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Nutrient Dietary Patterns and Gastric Cancer Risk in Italy

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Abstract

Background: **There have been several studies on diet and gastric cancer, but only a few investigations have considered the role of dietary patterns.**
Methods: **We investigated gastric cancer risk in relation to dietary patterns in a case-control study conducted in northern Italy between 1997 and 2007, including 230 patients with incident, histologically confirmed gastric cancer and 547 frequency-matched controls, admitted to the same hospitals as cases, with acute nonneoplastic conditions. Dietary habits were investigated through a validated food frequency questionnaire including 78 foods and beverages. We identified *a posteriori* dietary patterns on a selected set of 28 micro- and macro-nutrients through an exploratory principal component factor analysis. We estimated the odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) using conditional logistic regression models on quartiles of factor scores.**
Results: **We identified four major dietary patterns, named "animal products", "vitamins and fiber", "vegetable unsaturated fatty acids", and "starch-rich". We observed a positive association between gastric cancer risk and the "animal products" (OR, 2.13; 95% CI, 1.34-3.40, for the highest versus the lowest score quartile) and the "starch-rich" (OR, 1.67; 95% CI, 1.01-2.77) dietary patterns. The "vitamins and fiber" pattern (OR, 0.60; 95% CI, 0.37-0.99) was inversely associated with gastric cancer, whereas no significant association emerged with the "vegetable unsaturated fatty acids" pattern (OR, 0.89; 95% CI, 0.56-1.42).**
Conclusions: **Our analysis suggests a protective effect against gastric cancer risk of dietary patterns rich in fruits and vegetables, and a positive association of dietary patterns rich in meats and animal fats and starchy foods.** (Cancer Epidemiol Biomarkers Prev 2009;18(11): 2882–6)

Introduction

Most studies on diet and gastric cancer have considered the role of various food items and found inverse relations with fruit and vegetable consumption and positive associations with starchy foods and meats (1-4). Fewer investigations have considered the role of nutrients and dietary patterns, although, in the presence of a large number of possible associations, the integration of several dietary exposures into single dietary patterns may overcome problems of multiple testing and high correlations between various dietary exposures. An Italian case-control study found a significant inverse association between various measures of food diversity, particularly of vegetables and fruit diversity, and gastric cancer risk (5). Another Italian case-control study found a positive association with the "traditional" pattern (i.e., rich in starch, protein, alcohol and nitrite) and an inverse association with the "vitamin-rich" pattern (6). Two prospective studies were conducted in Japan. The first one found a positive association with the "traditional" Japanese pattern (7). The second one was an investigation of middle-aged men, which found a protective effect of the "vegetables and fruit" and "Western breakfast" patterns (8). With reference to American data, a study from Nebraska found positive associations between the "high meat" and "milk" patterns and distal stomach adenocarcinoma (9). A study from Uruguay found a positive association with gastric cancer for the "starchy" factor, whereas the "healthy" and "mixed" patterns were protective (10). These studies, however, differ in terms of methods used to define dietary patterns.

To further contribute to the issue, we applied an exploratory principal component factor analysis (PCFA) to a case-control study of gastric cancer conducted in northern Italy. Previous analyses on the same data found significant inverse associations with vitamin E, α-carotene and β-carotene among micronutrients (11), and with vegetable fats and polyunsaturated fatty acids among macronutrients (12).

Materials and Methods

Design and Participants. We derived data from a case-control study of gastric cancer conducted between 1997 and 2007 in the Greater Milan area, Northern Italy (11-13). Cases were 230 patients (143 men and 87 women; median age, 63 y; range, 22-80 y), admitted to major teaching and general hospitals in the study area with incident, histologically confirmed gastric cancer (Ninth Revision of the International Classification of Diseases: 151.0-151.9), diagnosed no longer than 1 y before the interview, and

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with no previous diagnosis of cancer. The control group included 547 patients (286 men and 261 women; median age, 63 y; range, 22-80 y), frequency matched to cases by age and sex (with a ratio of 2:1 for men and 3:1 for women), admitted to the same hospitals as cases for a wide spectrum of acute, nonneoplastic conditions that are unrelated to known or potential risk factors for gastric cancer and long-term diet modification. Of these, 20% were admitted for traumas, 23% for other orthopedic conditions, 22% for acute surgical, and 35% for other miscellaneous disorders. Less than 5% of cases and controls approached refused to be interviewed.

