Mediterranean Diet and Breast Density in the Minnesota Breast Cancer Family Study

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Mediterranean populations' lower breast cancer incidence has been attributed to a traditional Mediterranean diet, but few studies have quantified Mediterranean dietary pattern intake in relation to breast cancer. We examined the association of a Mediterranean diet scale (MDS) with mammographic breast density as a surrogate marker for breast cancer risk. Participants completed a dietary questionnaire and provided screening mammograms for breast density assessment using a computer-assisted method. Among 1,286 women, MDS was not clearly associated with percent density in multivariate linear regression analyses. Because of previous work suggesting dietary effects limited to smokers, we conducted stratified analyses and found MDS and percent density to be significantly, inversely associated among current smokers ($\beta = -1.68$, $P = 0.002$) but not among nonsmokers ($\beta = -0.08$, $P = 0.72$; P for interaction = 0.008). Our results confirm a previous suggestion that selected dietary patterns may be protective primarily in the presence of procarcinogenic compounds such as those found in tobacco smoke.

INTRODUCTION

Breast cancer is less frequent in Mediterranean populations than in northern Europeans (1). The lower incidence of breast cancer in Mediterranean populations has been attributed to a traditional Mediterranean diet, commonly characterized by high consumption of foods of plant origin, relatively low consumption of red meat, and high consumption of olive oil (1). Indeed, Trichopoulou et al. (1) estimated that approximately 15% of the incidence of breast cancer could be prevented if the populations of highly developed Western countries could shift to a traditional Mediterranean diet. Few studies, however, have quantified intake of a Mediterranean dietary pattern in relation to either breast cancer risk or surrogate markers of risk.

Breast density, the percentage of total breast area with a mammographically dense appearance, is a useful surrogate marker for breast cancer risk in epidemiologic studies (2). It is strongly associated with breast cancer risk (3,4) is modifiable (5–7), and changes in density have recently been associated with changes in risk (8). Understanding whether MDS and breast density are associated could have implications for breast cancer prevention. The objective of this analysis, therefore, was to examine the association of a Mediterranean diet with breast density.

MATERIALS AND METHODS

Study Sample

The study sample included participants in the Minnesota Breast Cancer Family Study (9). The Minnesota Breast Cancer Family Study was initiated in 1990 as a follow-up to a 1944 family study that included 544 breast cancer probands ascertained at the Tumor Clinic of the University of Minnesota Hospital. Eligible participants for the follow-up study included sisters, daughters, nieces, and granddaughters of the original probands, and spouses of male first- and second-degree relatives. Upon enrollment, women completed telephone interviews and dietary questionnaires. Women at least 40 years of age were also asked to provide a recent mammogram.

Of 9,084 women in the original cohort, we excluded those who were interviewed through a surrogate ($N = 2{,}903$), who did not return a food frequency questionnaire (FFQ; $N = 2{,}685$), who reported an infeasible energy intake (<600 kcal/day or >5,000 kcal/day; $N = 224$), or who left at least 30 missing responses on the FFQ ($N = 125$). We additionally excluded 1,710 women without mammographic images assessed for breast density and 53 women with a breast cancer diagnosis at enrollment into the follow-up study, leaving 1,384 women available for these analyses.

The project was conducted in accordance with the ethical standards of the Mayo Clinic and the Fox Chase Cancer Center and was approved by the institutional review boards at both institutions.

Data Collection

Data collection methods for the study have been described previously (9,10). Briefly, telephone interviews were completed for all available female relatives aged 18 yr and older. The collected data included history of cancer, marital status, education, menstrual and pregnancy history, oral contraceptive use, physical activity, and history of smoking and alcohol intake. Menopausal status was assessed by the response to a question of whether the participant had a menstrual period within the last year, excluding periods brought on by hormones. After the telephone interview, each subject additionally received in the mail a body measurement questionnaire designed to elicit measures of height, weight, and circumferences of the waist (2 inches above the umbilicus) and hip (maximal protrusion) (11). To assess usual food and beverage intake over the past year, participants were asked to complete a 153-item semiquantitative food frequency questionnaire adapted from Willett et al. (12), with frequency response options for each food item ranging from "never or less than once per month" to "six or more times per day."

