Diet Diversity and the Risk of Colorectal Cancer in Northern Italy[1]

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Abstract

The relationship between diet diversity (*i.e.,* variety in food intake computed as the total number of foods consumed at least once per week) and the risk of colorectal cancer was investigated using data from a hospital-based, case-control study carried out between 1985 and 1992 in Northern Italy. Subjects were patients with histologically confirmed incident cancers of the colon (n = 828) and rectum (n = 498) and 2024 controls admitted for acute, nonneoplastic, non-digestive tract conditions. A significant inverse association (multivariate relative risk, 0.7) for the highest (more diverse diet) *versus* the lowest quartile of total diet diversity was observed, together with a significant trend in risk. A similar risk was observed for diversity within vegetables (RR, 0.6, highest *versus* lowest quartile), but no consistent association was found for fruit, meat and fish, and "other food" diversity. A similar pattern was observed when colon and rectal cancers were considered separately or across separate strata of sex and age. Diet diversity is related to a moderately decreased risk of colorectal cancer. These results add epidemiological support to the dietary guidelines recommending a more varied diet, and, if confirmed by other studies, would have considerable public health implications.

Introduction

The relationship between colorectal cancer and dietary habits has been extensively studied during the past decades, with the aim of identifying those components of a diet (foods, nutrients, and micronutrients) associated with increased or decreased risks (1). Only scant attention, however, has been paid to the definition of potential correlates of colorectal cancer risk in terms of general dietary patterns. In particular, food diversity (variety of foods consumed) has been recommended to achieve a healthy diet and to prevent cancer (2–4), but only scant information is available on colorectal cancer risk (5).

Some reports have considered diversity in relation to other correlates of diet, including positive relationships with intakes of selected micronutrients (fat, cholesterol, and vitamin A; Ref. 6), "quality of diet" (7), income, and education (2), *i.e.,* a number of important correlates of colorectal carcinogenesis.

The relationship between diet diversity and all-cause mortality was analyzed in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (8). Total mortality was inversely related to diet diversity, after adjustment for several confounders (RR[3], 1.5 in men and 1.4 in women in the lowest quartile of diversity *versus* the highest; $P < 0.05$). That study, however, did not consider specific causes of death. The possible association of diet diversity with colon cancer risk was examined in a case-control study conducted between 1975 and 1984 in three counties of western New York on 228 cases and 228 matched controls (5). A positive association between colon cancer and total diversity (number of different foods reported usually eaten more than monthly) was observed among men (RR, 2.0) but not among women (RR, 0.8) in the highest quartile of diversity *versus* the lowest, after adjusting for several confounders, including energy intake and monthly servings of food. No consistent associations were observed according to diversity within specific food groups.

With the aim of further assessing the role of total and specific food group diversity on the risk of colorectal cancer, we analyzed data from a case-control study conducted in northern Italy.

Subjects and Methods

The data were derived from a case-control study of several digestive tract cancers, based on a network of teaching and general hospitals from the greater Milan area. Recruitment of cases and controls started in January 1985, and this report is based on data collected up to December 1992.

The general design of this investigation has already been described (9, 10). Briefly, the cases were 828 (423 males and 405 females) incident histologically confirmed colon cancers and 498 (288 males and 210 females) rectal cancers, who had been admitted to the National Cancer Institute, several university clinics, and the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan. The age range was 20–74 (median, 62) years for both colon and rectal cancers.

The comparison group included patients admitted for a wide spectrum of acute, nonneoplastic, non-digestive tract con-

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[3] The abbreviations used are: RR, relative risk; CI, confidence interval.

ditions to the same network of hospitals where cases had been identified. In total, 2024 controls were interviewed (1189 males and 835 females). Of these, 47% were admitted for traumatic conditions; 20% had nontraumatic orthopedic diseases; 19% had acute surgical conditions; and 14% had other miscellaneous disorders, such as skin, eye, nose and throat, and dental disorders. The age range was 19–74 (median, 55) years. The catchment areas of cases and controls were comparable: more than 80% of cases and controls resided in Lombardy, and more than 90% resided in Northern Italy. Less than 3% of eligible subjects (cases and controls) refused to be interviewed.