Food Frequency Questionnaire. For both cases and controls, data were collected during their hospital stay by centrally trained interviewers. The questionnaire included information on sociodemographic characteristics, anthropometric measures, selected lifestyle habits such as tobacco smoking and alcohol consumption, personal medical history, and family history of cancer. A satisfactorily reproducible (14) and valid (15) food frequency questionnaire (FFQ) was used to assess the patients' usual diet in the 2 y preceding diagnosis (for cases) or hospital admission (for controls). The FFQ included questions on 78 foods and beverages, including a range of the most common recipes in Italian diet. Subjects were asked to indicate the average weekly frequency of consumption for each dietary item; intakes lower than once a week but at least once a month were coded as 0.5 per week. From those data, we estimated the intake of macronutrients and selected micronutrients using an Italian food composition database, integrated with other sources whenever useful (16, 17).

Statistical Analysis

Factorability of the Original Matrix. We conducted the analyses on a selected set of 28 major micro- and macronutrients, as in our previous work on breast and ovarian cancers (18). We first evaluated their correlation matrix to determine if it was factorable through both visual inspection of the matrix and statistical procedures such as Bartlett's test of sphericity (using the Z approximation to the χ^2 distribution of the test statistic), Kaiser-Meyer-Olkin measure, and individual measures of sampling adequacy (19).

Identification of Dietary Patterns. We performed exploratory PCFA (20) on the correlation matrix of the overall original data to describe the variance-covariance structure among nutrients in terms of a few underlying unobservable and randomly varying factors, generally known as dietary patterns. The number of factors to retain was chosen combining the following criteria: factor eigenvalue >1, scree plot, and factor interpretability (20). A varimax rotation was done on the factor loading matrix to obtain a simpler loading structure with easier interpretability. Nutrients having rotated factor loadings $\geq$0.63 on a given factor were used to name the factors. We calculated factor scores following the weighted least square method. They indicate the degree to which each subject's diet conforms to one of the identified patterns.

To assess the robustness of the identified dietary patterns, we used the following approaches. First, we performed a principal axis factor analysis, using varimax rotation, and we obtained results comparable to the ones from PCFA. Second, we calculated factor scores referring to the multiple regression method and standardized the results (20). The correlations between scores referring to the same factor calculated with different methods were 0.99 for all the four comparisons. Third, we conducted stratified PCFA analyses by both sexes and quinquennia of period of interview. The identified dietary patterns were consistent with the ones obtained for the overall sample. Given the robustness in the patterns identified by these complementary approaches, we calculated factor scores in all subsequent analyses by using results from the original overall PCFA and the weighted least squares method.

To assess reliability and to refine the identified factors, we evaluated the internal consistency of those nutrients having rotated factor loadings $\geq$0.40 on any factor using standardized Cronbach's coefficient α for each factor (21). We calculated coefficient α for each factor and "coefficient α if item deleted" for each factor and for each nutrient (19). This indicated that most nutrients were contributing to a high reliability, and none of the nutrients appreciably reduced the value of coefficient α when removed from the factor.

Risk Estimates. For each factor, participants were grouped into four categories according to quartiles of factor scores among the control population. We estimated the odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) for each quartile, using conditional multiple regression models (22) conditioned on age and sex and adjusted for quinquennia of period of interview, education, body mass index, tobacco smoking, and family history of gastric cancer. We fitted a composite model allowing for all the identified dietary patterns simultaneously. We also fitted separate models for each factor and obtained comparable results. Tests for linear trend were also calculated, assigning to each subject the median value of each factor within the quartile class.

The analyses were conducted using SAS software, version 9.1 (SAS Institute, Inc.). The statistical software R[5] was used to perform Bartlett's test of sphericity and to use an alternative procedure for the estimation of factor scores.