Breast Density Assessment

Women aged 40 years or older were asked to provide a recent mammogram to verify their breast cancer status and to allow estimation of breast density. If no mammogram had been taken in the previous year (2 yr if <50 yr of age at time of interview), they were instructed to obtain a new one through their personal physician. Percent breast density was estimated using the semi-automated breast density method developed by Dr. Martin Yaffe and colleagues at the University of Toronto (13). The method involves dividing the mammographic image into a distribution of gray values, then setting two thresholds: one that differentiates the edge of the breast from the rest of the mammogram and the other that identifies the border of the region(s) in the pixel distribution representing the radiographically dense tissue in the image. Higher gray value pixels are thought to be a result of fibroglandular tissue, and lower gray values a result of fat tissue. Dividing the pixels related to fibroglandular tissue by the total number of pixels making up the entire breast allowed for an estimate of percent breast density. This measure has consistently been associated with breast cancer (14,15), and has high intraobserver correlation (>0.95 for our reader on over 700 mediolateral images).

Statistical Analyses

We quantified intake of a Mediterranean diet using a 9-item Mediterranean diet scale (16,17). For each of the 6 items considered beneficial [vegetables, legumes, fruits and nuts, cereals, fish, and monounsaturated:saturated (M:S) fat ratio], women with intake above the median were assigned a value of 1, whereas those with intake below the median were assigned a value of 0. For two items considered detrimental (meat, dairy), women with intake above the median received a score of 0, whereas those with intake below the median were assigned a value of 1. For alcohol, women with intake between 5 and 25 g per day received a value of 1, and all others received a value of 0. The resulting item-specific values were then summed to create an overall diet score ranging from 0 to 9.

We compared distributions of sociodemographic, lifestyle, reproductive, and dietary factors across MDS categories using previously defined cut points of 0–3, 4–5, and 6–9 (16). Categorical variables were compared using the Cochran-Mantel-Haenszel test statistic. Continuous variables were compared using analysis of variance. We used linear regression models, adjusting for age as a covariate, to examine associations of these same factors with percent breast density.

We assessed the association of MDS with percent density, after adjustment for covariates, using multivariate linear regression analysis. We used generalized estimating equations to account for autocorrelation resulting from including women from the same family (18,19). MDS was modeled both as a continuous variable and as a categorical variable, with the 0–3 category as the referent group. Variables were included as potential confounders in final models if they were significantly associated with either MDS or percent breast density. Final multivariate models included 1,286 women with complete covariate data and adjusted for age, total energy intake, menopausal status, education (<high school, high school graduate, some college, college graduate+), years of hormone replacement use (0, 1–5, 6+), body mass index (BMI), waist-to-hip ratio (WHR), age at menarche, a variable combining parity and age at first live birth (nulliparous, 1–2 children with age at first live birth >20 yr, 1–2 children with age at first live birth ≤20 yr, 3+ children with age at first live birth >20 yr, 3+ children with age at first live birth ≤20 yr), alcohol intake (g/day), and relation to proband

TABLE 1
Distribution of covariates by Mediterranean diet score (MDS) category and age-adjusted associations with breast density among 1,286 participants in the Minnesota Breast Cancer Family Study[a]

