Dietary Patterns and Risk of Breast Cancer in the ORDET Cohort

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Abstract

The aim of this study was to evaluate the association between dietary patterns and risk of developing breast cancer in an Italian cohort. Women volunteers were recruited from 1987 to 1992 from residents in Varese province, northern Italy, an area covered by a cancer registry. Participants completed a semiquantitative food frequency questionnaire, and anthropometric and other data were collected systematically. Using nutritional data from 8984 women with an average follow up of 9.5 years and 207 incident cases of breast cancer, we conducted an exploratory factor analysis to identify major dietary patterns. Four dietary patterns, which explained 30% of the variance, emerged: *salad vegetables* (mainly consisting of raw vegetables and olive oil); *western* (mainly consisting of potatoes, red meat, eggs and butter); *canteen* (pasta and tomato sauce); and *prudent* (cooked vegetables, pulses, and fish, with negative loading on wines and spirits). After adjustment for potential confounders, only the *salad vegetables* pattern was associated with significantly lower (34–35%) breast cancer incidence (RR = 0.66, $CI_{95\%}$ = 0.47±0.95 comparing highest with lowest tertile) with a significant linear trend (P = 0.016). Women with body mass index <25 had an even greater risk reduction in the highest tertile of the *salad vegetables* pattern (>50% less risk than the lowest tertile, RR = 0.39, $CI_{95\%}$ = 0.22–0.69) with a significant trend (P = 0.001); whereas women with body mass index ≥25 had no protective effect for the consumption of *salad vegetables*. These findings suggest that a diet rich in raw vegetables and olive oil protects against breast cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(4):567–572)

Introduction

Breast cancer is the most common cancer in women in almost all developed countries (1). However, incidence rates vary markedly between countries and are subject to change in migrant populations; it has therefore been suggested that diet is an important determinant of this disease (2). In fact, epidemiological studies have shown that the risk of breast cancer varies with diet (3). However, people eat many different foods containing various combinations of nutrients and nonnutrients. It is often difficult, therefore, to identify a single nutrient or food item as related to the risk of a disease. The corollary is that examining single aspects of diet (individual nutrients, food items, or food groups) may result in missing an association between diet and disease.

Exploratory factor analysis has recently emerged as an additional method of examining the relationship between diet and the risk of disease (4, 5). It is a statistical method that analyzes the covariate structure of a range of variables to identify a restricted number of underlying patterns (6). The method was first developed and applied in the field of psychology, but has been extended to etiological studies on coronary heart disease (6, 7), diabetes (8), colon cancer (9–11), and more recently other cancers (12–15).

When applied to the analysis of food group consumption, exploratory factor analysis identifies patterns of dietary behavior that represent a broad picture of food and nutrient consumption, and which may be better able to predict disease risk than specific foods or nutrients (6). Several studies have suggested that dietary patterns derived from factor analysis can predict disease risk and mortality (5).

In the present study, we investigated whether particular patterns of food consumption, rather than the consumption of a certain type or group of foods, were associated with the development of breast cancer. In particular, we assessed the association between dietary patterns and breast cancer using exploratory factor analysis in women of the ORDET cohort.

Materials and Methods

Study Subjects. Between June 1987 and June 1992, 10,786 healthy women, aged 34–70 years, residents of Varese province, northern Italy, were recruited to a prospective study on hormones, diet, and breast cancer risk (the ORDET study). The women were volunteers

from the general population who heard about the study at public meetings, through radio, television and newspaper advertising, and at breast cancer prevention/early diagnosis units. All participants signed an informed consent form. The Ethical Review Board of the Italian National Cancer Institute of Milan approved the study. Women with a history of cancer, bilateral ovariectomy, chronic or acute liver disease, and receiving hormone therapy in the 3 months before recruitment to the study, were excluded.

Information on menstrual and reproductive history, and lifestyle characteristics were collected by trained nurses at baseline. Height, weight, waist and hip circumferences, and other anthropometric measurements were recorded by the nurses using a standardized protocol.