Trained interviewers used a structured questionnaire to obtain information on general sociodemographic factors and lifestyle habits, weight and height, a problem-oriented medical history, and family history of colorectal cancer. Furthermore, information about the frequency of consumption per week of 29 indicator foods before the onset of the disease that led to the current admission was collected.

Food diversity was computed as the total number of different foods consumed at least once per week. The following foods were considered: potatoes, cabbages and Cruciferae, carrots, spinach, lettuce, tomatoes, pulses, and peppers (vegetable group); apples, citrus fruits, and watermelon (fruit group); beef and veal, poultry, fish, liver, ham, raw ham, salami and other sausages, and canned meat (meat and fish group); pasta or rice, bread, polenta, and pastries (carbohydrate group); and cheese, milk, and eggs (other food group). Subjects were subdivided into approximate quartiles of total diversity and quartiles of specific food group diversity based on the distribution of controls.

Odds ratios, as estimators of RR, together with their 95% CIs, were derived from unconditional multiple logistic regression equations, fitted by the method of maximum likelihood (11). All the regression equations included terms of age (in decades), sex, education (<7, 7–11, or ≥12 years of schooling), area of residence (Lombardy and other northern, central, and southern Italy), family history of colorectal cancer (no or yes), body mass index (quartiles), total number of weekly servings (quartiles), and total energy intake (quartiles). In addition, terms of total vegetable intake (quartiles), total fruit intake (quartiles), and total meat and fish intake (quartiles) were also included when indicated.

Table 1 Distribution of 828 cases of colon cancer, 498 of rectal cancer, and 2024 controls according to sex, age, and selected covariates, Milan, Italy, 1985–1992

	Colon cancer		Rectal cancer		Controls	
	n	%	*n*	%	*n*	%
Sex						
Male	423	51.1	288	57.8	1189	58.7
Female	405	48.9	210	42.2	835	41.3
Age (yr)						
<40	36	4.3	22	4.4	266	13.1
40–49	98	11.8	47	9.4	421	20.8
50–59	220	26.6	129	25.9	593	29.3
60–69	322	38.9	204	41.0	588	29.1
70–74	152	18.4	96	19.3	156	7.7
Education (yr)						
<7	429	51.8	298	59.8	986	48.7
7–11	223	26.9	126	25.3	591	29.2
≥12	176	21.3	74	14.9	447	22.1
Family history of colorectal cancer						
No	768	92.7	470	94.4	1958	96.7
Yes	60	7.3	28	5.6	66	3.3
Total energy intake (kcal)						
<1673	156	18.8	124	24.9	506	25.0
1673–1493.99	255	30.8	110	22.1	506	25.0
1494–2367.99	204	24.7	135	27.1	509	25.2
≥2368	213	25.7	129	25.9	503	24.8
Vegetable intake (approximate quartiles)						
First (lowest)	292	35.3	185	37.1	447	22.1
Second	245	29.6	149	29.9	603	29.8
Third	165	19.9	81	16.3	518	25.6
Fourth (highest)	126	15.2	83	16.7	456	22.5
Fruit intake (approximate quartiles)						
First (lowest)	247	29.8	136	27.3	519	25.6
Second	220	26.6	142	28.5	485	24.0
Third	201	24.3	139	27.9	556	27.5
Fourth (highest)	160	19.3	81	16.3	464	22.9
Meat/fish intake (approximate quartiles)						
First (lowest)	165	19.9	114	22.9	421	20.8
Second	257	31.0	161	32.3	714	35.3
Third	186	22.5	95	19.1	417	20.6
Fourth (highest)	220	26.6	128	25.7	472	23.3
Total servings (approximate quartiles)						
First (lowest)	240	29.0	150	30.1	488	24.1
Second	221	26.7	142	28.5	534	26.4
Third	205	24.7	109	21.9	495	24.5
Fourth (highest)	162	19.6	97	19.5	507	25.0

Results

The distribution of cases and controls according to sex, age, and other selected covariates is shown in Table 1. Colorectal cancer risk was positively related to family history of colorectal cancer (RR, 2.2; 95% CI, 1.6–3.1) and to total energy intake (RR, 1.6; 95% CI, 1.3–2.1, highest *versus* lowest quartile) but was inversely related to total number of servings (RR, 0.8; 95% CI, 0.6–1.0, highest *versus* lowest quartile).