	Mediterranean Diet Score[b]			Percent Breast Density		
Variable	0–3 ($N = 457$)	4–5 ($N = 520$)	6–9 ($N = 309$)	Beta[c]	SE	P Value
Mean (± SD) age (yr)	54.5 (12.2)	57.8 (11.6)	59.4 (10.9)[d]	–0.5	0.04	<0.0001
Level of education (%)						
< High school	13	10	10	Referent	—	—
High school graduate	43	41	28	1.7	1.2	0.2
Some college	28	33	38	1.8	1.2	0.2
College graduate+	16	16	24[d]	4.6	1.3	0.003
Mean (±SD) BMI (kg/m^2)	27.3 (6.4)	27.0 (5.1)	26.6 (5.5)	–1.2	0.08	<0.0001
Mean (±SD) WHR	0.84 (0.07)	0.83 (0.08)	0.82 (0.08)	–5.7	0.6	<0.0001
Mean (±SD) age at menarche (yr)	13.0 (1.6)	12.9 (1.4)	12.9 (1.5)	1.1	0.3	<0.0001
Parity and age at first live birth (%)						
Nulliparous	10	12	10	Referent	—	—
1–2, >20 yr	25	25	27	–3.3	1.6	0.03
1–2, ≤20 yr	8	7	6	–7.7	1.9	<0.0001
3+, >20 yr	34	38	38	–6.3	1.6	<0.0001
3+, ≤20 yr	23	19	19	–8.9	1.7	<0.0001
Postmenopausal (%)	63	76	79[d]	–6.4	1.4	<0.0001
Hormone replacement use (%)						
0 yr	58	52	45	Referent	—	—
1–5 yr	23	24	26	–0.1	1.0	0.96
≥ 6yr	20	24	29[e]	3.4	1.1	0.002
Smoking status (%)						
Never	49	58	59	Referent	—	—
Former	30	30	34	0.7	0.9	0.4
Current	20	12	7[d]	–0.05	1.4	0.97
Relation to proband						
Married in	34	38	38	Referent	—	—
Second-degree relative	46	46	45	1.6	0.9	0.07
First-degree relative	19	17	17	2.6	1.3	0.05
Mean (±SD) energy intake (kcal)	1,803 (618)	2,010 (655)	2096 (629)[d]	–0.002	0.001	<0.0001
Mean (±SD) servings/wk						
Vegetables	13.8 (9.1)	22.2 (12.6)	31.9 (15.1)[d]	0.0	0.04	0.99
Legumes	2.1 (1.7)	3.4 (3.2)	4.9 (3.3)[d]	0.08	0.18	0.65
Fruits and nuts	13.2 (9.4)	21.2 (11.5)	28.9 (14.2)[d]	0.04	0.04	0.39
Cereals	5.7 (6.6)	9.9 (8.7)	12.4 (8.0)[d]	–0.11	0.12	0.37
Fish	0.8 (0.8)	1.4 (1.7)	2.3 (1.8)[d]	0.27	0.26	0.31
Dairy	25.3 (13.7)	24.3 (13.4)	19.8 (11.8)[d]	0.03	0.08	0.70
Meats	9.7 (6.1)	9.2 (5.4)	8.6 (5.2)[f]	–0.27	0.09	0.002
Mean (±SD) alcohol intake (g)	4.9 (11.5)	4.2 (9.0)	4.2 (6.4)	0.11	0.05	0.02
Mean (±SD) ratio of monounsaturated:saturated fat	1.1 (0.2)	1.2 (0.2)	1.2 (0.2)[d]	–1.5	2.7	0.57
Mean (±SD) percent density	24.1 (16.6)	21.5 (15.9)	22.2 (14.5)[f]	—	—	—

[a]Abbreviations are as follows: BMI, body mass index; WHR, waist-to-hip ratio.

[b]Number of MDS categories (out of 9) for which the subject was assigned a positive value.

[c]Betas represent absolute estimated mean change in percent breast density per unit increment in continuous variables (age, BMI, age at menarche, dietary intake) but per 0.1 increment in WHR. For nominally coded predictor variables, betas represent absolute mean change in percent breast density relative to referent category. Associations with age are unadjusted, whereas all other associations are adjusted for age.

[d]$P < 0.0001$, assessing the association between Mediterranean diet score and covariates; P values were determined by Cochran-Mantel-Haenszel test statistic for categorical variables or by analysis of variance of continuous variables.

[e]$P < 0.01$.

[f]$P < 0.05$.

TABLE 2
Multivariate-adjusted betas for association of Mediterranean Diet Score (MDS) with percent breast density[a]

Variable	N	Mediterranean Diet Score Beta	SE	P Value	Revised Mediterranean Diet Score[b] Beta	SE	P Value
All women	1,286						
MDS (continuous)		–0.27	0.20	0.17	–0.33	0.20	0.09
MDS category							
457	Referent	—	—	Referent	—	—	
4–5	520	–1.32	0.87	0.13	–1.22	0.92	0.18
6–9	309	–0.54	0.92	0.56	–1.40	0.98	0.15
Nonsmokers	1,110						
MDS (continuous)		–0.08	0.22	0.72	–0.12	0.21	0.58
MDS category							
0–3	365	Referent	—	—	Referent	—	—
4–5	457	–1.15	0.92	0.21	–0.61	1.00	0.54
6–9	288	0.13	1.02	0.90	–0.58	1.08	0.59
Current smokers	176						
MDS (continuous)		–1.68	0.55	0.002	–1.90	0.55	0.0005
MDS category							
0–3	92	Referent	—	—	Referent	—	—
4–5	63	–1.88	2.09	0.37	–4.26	2.31	0.07
6–9	21	–7.17	2.77	0.01	–8.07	2.82	0.004

[a]Abbreviations are as follows: BMI, body mass index; WHR, waist-to-hip ratio. Betas adjusted for age, total energy intake, menopausal status, education, years of use of hormone replacement, BMI, WHR, age at menarche, parity and age at first live birth (combined variable), alcohol intake, and relation to proband. Betas represent absolute estimated mean change in percent breast density per unit increment in continuous MDS or absolute estimated mean change in percent density relative to 0–3 category for categorized MDS.