A self-given semiquantitative food frequency questionnaire (FFQ), a detailed description of which is given elsewhere (16), was also completed at enrollment. After completion, the FFQ was reviewed by a nurse with the participant to fill in any missing items.

Cancer incidence information, available from the local cancer registry (Lombardy Cancer Registry) was linked to the ORDET file to identify breast cancer cases incident up to December 1999. The Lombardy Cancer Registry is characterized by high completeness and quality. Less than 2% of breast cancer cases are known to the registry by death certificate only and 96.3% of cases are confirmed histologically or cytologically. The ORDET file was also linked with the Varese residents file to check vital status.

After excluding 37 women diagnosed with cancer before enrollment, 4 women with *in situ* breast cancer carcinoma diagnosed after enrollment, and 10 women lost to early follow-up, 10,735 ORDET women were followed. An additional 1,552 women were excluded from the analysis who did not fill in the FFQ because it was not available at the beginning of recruitment. We also excluded women if the ratio of total energy intake (determined from the questionnaire) to calculated basal metabolic rate (17) was at either extreme of the distribution (cut-offs were the first and last half percentiles), to reduce the impact of implausible extreme values on the analysis. After these exclusions, 8,984 women including 207 incident cases of invasive breast cancer remained, for a total of 81,634 person-years of follow-up.

Food Grouping and Factor Analysis. The 107 food items contained in the ORDET dietary FFQ were first grouped into 34 predefined *food groups* based on similarities in nutrient profile and culinary usage. We classified a single food item as a *food group* if its composition differed substantially from that of other food groups (*e.g.*, eggs or pizza). Furthermore, if we suspected that a given food item was representative of a particular dietary habit if consumed raw and another dietary habit if consumed cooked, we classified the cooked and raw items separately (examples: leaf vegetables, tomatoes, and carrots).

Exploratory factor analysis was then applied to reduce the food groups to small number of factors that explained the maximum fraction of the variance. An orthogonal rotation procedure (18), varimax rotation, was performed to simplify the factor structure and render it more easily interpretable. To determine the number of factors to retain (four factors), we used the Scree test (19). The next step was to name the factors that emerged. Food groups with an absolute loading greater than 0.25 on a given factor were considered to contribute importantly to that factor; factors were thereby interpreted as dietary patterns and named after the food groups having the highest loadings. Food groups with a positive loading contributed directly to a dietary pattern and food groups with negative loading were inversely associated with a dietary pattern. Factor loadings can be considered correlation coefficients between food groups and dietary patterns and take values between −1 and +1.

We next calculated the factor score for each dietary pattern for each woman. Briefly, factor scores are formed by standardizing each variable (food group) to have zero mean and standard deviation of 1, weighting it with a corresponding factor score coefficient, and then summing the terms. Thus, for each woman, the factor score indicated the degree to which her diet conformed to one of the dietary patterns identified. A high factor score for a given dietary pattern indicated high intake of the food groups constituting that food pattern, and a low score indicated low intake of those food groups.

Risk Analysis. Factor scores were used (*a*) to assess the associations of the dietary patterns with risk factors for breast cancer and (*b*) to assess the risk of breast cancer itself. For (*a*), we calculated the mean factor score for each dietary pattern according to categories of breast cancer risk factors [body mass index (BMI), age, education, parity, height, age at menarche, smoking, and menopausal status].

For (*b*), we estimated the relative risks (RRs) and 95% confidence interval (CI$_{95\%}$) for developing breast cancer by constructing Cox proportional hazard regression models that included tertiles of all four dietary factor scores in the model and used the lowest tertile as reference category, adjusting for energy intake and age (*Model 1*). *Model 2* included other potential confounders in addition to energy intake and age, specifically: years of education, parity, height, age at menarche, smoking, and menopausal status.

Because we found, unexpectedly, that BMI was positively associated with the first factor that emerged from the factor analysis (*salad vegetables*), we divided this potential effect modifier into two categories, <25 and ≥25 (WHO cut-off for overweight) and performed the Cox analysis stratified by BMI (*Model 3*).

As test for trend, we used a likelihood ratio test comparing models that included and omitted the variable whose value was the number of the tertile to which the subject belonged. All analyses were performed using the STATA statistical package (7.0).