Results

The correlation matrix of the nutrients was amenable to factor analysis. All the nutrients showed at least 10 correlation coefficients >0.30 in absolute value, thus allowing to perform the analyses on the entire set of selected nutrients. Retinol and vitamin D showed a more limited number of correlations >0.30 in absolute value in the correlation matrix.

Statistical procedures for matrix factorability also showed satisfactory results (Table 1). Bartlett's test of sphericity was highly significant ($P < 0.0001$), thus allowing to reject the null hypothesis that the correlation matrix is an identity matrix. The Kaiser-Meyer-Olkin statistic was equal to 0.82, suggesting that we had an adequate sample size relative to the number of nutrients. Moreover,

[5] R Development Core Team: a language and environment for statistical computing. R Fundation for Statistical Computing. Vienna, Austria, 2009. Available at URL: http://www.R-project.org.

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Table 1. Factorability of the correlation matrix of the 28 original nutrients: Bartlett's test of sphericity and measures of sampling adequacy

Bartlett's test of sphericity: $P < 0.001$	
Kaiser-Meyer-Olkin statistic—overall measure of sampling adequacy: 0.82	
Individual measures of sampling adequacy	
<0.60	Retinol
0.60-0.69	Linoleic acid
0.70-0.79	Monounsaturated fatty acids, starch, calcium, vitamin C, lycopene, vitamin D, vitamin E, total fiber
0.80-0.89	Animal protein, vegetable protein, cholesterol, saturated fatty acids, other polyunsaturated fatty acids, soluble carbohydrates, sodium, potassium, phosphorus, iron, zinc, thiamin, riboflavin, total folate, niacin
≥0.90	Linolenic acid, vitamin B6, β-carotene equivalents

individual measures of sampling adequacy were generally high: 26 of 28 measures were >0.70.

Table 2 shows the factor loading matrix for the four retained factors, or dietary patterns. These factors explained 75% of the total variance in the original nutrients, accounting for about 22%, 20%, 18%, and 15%, respectively. The larger the loading of a given nutrient to the factor, the greater the contribution of that nutrient was on that factor. Thus, the first pattern, named "animal products", had the greatest loadings on animal protein, riboflavin, cholesterol, phosphorus, calcium, and zinc. The second pattern, named "vitamins and fiber", had the greatest loadings on vitamin C, total fiber, potassium, total folate, β-carotene equivalents, and soluble carbohydrates. The third pattern, named "vegetable unsaturated fatty acids" (VUFA), had the greatest loadings on other polyunsaturated fatty acids, vitamin E, monounsaturated fatty acids, linoleic acid, and linolenic acid. The fourth pattern, named "starch-rich", had the greatest loadings on starch, vegetable protein, and sodium. All the examined nutrients showed at least one loading >0.30 on any factor, thus confirming a role for each nutrient.

Table 3 shows the ORs and the corresponding 95% CIs for gastric cancer according to quartiles of factor scores. Results refer to the composite model including all the four patterns simultaneously, and the confounding variables as well. We observed an increased risk of gastric cancer with the "animal products" pattern (OR, 2.13; 95% CI, 1.34-3.40, for the highest versus the lowest quartile of factor score; $P_{\text{trend}} = 0.0003$) and the "starch-rich" pattern (OR, 1.67; 95% CI, 1.01-2.77; $P_{\text{trend}} = 0.0463$). In contrast, the "vitamins and fiber" pattern was inversely associated with gastric cancer, with an OR of 0.60 (95% CI, 0.37-0.99; $P_{\text{trend}} > 0.05$) for subjects in the highest quartile as compared with those in the lowest one. The "VUFA" pattern was not significantly inversely related to gastric cancer. Consistent results were observed for the four models including each factor separately.

