	0.67	0.50, 0.88	0.001
Multivariable model[b]	1.00	0.95	0.74, 1.23	0.70	0.53, 0.92	0.65	0.49, 0.87	0.001

Abbreviations: CI, confidence interval; E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.

[a] Reference category.

[b] HRs were adjusted as described in Table 3.

A statistically significant interaction was observed between pattern score and body mass index ($P = 0.02$). In women with a body mass index less than 25, a positive association was observed (multivariable HR = 1.34, 95% CI: 1.13, 1.60; $P = 0.001$ for linear trend). In heavier women, the multivariable hazard ratio was 0.97 (95% CI: 0.76, 1.25; $P = 0.99$ for linear trend).

Healthy/Mediterranean pattern and breast cancer risk

The healthy/Mediterranean dietary pattern was inversely associated with breast cancer risk (for quartile 4 vs. quartile 1, HR = 0.85, 95% CI: 0.75, 0.95; $P = 0.003$ for linear trend) (Table 4). The association was not modified by further adjustment for alcohol intake (for quartile 4 vs. quartile 1, multivariable HR = 0.85, 95% CI: 0.75, 0.95; $P = 0.003$ for linear trend).

The association was statistically significant only for ER+/PR− tumors (for quartile 4 vs. quartile 1, multivariable HR = 0.65, 95% CI: 0.49, 0.87; $P = 0.001$ for linear trend), although nonsignificant results for other case groups pointed in the same direction (except for ER−/PR+, for which the number of cases was very small). The P value for homogeneity between ER+/PR− and ER+/PR+ tumors was 0.03, and the P value for homogeneity between ER+/PR− tumors and tumors of all other receptor statuses was 0.14.

Associations between this pattern and breast cancer risk did not vary significantly across ductal and lobular tumors (P for homogeneity = 0.74). Multivariable hazard ratios (quartile 4 vs. quartile 1) were 0.83 (95% CI: 0.72, 0.96; $P = 0.007$ for linear trend) and 0.86 (95% CI: 0.65, 1.15; $P = 0.30$ for linear trend) for ductal and lobular tumors, respectively.

There was a significant interaction between healthy/Mediterranean pattern scores and energy intake ($P = 0.03$) (Table 5). In women with energy intake below the median (2,037 kcal/day), the pattern was inversely associated with breast cancer risk (for quartile 4 vs. quartile 1, multivariable HR = 0.75, 95% CI: 0.63, 0.90; $P = 0.002$ for linear trend), while no association was observed among women with higher energy intake (for quartile 4 vs. quartile 1, multivariable HR = 0.93, 95% CI: 0.79, 1.10; $P = 0.29$ for linear trend).

Among women classified in the fourth quartile of the healthy/Mediterranean pattern, we compared mean intakes of foods between women with energy intakes above and below the median. Differences between these 2 subgroups were

Table 5. Hazard Ratios for Invasive Postmenopausal Breast Cancer by Quartile of Dietary Pattern Score, According to Body Mass Index or Daily Energy Intake ($n = 65,374$), Among Women in the E3N-EPIC Cohort, France, 1993–2005

	Quartile of Dietary Pattern Score							*P* for Linear Trend
	1 (HR = 1)[a]	2		3		4		
		HR	95% CI	HR	95% CI	HR	95% CI	
Alcohol/Western dietary pattern								
Body mass index[b] <25								
No. of cases	387		410		431		386	
Age-adjusted model	1.00	1.17	1.02, 1.34	1.33	1.15, 1.52	1.42	1.23, 1.64	<0.001
Multivariable model[c]	1.00	1.14	0.99, 1.32	1.27	1.09, 1.49	1.34	1.13, 1.60	0.001
Body mass index ≥25								
No. of cases	187		173		189		218	
Age-adjusted model	1.00	0.91	0.74, 1.11	1.01	0.82, 1.24	1.01	0.82, 1.23	0.70
Multivariable model[c]	1.00	0.88	0.71, 1.10	0.97	0.77, 1.21	0.97	0.76, 1.25	0.99
Healthy/Mediterranean dietary pattern								
Energy intake ≤ median[d]								
No. of cases	344		314		275		204	
Age-adjusted model	1.00	0.92	0.79, 1.08	0.89	0.76, 1.05	0.83	0.70, 0.99	0.03
Multivariable model[e]	1.00	0.89	0.77, 1.04	0.84	0.72, 0.99	0.75	0.63, 0.90	0.002
Energy intake > median[d]								
No. of cases	249		292		319		384	
Age-adjusted model	1.00	1.03	0.87, 1.22	0.97	0.82, 1.14	0.95	0.81, 1.11	0.37
Multivariable model[e]	1.00	1.03	0.87, 1.22	0.96	0.81, 1.14	0.93	0.79, 1.10	0.29

Abbreviations: CI, confidence interval; E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.
[a] Reference category.
[b] Weight (kg)/height (m)^2.
[c] HRs were adjusted as described in Table 3, with the exception of body mass index.
[d] Median energy intake was 2,037 kcal/day.
[e] HRs were adjusted as described in Table 3, with the exception of energy intake.

mostly due to "unhealthy" food items (i.e., foods associated with the alcohol/Western pattern, such as sandwiches, French fries, cakes, or processed meats), while intakes of "healthy" foods were quite similar (fruit, raw vegetables, cooked vegetables, olive oil, sunflower oil, or fish).