Results

Four factors or dietary patterns, which explained 30% of the variance in the food groups, were identified by the factor analysis. The first dietary pattern was characterized by greatest loadings on raw vegetables and olive oil; it was therefore designated *salad vegetables*. The second pattern, characterized by high loadings on potatoes, red meat, eggs, butter, seed oil (as added fat) and cakes was

designated *western*. The third pattern, *canteen*, was characterized by high consumption of pasta, tomato sauce, and wine. The last pattern, *prudent*, was characterized by high consumption of cooked vegetables, rice, poultry, fish, and low consumption of alcohol (Table 1).

Table 2 shows the mean standardized factor score for each dietary pattern categorized according to risk factors (BMI, age, education, parity, height, age at menarche, smoking, and menopausal status). BMI was strongly associated with the *salad vegetables* and *canteen* dietary patterns. Older women had high scores for the *canteen* pattern. Women with no children had high scores for the *canteen* pattern and low scores for the *western* pattern. Tall women had high scores for the *western* dietary pattern, as did younger women. Smokers had high scores for the *prudent* pattern, while ex-smokers had low scores for the *salad vegetables* pattern. Women in menopause had low scores for the *prudent* and *western* patterns and high scores for the *canteen* pattern.

Table 1. Food group loadings for the four dietary patterns identified by factor analysis

Food group	Factor 1 (Salad vegetables)	Factor 2 (Western)	Factor 3 (Canteen)	Factor 4 (Prudent)
Potatoes	0.06	0.53	0.17	0.29
Mixed vegetables in salad	0.72	−0.01	−0.05	0.04
Leaf vegetables —cooked	0.30	0.11	0.11	0.45
Leaf vegetables —raw	0.78	−0.02	−0.03	0.03
Tomatoes —cooked	0.00	0.06	0.81	0.02
Tomatoes —raw	0.71	0.04	0.06	0.00
Other fruiting vegetables	0.30	0.10	0.35	0.41
Carrots—raw	0.51	−0.04	−0.06	0.31
Carrots—cooked	0.14	0.06	0.04	0.57
Pulses	0.13	0.06	0.36	0.39
Fruit	0.23	−0.02	−0.12	0.24
Milk	0.04	0.21	−0.11	0.22
Yoghurt	0.18	0.05	−0.19	0.28
Cheese	0.20	0.24	0.06	−0.03
Pasta	−0.05	0.06	0.82	0.01
Rice	−0.08	0.21	0.23	0.43
Other pasta (*e.g.*, ravioli)	−0.18	0.50	0.03	0.10
Bread	0.03	0.16	0.28	−0.13
Beef	0.02	0.36	0.11	0.00
Veal	0.16	0.42	0.29	−0.16
Pork	0.11	0.30	0.13	−0.16
Poultry	0.12	0.10	0.04	0.32
Processed meat	0.08	0.46	−0.01	−0.16
Offal	0.08	0.30	−0.06	0.05
Fish	0.17	−0.10	0.01	0.43
Eggs	0.15	0.39	0.12	0.04
Seed oils	0.13	0.35	−0.17	−0.12
Olive oil	0.46	−0.06	0.43	0.25
Butter	−0.17	0.55	0.19	0.06
Margarine	0.02	0.24	−0.08	0.07
Cakes	−0.16	0.38	−0.03	0.13
Wine	0.09	0.06	0.28	−0.39
Spirits	0.11	0.12	0.13	−0.34
Pizza	−0.02	0.22	0.09	0.00

Table 2. Mean standardized factor scores for categories of common risk factors for breast cancer