Discussion

Only a few studies on gastric cancer were conducted to identify dietary patterns. *A posteriori* dietary patterns were identified in eight studies: five of them used factor analysis (7, 10, 23-25), one used cluster analysis (9), one used principal component analysis (8), and one used factor analysis and correspondence analysis in combination (6). The four dietary patterns identified in our population are in several aspects consistent with those of a previous case-control study (6) conducted in central Italy, which found four dietary profiles based on 20 different nutrients, explaining 75% of total variance. In that study, adherence to the "traditional" dietary pattern, characterized by starch, protein, alcohol, and nitrites, was associated to an increased risk of gastric cancer (OR, 3.0 for the highest versus the lowest tertile), and the "vitamin-rich" pattern to a decreased risk (OR, 0.5). Our "starch-rich" pattern shares several characteristics with the "traditional" one in that study, and our "vitamins and fiber" pattern is comparable to the "vitamin-rich" one, based on fiber, vitamin C, and β-carotene.

Among studies that applied factor analysis on food groups, a prospective study conducted in Japan identified three dietary patterns, defined as "healthy", "traditional", and "Western" (7). There was a significant positive relation with the "traditional" pattern (indicator of a diet mainly rich in pickled vegetables, salted fish and roe, fish, rice, and miso soup) in both males (OR, 2.88; 95% CI, 1.76-4.72 for the highest versus the lowest quartile) and females (OR, 2.40; 95% CI, 1.32-4.35). The "healthy" dietary pattern, in contrast, was strongly inversely associated with the risk of gastric cancer, particularly for females. A study from Uruguay (10) also identified three major patterns, named "starchy", "healthy", and "mixed". Of these, a significant positive relation emerged with the "starchy" pattern (OR, 2.51; 95% CI, 1.54-4.10 for the highest versus the lowest load of the factor), mainly correlated to intakes of grains and tubers. In contrast, the "healthy" pattern (OR, 0.48; 95% CI, 0.32-0.71), mainly correlated to white meat, dairy foods, desserts, raw vegetables, and fruits, and the "mixed" pattern (OR, 0.59; 95% CI, 0.38-0.90), mainly correlated to red meat, processed meat, eggs, and pulses, were inversely associated with the risk of gastric cancer.

Given the different diet in Italy, Japan, and South America, it is remarkable that the dietary patterns identified in such different areas of the world show similar composition associations with gastric cancer risk. Thus, rice and miso soup in Japan is assimilable to traditional or starch-rich foods in Italy and to the "starchy" pattern in Uruguay. This suggests that the dietary patterns in various high-risk areas for gastric cancer worldwide (26) share several similarities and define local characteristics of high-risk diet for gastric cancer.

This was a hospital-based case-control study and shares some of the limitations of such a design. It was based on a relatively small number of cases, thus not allowing meaningful analysis by separate histotype or tumor site. Further, we had no information on *Helicobacter pylori* infection, the strongest risk factor for gastric cancer (27). Case-control studies, in any case, have limited ability to measure *H. pylori* because blood samples obtained at cancer diagnosis are of limited value. However, the role of dietary factors is considered independent from that of *H. pylori* (4, 28). The strengths of this study include the almost complete participation of both cases and controls, which should reduce the role of selection bias. Hospital controls may have different dietary habits as compared with the general population. However, we excluded from the comparison group subjects admitted for conditions

Table 2. Factor loading matrix and explained variances for the four major dietary patterns identified by factor analysis