DISCUSSION

In the present study, 2 independent dietary patterns were found to be associated with postmenopausal breast cancer risk. The first, characterized by Western-type foods and alcohol, was associated with a high risk of ER+ tumors; the second, a Mediterranean pattern high in fruits, vegetables, fish, and olive and sunflower oils, was associated with reduced risk of breast cancer, especially for ER+/PR− tumors. However, associations were restricted to slim or normal-weight women for the alcohol/Western pattern and to women with low energy intake for the healthy/Mediterranean pattern.

The recent global approach to dietary patterns is particularly advantageous when planning dietary preventive strategies, as it considers diet in all its complex relations and potential interactions. Subjective definition of food groups included in factor analysis, along with labeling of identified patterns, has been described as a major limitation of this approach to standardizing patterns (6, 28, 29). However, major dietary patterns derived from factor analysis have been found to be stable over time and reproducible across populations (23, 30, 31). A Western pattern has been consistently described in several epidemiologic studies (5, 10, 23, 32, 33). Patterns associated with healthy behavior are less homogeneous, although most of them are described as diets high in fruits, vegetables, whole grains, fish, poultry, and salad dressing (10, 15, 32–34) or a Mediterranean diet rich in fruits, vegetables, and olive oil (35).

An important finding of the present study was the interaction with energy intake. There was no association between breast cancer risk and a high score in the healthy/Mediterranean pattern in cases of high energy intake due to concomitant intake of energy-dense Western foods. This may explain previously published negative findings regarding healthy or prudent diets (13, 14); a beneficial effect of such diets could be offset by simultaneous intake of "unhealthy" foods, that is, foods characteristic of a Western diet. This hypothesis was supported by our results regarding the higher increased intakes of "unhealthy" foods than of "healthy" foods among women with an above-median energy intake and classified in the fourth quartile of the healthy/Mediterranean pattern. Our findings indicate that a healthy/Mediterranean pattern is associated with a reduced risk of breast cancer only if energy intake remains within recommendations and if ''unhealthy'' foods are not consumed in large quantities.

It is difficult to determine which components of the healthy/Mediterranean pattern explain the inverse association with breast cancer risk. Although some components of fruits and vegetables, such as folates (36) and lignans (17), have been inversely associated with postmenopausal breast cancer risk in our cohort, a protective effect of fruits and vegetables has not been solidly established (5, 37, 38). Other candidates, although not established either, include n-3 fatty acids from fish and the overall balance between fatty acids (5).

The association between alcohol intake and breast cancer risk is convincing (5). However, the above-described alcohol/Western pattern was only moderately associated with alcohol intake (correlation coefficient = 0.36). Other components of the pattern, such as processed foods rich in *trans*-fatty acids, may participate in the association (39). The observed interaction with body mass index suggests that being overweight has an impact on postmenopausal breast cancer risk (5) that outweighs any dietary effect. Therefore, avoiding Western-type foods might reduce breast cancer risk only in normal-weight women.

In agreement with our findings, in a prospective study investigating the association between food patterns and breast cancer risk in Uruguay, Ronco et al. (11) found no heterogeneity according to histologic type. In contrast, it can be hypothesized that a hormonal pathway effect could be involved in the etiology of the association between dietary patterns and breast cancer, as investigators in several studies (40–46) have described heterogeneity of this association according to hormone receptor status. Indeed, results regarding prudent (40) or fruit- and vegetable-rich (41, 44) diets are inconsistent. Regarding components of the Western diet, a stronger association with alcohol intake was observed with ER+ tumors than with ER− tumors (46); a high fat intake has been associated with increased risk of ER+/PR+ tumors (42), although not consistently (43). In 1 intervention study, decreased fat intake was associated with risk reduction, mainly for ER+/PR− tumors (45).

Nevertheless, our study had some limitations. First, despite the use of a validated detailed questionnaire, some degree of misclassification of dietary intake is to be expected, as in similar dietary studies. In addition, we estimated the usual diet through a single dietary assessment; thus, we cannot rule out the possibility that some changes occurred in the diet during follow-up. Second, associations derived from an observational study may partly result from residual confounding, although we carefully adjusted all results for known breast cancer risk factors. Third, findings from cohorts of volunteers demand cautious extrapolation to the general population. Indeed, our population involved mostly teachers or their families—persons with a high level of education and health-consciousness, especially regarding dietary practices, but also a higher rate of breast cancer than the general French population (47). Finally, the reduced amount of total variance explained by our 2 dietary patterns may be a subject of concern, although it was comparable with that in other dietary studies (9, 48). The proportion of variance explained by the factors strongly depends on the number of food groups included in the principal-components analysis (48). The fewer food items (i.e., the broader the food groups), the higher the proportion of variance explained. We chose to consider a relatively high number of food groups in order to better comprehend the diversity and complexity of French food.