	Salad vegetables	Western	Canteen	Prudent
Characteristic				
BMI (kg/m^2)				
15−23	−0.166	−0.012	−0.123	−0.057
24−26	0.020	0.005	0.000	0.004
27−51	0.148	0.015	0.115	0.055
Age (years)				
34−43	−0.051	0.132	−0.167	0.047
44−52	0.080	0.065	0.002	0.068
53−70	−0.026	−0.188	0.162	−0.114
Education (months)				
0−60	−0.008	−0.018	0.080	0.058
96	−0.007	0.042	−0.067	−0.020
132−204	0.023	0.007	−0.091	−0.082
Parity				
No children	−0.003	−0.168	0.143	−0.048
One or two children	−0.004	0.023	0.006	0.001
More than two children	0.012	0.004	−0.070	0.019
Height (cm)				
127−155	−0.053	−0.147	0.006	0.075
156−160	−0.012	0.032	0.034	0.022
161−180	0.046	0.130	0.048	0.054
Age at menarche (yrs)				
8−12	0.031	−0.002	0.008	0.014
13−14	−0.028	0.010	−0.007	−0.006
15−20	0.010	−0.025	−0.021	−0.022
Smoking				
Nonsmokers	−0.033	0.008	0.024	−0.054
Ex-smokers	−0.110	0.064	−0.034	0.049
Smokers	0.025	0.040	−0.064	0.217
Menopausal status				
No	0.006	0.100	−0.089	0.059
Yes	−0.008	−0.171	0.145	−0.100

RRs for breast cancer by tertiles of factor scores for the four dietary patterns are shown in Table 3. For the *salad vegetables* pattern, women with factor scores in the second and third tertiles had a significantly lower RR for breast cancer than the reference first tertile (RR = 0.65 second tertile; RR = 0.66 highest tertile), with a significant linear trend ($P = 0.014$). The risk in the second and third tertiles was 34–35% lower than in the first tertile but did not differ between them. When the multivariate model included parity, age at menarche, menopausal status, education, smoking, and height (*Model 2*), the reduction in risk for the *salad vegetables* pattern remained. No other dietary pattern was significantly related to breast cancer risk.

The results of multivariate *Model 3*, which considered two categories of BMI (<25 and ≥25), are shown in Table 4. BMI had a major effect on the relationship between the *salad vegetables* dietary pattern and breast cancer risk. For women with BMI <25, the highest tertile of the *salad vegetables* factor score was associated with a more than 50% reduction in breast cancer risk compared to the lowest tertile, with a significant linear trend ($P = 0.001$). For women with BMI ≥25, there was no difference in RR between the three tertiles of *salad vegetables* score, so for these women, this dietary pattern was not protective.

Table 3. Relative risk of breast cancer according to tertiles of factor scores for each dietary pattern (81,634 person-years of follow-up)

Dietary pattern	RR by increasing tertiles of factor score			P for trend
	1 (low score)	2	3 (high score)	
Salad vegetables				
Cases	91	58	58	
Model 1[a]	1	0.65 (0.47–0.91)	0.66 (0.46–0.94)	0.014
Model 2[b]	1	0.65 (0.47–0.91)	0.66 (0.47–0.95)	0.016
Western				
Cases	73	74	60	
Model 1[a]	1	1.05 (0.74–1.48)	0.90 (0.58–1.40)	0.680
Model 2[b]	1	1.04 (0.73–1.47)	0.90 (0.58–1.41)	0.705
Canteen				
Cases	71	80	56	
Model 1[a]	1	1.18 (0.85–1.65)	0.91 (0.60–1.39)	0.763
Model 2[b]	1	1.22 (0.87–1.70)	0.95 (0.63–1.45)	0.935
Prudent				
Cases	57	73	77	
Model 1[a]	1	1.20 (0.85–1.70)	1.33 (0.94–1.88)	0.114
Model 2[b]	1	1.19 (0.84–1.68)	1.28 (0.90–1.83)	0.169

[a]Multivariate model adjusted for energy intake and age.
[b]Multivariate model also adjusted for education, parity, height, age at menarche, smoking, and menopausal status as well as energy intake and age.

Discussion

In this prospective study, we used exploratory factor analysis to identify four dietary patterns in a cohort of women volunteers resident in northern Italy. The *western* pattern we found was not identical with western patterns identified in other studies (9, 11, 12); nevertheless, several food items were common to all. Furthermore, we identified two potentially healthy diet patterns: *prudent* and *salad vegetables*, whereas other studies only identified one such pattern, usually named prudent or healthy (9, 11, 12). Only the *salad vegetables* pattern, characterized by high consumption of raw vegetables and olive oil as added fat, had a significant protective effect against breast cancer in our Mediterranean population.