[b]Revised so that for alcohol component of MDS, individual receives a score of 1 for 0 g/day of alcohol rather than for 5–25 g/day as in original scale and a score of 0 otherwise.

(first-degree relative, second-degree relative, married in). Categorical covariates were coded using dummy variables to allow for nonlinear associations across categories. Other variables evaluated as confounders but not included in final models were smoking status, age at menopause, years of use of oral contraceptives, history of hysterectomy, and history of oophorectomy.

We examined the possibility of effect modification by menopausal status by examining P values for interaction, estimated from a model including a Variable $\times$ Menopausal Status interaction term. We used the same strategy to assess possible effect modification by relation to proband (first-degree relative, second-degree relative, married in) and smoking status (current vs. nonsmoker).

RESULTS

Among 1,286 women with complete covariate data, mean (SD) age was 57 (12) yr, 72% were postmenopausal, mean (SD) BMI was 27.0 (5.7) kg/m^2, and mean (SD) percent breast density was 22.6 (15.9). Women with higher MDS tended to be older and better educated, had lower WHR, and were less likely to be current smokers (Table 1). MDS was also associated with postmenopausal status, use of hormone replacement, and lower breast density, probably because of its association with age. Not surprisingly, higher MDS was associated with higher intake of vegetables, legumes, fruits and nuts, cereals, fish, and with higher M:S fat ratio but with lower intake of meats and dairy.

In age-adjusted analyses, breast density was associated with higher education, age at menarche, age at first live birth, alcohol intake, and being a first-degree relative to the breast cancer proband. It was inversely associated with BMI, WHR, parity, postmenopausal status, hormone replacement use, and intake of energy and meats (Table 1).

In fully adjusted models, MDS was not associated with percent density in analyses including all women (Table 2). The association varied by smoking status, however. Although MDS was not associated with percent density among nonsmokers, it was significantly, inversely associated with percent density among current smokers (β = –1.68, P = 0.002; P for interaction = 0.008). To further explore this finding, we examined associations of percent density with the individual components of MDS within current smokers. Vegetables, legumes, and cereals were the individual components of the MDS that were most strongly inversely related to percent density within this subgroup (Table 3).

Previous investigations have hypothesized an anticancer effect for resveratrol, found in red wine and selected other foods. When we revised the alcohol component of the MDS to consider only g/day of alcohol from red wine, however, results were not appreciably different (not shown). In addition, because alcohol is known to increase breast cancer risk, we also revised the MDS such that women received a score of 1 if they consumed zero g/day of alcohol, instead of 5–25 g/day, and a score of 0 otherwise. Revising the alcohol component of the MDS in this way strengthened the inverse association between the MDS and percent density among all women, as well as among current smokers, although the association among all women remained nonsignificant (Table 2). We saw no effect modification by menopausal status or family history of breast cancer.

TABLE 3
Multivariate-adjusted betas for association of individual components of the Mediterranean Diet Score with percent breast density among current smokers[a]

Diet Component	Beta[b]	SE	P Value
Vegetables	–4.92	1.98	0.01
Legumes	–4.49	2.22	0.04
Fruits	–2.38	1.97	0.23
Cereals	–6.60	2.02	0.001
Fish	–0.96	2.18	0.66
Monounsaturated:saturated fat ratio	–3.29	1.79	0.07
Dairy	1.42	2.19	0.52
Meat	0.29	2.24	0.90
Alcohol	1.93	1.76	0.27

[a] $N = 176$. Abbreviations are as follows: BMI, body mass index; WHR, waist-to-hip ratio. Betas adjusted for age, total energy intake, menopausal status, education, years of use of hormone replacement, BMI, WHR, age at menarche, parity and age at first live birth (combined variable), and relation to proband. All models except for alcohol additionally adjusted for alcohol intake.

[b] Betas represent absolute estimated mean change in percent breast density for above vs. below median for all items except alcohol. Beta for alcohol represents absolute estimated mean change in percent density for intake of 5–25 g/day vs. all others.

DISCUSSION

In this first study to examine a Mediterranean diet in relation to breast density, we found evidence for an inverse association that appeared to be limited to current smokers. The association was strengthened slightly when the alcohol component of the MDS, which favors moderate consumption over no or excessive consumption, was revised to favor no consumption over any consumption.