Strengths of our study include the prospective design, the study size, the availability of data on histologic type and hormone receptor type, careful adjustment for breast cancer risk factors, and validated dietary data. All cases of prevalent tumors at baseline were excluded so as to produce dietary patterns from cancer-free subjects. The median 9.7-year follow-up period provided a large latency period for potential disease occurrence.

In conclusion, our findings suggest that postmenopausal breast cancer risk in women may be influenced by dietary habits. Public health advice should emphasize the importance of increasing intake of foods associated with a healthy/Mediterranean pattern while maintaining energy intake within recommendations, in view of reducing the breast cancer burden. Avoidance of Western-type foods may reduce breast cancer risk in normal-weight women.

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Appendix Table. Food Groups and Food Items Introduced Into Factor Analysis, E3N-EPIC Cohort, France, 1993–2005

Food Group	Food Item(s) Included
Appetizers	Savory biscuits, olives, and nuts
Artificial sweeteners	Artificial sweeteners (mostly aspartame) added to hot drinks, yogurt, etc.
Biscuits	Sweet biscuits such as cookies and chocolate-coated biscuits
Breakfast cereals	Sweetened and unsweetened cereals
Butter, cream[a]	Salted and regular butter, clotted cream
Cakes	Cakes, sweet pies
Canned fish	Canned fish: anchovies, sardines, tuna
Canned fruit	Canned fruits in light syrup
Cheese	All cheeses except cottage cheese and yogurt
Chicory	Chicory as a hot drink (substitute for coffee)
Chocolate	Chocolate, chocolate bars
Chocolate beverages	Beverages consisting of mostly milk plus sweetened cocoa powder
Coffee	Espresso, instant coffee, coffee from a machine, etc.
Cooked vegetables	Cooked vegetables
Crisp bread	Manufactured rusks
Crustaceans	Crustaceans and mollusks
Dairy-based sweet puddings	Cream or milk desserts, rice or semolina puddings, ice cream
Eggs	Hard-boiled eggs, omelettes, etc.
Fish	Fresh or deep-frozen fish
French fries	Homemade, frozen, or fast-food deep-fried potatoes
Fruits	All fresh and preserved fruits except nuts, olives, and juices
Ham[b]	Cured and cooked ham
High-alcohol beverages	Spirits, vodka, gin, whisky, aniseed beverages, and cocktails
High-fat dairy products	Full-fat milk, full-fat yogurt and cottage cheese
Juices	Homemade or commercial pure fruit juice
Low-alcohol beverages	Beer and cider
Low-fat dairy products	Half-fat and semi-skimmed milk, low-fat yogurt
Margarine[a]	Margarine used as a spread and for home cooking
Sugar, marmalade, honey	Added sugar, honey; homemade and commercial jam and marmalade
Mayonnaise	Homemade or manufactured mayonnaise
Meat	Pork, beef, veal, mutton, lamb
Mineral water	Bottled mineral water, spring water (plain or sparkling)
Offal	Liver, kidney, tongue, etc.
Olive oil[a]	Olive oil used for cooking and dressings
Other fats[a]	Goose, duck fat
Croissant-like/Danish pastries	Breakfast pastries such as croissants
Pizza, pies	Pizza, savory tarts and pies

Table continues

Appendix Table. Continued

Food Group	Food Item(s) Included
Potatoes	Potatoes, except French fries
Poultry and rabbit	Chicken, turkey, duck, goose, and rabbit
Processed meat[b]	All processed meats (sausages, pâté, etc.) except ham
Pulses	Dried peas, lentils
Raw vegetables	Raw vegetables
Rice, pasta, semolina	Rice, pasta, wheat or corn semolina
Salad dressing	Manufactured salad dressing
Salad dressing—light	Low-fat manufactured salad dressing
Sandwiches	Sandwiches, including hamburgers
Soft drinks—diet	Soda and fruit beverages (except pure fruit juice) with artificial sweeteners
Soft drinks—regular	Soda and fruit beverages (except pure fruit juice)
Soup	Soups and broths (homemade or commercial)
Sunflower oil	Sunflower oil used for cooking and dressings
Sweets	Sweets, assorted candy, caramels, toffee, gum, liquorice
Tap water	Tap water
Tea	Hot tea
Other vegetable oil[a]	Oils used for cooking and dressings, except olive oil and sunflower oil
White bread	White bread, toast
Whole-grain bread	Whole-grain bread
Wine	Wine (red and white), champagne

Abbreviations: E3N, Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale; EPIC, European Prospective Investigation into Cancer and Nutrition.

[a] Various types of seasoning and cooking fats were studied separately because of large regional differences, as well as differences in perception as healthy or unhealthy.

[b] Ham was studied separately from other processed meats, as it is often part of a low-energy diet, unlike other processed meats such as sausage or pâté.