Previous studies on the relation between vegetables consumption and risk of breast cancer have produced mixed results. Of 11 case-control and cohort studies examined in a review of vegetables consumption and breast cancer (3), eight reported an inverse association (significant in four studies) between vegetable consumption in general and breast cancer risk; the others found no association. Only 3 of these 11 studies reported a protective effect for raw vegetables (20–22), significant in 1 (21). Another case-control study, conducted in six areas of Italy, found that breast cancer risk decreased with increasing intake of raw vegetables (23); while a case-control study in a Spanish population found that breast cancer cases had significantly lower consumption of fruits, vegetables, and fish (24).

A recent pooled analysis of cohort studies found that neither high overall vegetable consumption in general nor high consumption of certain groups of vegetables were significantly associated with reduced breast cancer risk (25). However, a meta-analysis of 26 published studies produced results more in agreement with our findings, in that high consumption of vegetables in general was found protective against breast cancer in 17 of the studies (14 case-control and 3 cohort) (26).

Only one previously published study, on a Swedish population, has investigated the relationship between diet and breast cancer using factor analysis (12). A "high vegetable consumption" dietary pattern was not identified in this population, which was characterized by low consumption of vegetables in general. The dietary pattern identified as "healthy" (characterized by consumption of vegetables, poultry, fish, cereals, and dairy products) was not related to the risk of breast cancer.

Our study is the first prospective cohort study to use exploratory factor analysis in a Mediterranean population, that is, one characterized by high consumption of vegetables in general (27). However, a case-control study conducted in Greece to elucidate the role of diet in the development of thyroid cancer found a reduced risk for a raw vegetables dietary pattern (obtained by factor analysis) that was similar to our *salad vegetables* pattern in that it was characterized by generally high consumption of vegetables, a large proportion of which were the ingredients of the traditional Greek salad (28). We suggest that the main reason for the discrepancy between our findings and

Table 4. Relative risk for breast cancer by tertiles of factor score for each dietary pattern, stratified by BMI

Dietary pattern	RR by increasing tertiles of factor score			P trend
	1 (low score)	2	3 (high score)	
BMI <25 (44,165 person/year)				
Salad vegetables				
Cases	56	30	18	
Model 3[a]	1	0.58 (0.37–0.92)	0.39 (0.22–0.69)	0.001
Western				
Cases	36	33	35	
Model 3[a]	1	0.75 (0.45–1.24)	0.75 (0.41–1.38)	0.342
Canteen				
Cases	30	45	29	
Model 3[a]	1	1.19 (0.74–1.93)	0.72 (0.40–1.30)	0.291
Prudent				
Cases	28	34	42	
Model 3[a]	1	1.02 (0.62–1.69)	1.24 (0.76–2.03)	0.374
BMI <25 (37,469 person/year)				
Salad vegetables				
Cases	36	28	39	
Model 3[a]	1	0.74 (0.45–1.22)	0.99 (0.60–1.61)	0.977
Western				
Cases	37	41	25	
Model 3[a]	1	1.38 (0.86–2.24)	1.01 (0.53–1.96)	0.780
Canteen				
Cases	41	36	26	
Model 3[a]	1	1.26 (0.78–2.03)	1.34 (0.73–2.45)	0.320
Prudent				
Cases	29	39	35	
Model 3[a]	1	1.37 (0.84–2.24)	1.33 (0.80–2.19)	0.282

[a]Multivariate model adjusted for energy intake, age, education, parity, height, age at menarche, and smoking.

those of previous prospective studies is that the latter were carried on out on non-Mediterranean populations characterized in general by low consumption of vegetables. Many of the case-control studies, the results of which were consistent with ours, were performed in Mediterranean populations.