Total food diversity and diversity within various food groups are presented in Table 2. Colorectal cancer risk was inversely associated with total diet diversity. A significant inverse association (multivariate RR, 0.7) for the highest (more diverse diet) *versus* the lowest quartile was observed, together with a significant linear trend (χ^2_1 trend, 8.5; $P < 0.01$). After adjustment for total vegetable, fruit, and meat and fish intake, the RR was 0.8 (χ^2_1 trend, 3.9; $P < 0.05$). A similar protection was observed for diversity within vegetables (RR, 0.6, highest *versus* lowest quartile; χ^2_1 trend, 29.6; $P < 0.01$). Again, after adjustment for total vegetable, fruit, and meat and fish intake, the RR for the highest quartile was 0.7 (χ^2_1 trend, 8.9; $P < 0.01$). No consistent association was found for fruit, meat and fish, and other food group diversity, whereas diversity in carbohydrate consumption seemed to increase the risk of colorectal cancer (RR, 1.4). No differences in the pattern of risk for various measures of diet diversity were observed when colon and rectal cancers were considered separately (Table 2).

A similar pattern of risk between total diversity and colorectal cancer was observed across separate strata of sex and age (Table 3), although the protection was somewhat stronger among women and subjects younger than 60 years. No notable differences in risk patterns appeared when colon and rectal

Table 2 RR estimates and 95% CIs of colorectal cancer in relation to selected measures of diet diversity, Milan, Italy, 1985–1992

Approximate quantiles of diversity	Colon cancer		Rectal cancer		Controls		RR (95% CI)[a]		
	n	%	*n*	%	*n*	%	Colon	Rectal	Colorectal
Total diversity									
First (lowest)	263	31.8	164	32.9	563	27.8	1[b]	1[b]	1[b]
Second	188	22.7	113	22.7	382	18.9	1.2 (0.9–1.5)	1.2 (0.9–1.6)	1.2 (0.9–1.4)
Third	239	28.8	149	29.9	642	31.7	0.9 (0.7–1.1)	0.9 (0.7–1.3)	0.9 (0.7–1.1)
Fourth (highest)	138	16.7	72	14.5	437	21.6	0.7 (0.6–1.0)	0.7 (0.5–0.9)	0.7 (0.6–0.9)
χ^2_1 *trend*							*6.4 (P = 0.01)*	*4.7 (P = 0.02)*	*8.5 (P < 0.01)*
Vegetable diversity									
First (lowest)	334	40.4	190	38.1	598	29.6	1[b]	1[b]	1[b]
Second	158	19.1	113	22.7	363	17.9	0.8 (0.6–1.1)	1.0 (0.8–1.4)	0.9 (0.7–1.1)
Third	151	18.2	89	17.9	389	19.2	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.8 (0.6–1.0)
Fourth (highest)	185	22.3	106	21.3	674	33.3	0.6 (0.4–0.7)	0.6 (0.4–0.8)	0.6 (0.4–0.7)
χ^2_1 *trend*							*22.9 (P < 0.01)*	*12.9 (P < 0.01)*	*29.6 (P < 0.01)*
Fruit diversity									
First (lowest)	194	23.4	105	21.1	391	19.3	1[b]	1[b]	1[b]
Second	295	35.6	200	40.2	720	35.6	0.9 (0.7–1.2)	1.2 (0.9–1.5)	1.0 (0.8–1.3)
Third (highest)	339	41.0	193	38.7	913	45.1	0.9 (0.7–1.1)	0.9 (0.7–1.3)	0.9 (0.7–1.1)
χ^2_1 *trend*							*1.1 (P = 0.29)*	*0.7 (P = 0.40)*	*1.0 (P = 0.31)*
Meat diversity									
First (lowest)	231	27.9	147	29.5	544	26.9	1[b]	1[b]	1[b]
Second	215	26.0	138	27.7	481	23.8	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.1 (0.9–1.3)
Third	218	26.3	121	24.3	549	27.1	1.0 (0.8–1.3)	1.0 (0.7–1.3)	1.0 (0.8–1.2)
Fourth (highest)	164	19.8	92	18.5	450	22.2	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.8 (0.7–1.0)
χ^2_1 *trend*							*0.5 (P = 0.49)*	*1.3 (P = 0.25)*	*1.2 (P = 0.28)*
Carbohydrate diversity									
First (lowest)	468	56.5	289	58.0	1276	63.0	1[b]	1[b]	1[b]
Second (highest)	360	43.5	209	42.0	748	37.0	1.3 (1.1–1.6)	1.4 (1.1–1.8)	1.4 (1.2–1.6)
Other food diversity									
First (lowest)	170	20.5	109	21.9	395	19.6	1[b]	1[b]	1[b]
Second	323	39.0	210	42.2	855	42.2	0.8 (0.6–1.0)	0.9 (0.7–1.3)	0.9 (0.7–1.1)
Third (highest)	335	40.5	179	35.9	774	38.2	1.0 (0.8–1.2)	0.9 (0.7–1.2)	0.9 (0.8–1.2)
χ^2_1 *trend*							*0.1 (P = 0.77)*	*0.3 (P = 0.59)*	*0.1 (P = 0.94)*