Specific factors in the Mediterranean diet that may be relevant in protecting against breast cancer include its high content of selenium, glutathione, fiber, polyphenols, and vitamins E and C and its favorable n-6/n-3 fatty acid ratio (20). Olive oil or oleic acid has also been of particular interest for its potential role in protecting against peroxidation and inducing transcriptional repression of Her-2/neu (21,22). Previous breast density studies, however, have not offered convincing evidence for associations with individual components of a Mediterranean diet. A previous analysis of food and nutrient intake and breast density in the same sample of participants from the Minnesota Breast Cancer Family Cohort (23) showed associations of percent breast density with alcohol and vitamins C and E and inverse associations for saturated fat and dairy intake among premenopausal women—with the exception of alcohol, all contrary to expectation. Among postmenopausal women, whereas percent density was associated with white wine intake, it was inversely associated with intake of red wine, known to be a good source of polyphenols such as resveratrol. This previous analysis, however, used a subjective estimate of percent density determined by an experienced radiologist. Other breast density studies have reported no associations for fruits (24), nuts and seeds (25), or cereals (24,25), and mixed findings regarding intake of vegetables (24,26), fish (24,26), dairy (24,27), and monounsaturated fatty acids or olive oil (27–30).

A Mediterranean diet effect may be more pronounced when quantified as an overall dietary pattern than when examined in terms of its specific components. Among current smokers in our sample, only 3 of the 9 MDS components were statistically significantly associated with breast density, whereas 6 of the 9 components were associated in the expected direction. However, studies that have examined overall (rather than components of) Mediterranean diet have been, in fact, also suggestive of an inverse association with breast cancer risk. In one 6-month intervention study, women who were randomized to receive instruction in preparing a traditional Mediterranean diet, designed to increase their intake of whole grains, legumes, vegetables, fish, and olive oil, exhibited a significant, >40% decrease in endogenous estrogen levels relative to the control group (31). Other studies have examined a Mediterranean diet pattern in relation to breast cancer. In the Nurses' Health Study, women in the highest quintile for the MDS had a risk for estrogen receptor negative breast cancer of 0.8 (trend $P = 0.03$) relative to women in the lowest quintile (32). The MDS was also inversely, albeit not significantly, associated (odds ratio ≈ 0.6) with breast cancer risk in a small case-control study including primarily BRCA gene mutation carriers (33). In another study that used factor analysis to identify dietary patterns in women in northern Italy, breast cancer risk was inversely related to intake of a "salad vegetables" pattern, characterized by intake of raw vegetables and olive oil (34).

Others have remarked on the paradoxical role of the alcohol component of the Mediterranean diet, noting its cardiovascular benefits but, simultaneously, its risk with respect to cancer (35). Because alcohol is a known risk factor for breast cancer, we calculated a revised MDS in which women received a point for no alcohol rather than for moderate alcohol consumption.

Although the association remained nonsignificant, revising the score resulted in a slight strengthening of the inverse association between the MDS and breast density. Our results suggest that the breast health benefits of a Mediterranean diet may be enhanced if the diet is modified to minimize alcohol intake. Revising the MDS to consider alcohol only from red wine rather than from all sources did not change results.

We observed an inverse association of the MDS only among current smokers. Although our observation is based on a relatively small number of smokers, it is consistent with previous findings in this population for fruit-vegetable-cereal and salad-sauce-pasta/grain dietary patterns identified from principal components analysis (36). It is also consistent with the finding of inverse associations of "prudent" and "southern" dietary patterns with breast cancer only among smokers in other studies (37,38). Ahn et al. (39) recently reported an increase in breast cancer risk with the lower activity glutathione S-transferase A1 (GSTA1) *B/*B genotype but only among women with lower cruciferous vegetable consumption and among current smokers. Although we did not assess GSTA1 genotype for this analysis, our observation might reflect a protective effect of the Mediterranean diet that is masked if individuals are not distinguished by genotype but more visible in the presence of carcinogenic compounds found in tobacco smoke. Together, these findings suggest that genetic analyses may clarify mechanisms underlying interactions between dietary intake and smoking, but also that diet modification merits further investigation as a preventive measure among smokers.

Nonparticipation in the mammography phase of the study may have biased estimates of the association between dietary intake and breast density. A previous analysis (23) indicated that women at higher risk for dense breasts and women with a more health-conscious lifestyle were more likely to participate in this component of the study. Overrepresentation of such women in our sample likely biased our estimates toward the null. Strengths of the study include its relatively large sample size and its use of quantitative, highly reliable estimates of breast density.

Overall, our results indicate an inverse association of a Mediterranean diet with breast density, although any protective effect may be limited to smokers. Our findings suggest that a Mediterranean diet is protective primarily in the presence of procarcinogenic compounds such as those found in tobacco smoke. Our findings also raise the question of whether other subsets of the population can be identified who might benefit more from diet modification as a means of reducing breast cancer risk.

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