Vegetables are rich in substances that may be responsible for a protective action of a vegetable-rich diet. Carotenoids for example may protect against breast cancer via their role in the regulation of epithelial cell differentiation and their ability to quench singlet oxygen (29). The common finding of epidemiological studies that raw vegetables consumption is generally associated with a lower risk of cancer than cooked vegetables consumption supports a role for oxygenated carotenoids in protecting against cancer (29).

Vitamin C acts in several ways that may reduce the risk of cancer: it is important for the integrity of the extracellular matrix, enhances immune responses, may prevent the formation of carcinogens from precursors, and may promote tumor encapsulation (30). Vitamin E may inhibit cancer through its functions as antioxidant, inhibitor of nitrosamine formation, and inhibitor of oncogene expression (31). Green vegetables are rich in folic acid and deficient folate can reduce the availability of S-adenosylmethionine for DNA methylation and may thereby influence gene expression (32, 33). Finally, dietary fiber—a major constituent of vegetables—may affect breast cancer risk by decreasing gut reabsorption of estrogen excreted in bile (29).

Unexpectedly, we found no association between our western (fat-rich) pattern and the risk of breast cancer, although in a previous nested case-control study on a subset of the present cohort, we found that high total fat and animal protein consumption were associated with increased risk of postmenopausal breast cancer (16). However, this earlier study had a shorter follow-up (5.5 years versus 9.5) and concerned only postmenopausal ORDET women (16).

Although factor analysis has emerged as a method that may be able to predict disease risk better than specific foods or nutrients (4–6), it is not without limitations (34). For example, the number of factors (dietary patterns) extracted, the prior classification of food items into food groups, the rotation method used, and the naming of the factors are all subjective decisions (8, 34). The decision as to the number of factors (dietary patterns) extracted is usually based on empirical guidelines because exact quantitative solutions are not available. We used one of the most commonly used empirical methods [the Scree test (19)] for deciding the number of factors to adopt.

The classification of food items into food groups is also to some extent subjective although guided by knowledge of how individual foods are related to broader dietary patterns. Notwithstanding this subjectivity, it is noteworthy that the western and prudent dietary patterns identified in this and other studies were composed of similar food items, suggesting that these factors represent similar dietary patterns in different populations. Furthermore, because there is no direct link between a dietary pattern and the intake of a particular nutrient related to disease risk, factor analysis cannot provide clues to the biological

mechanisms that may influence the risk of breast cancer. Strengths of our study are that exposure was assessed prospectively in a large cohort, and that very few were lost to follow-up.

The second finding of our study was that the protective effect of the salad vegetables dietary pattern against breast cancer was especially strong for women with BMI less than 25, but was no longer present in overweight women. This effect was independent of menopausal status (data not shown). Numerous studies have investigated a possible relation between BMI and breast cancer. Some have found a positive association between overweight and postmenopausal breast cancer risk, considered due mainly to the conversion of androgens into estrone in adipose tissue (35–37); while in young women, overweight seems protective against breast cancer, probably in relation to greater frequency of anovulatory cycles (38). In the present study, we found no effect of BMI on the risk of breast (data not shown). Thus, the interaction between BMI and the salad vegetables pattern may arise simply because eating vegetables and conscientious weight control characterize women whom we may call "health conscious", who try to put health messages into practice by adopting behavior that may reduce their risk of breast cancer.

A possible explanation of the lack of protective effect of the salad vegetables dietary pattern in overweight women could be that they were dieting to reduce weight before recruitment to the study, so that eating large quantities of vegetables was an aspect of their weight-reducing rather than normal diet. Another explanation could be that overweight women may have underreported their consumption of certain types of foods in the food-frequency questionnaire, and overreported their vegetables consumption because they believed a diet rich in vegetables—increasingly promoted as healthy—was more socially acceptable (39).

To conclude, we have found that the salad vegetables dietary pattern is associated with reduced breast cancer risk. A diet rich in raw vegetables implies adequate intake of vitamins, dietary fiber, and a variety of biologically active compounds, all of which may contribute to the protective effect. Our finding that the effect was especially pronounced in lean women suggests that high consumption of raw vegetables plus successful weight control is particularly protective against breast cancer, although it may identify a subgroup who were simply particularly healthy conscious.

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