Nutrient	Animal products	Vitamins and fiber	VUFA	Starch-rich
Animal protein	**0.80**	0.10	0.41	0.23
Vegetable protein	0.15	0.39	0.29	**0.80**
Cholesterol	**0.72**	0.07	0.41	0.30
Saturated fatty acids	0.56	0.15	0.50	0.41
Monounsaturated fatty acids	0.20	0.29	**0.72**	0.28
Linoleic acid	0.19	0.16	**0.71**	0.33
Linolenic acid	0.33	0.27	**0.68**	0.34
Other polyunsaturated fatty acids	0.48	−0.02	**0.75**	−0.04
Soluble carbohydrates	0.40	**0.66**	0.02	0.17
Starch	0.18	0.11	0.26	**0.88**
Sodium	0.41	0.06	0.16	**0.80**
Calcium	**0.65**	0.34	0.03	0.28
Potassium	0.42	**0.76**	0.29	0.28
Phosphorus	**0.70**	0.37	0.31	0.45
Iron	0.42	0.48	0.39	0.37
Zinc	**0.63**	0.29	0.45	0.47
Thiamin (vitamin B1)	0.53	0.51	0.30	0.45
Riboflavin (vitamin B2)	**0.76**	0.47	0.10	0.26
Vitamin B6	0.53	0.58	0.41	0.29
Total folate	0.40	**0.71**	0.22	0.28
Niacin	0.54	0.37	0.47	0.21
Vitamin C	0.12	**0.85**	0.13	−0.11
Retinol	0.47	0.08	0.03	0.00
β-Carotene equivalents	0.04	**0.67**	0.20	0.02
Lycopene	−0.05	0.26	0.49	0.32
Vitamin D	0.54	0.04	0.54	−0.23
Vitamin E	0.08	0.53	**0.74**	0.22
Total fiber (Englyst)	0.06	**0.85**	0.15	0.31
Proportion of explained variances (%)	21.67	20.30	18.02	15.10
Cumulative explained variances (%)	21.67	41.97	59.99	75.09

NOTE: Estimates from a PCFA done on 28 nutrients. Loadings ≥0.63 are shown in boldface.

associated with long-term dietary modifications (e.g., diabetes mellitus, cardiovascular diseases, etc.). Other strengths are the use of a reproducible and valid FFQ (14, 15) and the similar setting of interviews for cases and controls, which should limit information bias. With reference to confounding, we were able to allow for a large number of potential confounding factors, including socioeconomic indicators, tobacco, and family history. We also fitted a model without terms for body mass index and tobacco, and the main findings were not materially modified: the ORs for the highest quartile were 2.23 (95% CI, 1.40-3.54) for the "animal products" pattern, 0.61 (95% CI, 0.38-0.99) for the "vitamins and fiber" pattern, 0.84 (95% CI, 0.53-1.32) for the "VUFA" pattern, and 1.73 (95% CI, 1.05-2.85) for the "starch-rich" pattern.

Factor analysis is a method that allows to investigate the relationship between dietary habits and cancer more comprehensibly than others based on single foods or nutrients, accounting for complex forms of interaction between dietary components. Intake of different foods or nutrients may interact to increase or decrease cancer risks, and this interaction may make it difficult to tease out associations between individual foods and cancers. Limitations of factor analysis arise from subjective decisions involved in the definition of dietary patterns, including the number of factors to retain, the type of rotation (if any), and the interpretation and naming of the factors. However, in the current study, a series of analyses suggested that the identified set of patterns is both stable and robust.

In conclusion, our study highlights the protective effect of the "vitamins and fiber" dietary pattern against gastric cancer risk, and the positive association of the "animal products" and "starch-rich" dietary patterns, indicating

Table 3. OR of gastric cancer and corresponding 95% CIs on quartiles of factor scores from a PCFA

Dietary pattern	Quartile category, OR (95% CI)				P_{trend}*
	I†	II	III	IV	
Animal products	1	1.08 (0.64-1.80)	1.47 (0.90-2.40)	2.13 (1.34-3.40)	0.0003
Vitamins and fiber	1	0.84 (0.53-1.32)	1.00 (0.64-1.56)	0.60 (0.37-0.99)	0.0861
VUFA	1	0.84 (0.53-1.34)	0.89 (0.56-1.42)	0.89 (0.56-1.42)	0.7325
Starch-rich	1	1.37 (0.83-2.25)	1.37 (0.82-2.28)	1.67 (1.01-2.77)	0.0463

NOTE: Estimates from a logistic regression model conditioned on age and sex and adjusted for quinquennia of period of interview, education, body mass index, tobacco smoking, and family history of gastric cancer. Results refer to the composite model including all the four factors simultaneously.
*P value for linear trend.
†Reference category.

that a diet poor in fruits and vegetables (and vegetable oils) and rich in animal foods and fats and in starchy foods has an unfavorable role in gastric cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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