[a] Estimates from multiple logistic regression equations, including terms for age, sex, area of residence, education, family history of colorectal cancer, total number of servings, body mass index, and total energy intake.
[b] Reference category.

cancers were considered separately or when vegetable, fruit, meat and fish, carbohydrate, and other food diversity were analyzed in separate strata of sex and age (data not shown).

Discussion

This study, based on a large data set, suggests that total diet diversity and vegetable diversity are related to a moderately decreased risk of colorectal cancer, whereas no clear pattern emerged for fruit diversity. This could be explainable, in part, because of the low number of foods included in the fruit group, although a real difference cannot be disregarded. Similarly, a previous report from this study failed to establish a protective effect of fruit intake (9). In this study, as well as in several other reports (1), red meat but not poultry or fish was associated with colorectal cancer risk (9). Therefore, the absence of an association with overall meat and fish diversity is not surprising. The inverse associations observed were independent of total energy intake and other recognized or likely confounding factors and were consistently observed for colon and rectal cancer and in separate strata of sex and age.

These findings are apparently at variance with those from a case-control study of colorectal cancer from New York State (5) but are in broad agreement with the results on food diversity and total mortality from the First National Health and Nutrition Examination Survey follow-up study (8).

Table 3 RR estimates and 95% CIs of colorectal cancer in relation to total diet diversity in separate strata of sex and age, Milan, Italy, 1985–1992

	Total diversity (approximate quartiles)				χ^2_1 trend
	First	Second	Third	Fourth	
Sex					
Male[a]	236/347	166/234	200/361	109/247	
RR[b]	1[c]	1.2	0.9	0.8	2.0
(95% CI)		(0.9–1.6)	(0.7–1.3)	(0.6–1.2)	(P = 0.16)
Female[a]	191/216	135/148	188/281	101/190	
RR[b]	1[c]	1.0	0.6	0.6	13.8
(95% CI)		(0.8–1.1)	(0.4–0.9)	(0.4–0.8)	(P < 0.01)
Age					
<60 yr[a]	152/313	122/247	186/413	92/307	
RR[b]	1[c]	1.1	0.9	0.6	5.9
(95% CI)		(0.8–1.5)	(0.7–1.3)	(0.4–0.9)	(P = 0.02)
≥60 yr[a]	275/250	179/135	202/229	118/130	
RR[b]	1[c]	1.2	0.8	0.8	2.7
(95% CI)		(0.9–1.7)	(0.6–1.1)	(0.6–1.2)	(P = 0.10)

[a] Cases/controls.
[b] Estimates from multiple logistic regression equations, including terms for age and sex (if applicable), area of residence, education, family history of colorectal cancer, body mass index, total number of servings, and total energy intake.
[c] Reference category.

A possible explanation for the observed protective effect of a more varied diet on colorectal cancer risk is that individuals eating more varied foods are more likely to consume a number (and quantity) of beneficial components of a diet, although a similar line of reasoning would apply to foods related to a higher risk of cancer. A more heterogenous diet, however, could have also been related to a number of healthier lifestyle habits not yet clarified (2). In the analysis, however, we were able to allow for major identified potential confounding factors, including major indicators of socioeconomic status and lifestyle habits.

This is a typical hospital-based, case-control study and, as such, has all the related limitations and strengths (11). A major limitation is the low number (and types) of foods investigated, which consequently reduces the scope for analyzing diet diversity. Differential recall of diet by cases and controls is, however, unlikely, because the potential relationship between diet diversity and colorectal cancer risk was unknown to the interviewers and to the subjects interviewed. Among the strengths of the study, the comparable catchment area of cases and controls and the almost complete participation which are reassuring against selection bias. Cases and controls, moreover, were directly interviewed in the same setting, thus allowing us to obtain reasonably comparable information. With reference to confounding, the results were virtually unmodified after allowance for several covariates, including weekly number of servings and total energy intake. The absence of a material effect variation for total diet diversity and vegetable diversity after adjustment for total vegetable and fruit intake is noteworthy (even considering the possibility of overadjustment in these models) and suggests that the inverse associations observed are not simply explained by a protective effect from an increased intake of vegetables and fruits. Furthermore, this study was able to find significant associations with specific food items and nutrients (9, 10), generally consistent with our knowledge on dietary habits in colorectal carcinogenesis (1).

The findings here reported for colorectal cancer—the most common human cancer in nonsmokers in developed countries and one of major diet-related neoplasms—add epidemiological support to the dietary guidelines recommending a more varied diet (2–4) and, if confirmed, would have relevant public health implications.

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References

1. Potter, J. D., Slattery, M. L., Bostick, R. M., and Gapstur, S. M. Colon cancer: a review of the epidemiology. Epidemiol. Rev., *15:* 499–545, 1993.

2. Kant, A. K., Block, G., Schatzkin, A., Ziegler, R. G., and Nestle, M. Dietary diversity in the US population, NHANES II, 1976–1980. J. Am. Diet Assoc., *91:* 1526–1531, 1991.

3. Butrum, R. R., Clifford, C. K., and Lanza, E. NCI dietary guidelines: rationale. Am. J. Clin. Nutr., *48:* 888–895, 1988.

4. National Research Council. Diet and Health: Implications for Reducing Chronic Disease Risk. Washington, DC: National Academy Press, 1989.

5. McCann, S. E., Randall, E., Marshall, J. R., Graham, S., Zielezny, M., and Freudenheim, J. L. Diet diversity and risk of colon cancer in Western New York. Nutr. Cancer, *21:* 133–141, 1994.

6. Randall, E., Nichaman, M. Z., and Contant, C. F. Diet diversity and nutrient intake. J. Am. Diet. Assoc., *85:* 830–836, 1985.

7. Krebs-Smith, S. M., Smiciklas-Wright, H., Guthrie, H. A., and Krebs-Smith, J. The effects of variety in foods choices on dietary quality. J. Am. Diet Assoc., *87:* 897–903, 1987.

8. Kant, A. K., Schatzkin, A., Harris, T. B., Ziegler, R. G., and Block, G. Dietary diversity and subsequent mortality in the First National Health and Nutrition Examination Survey epidemiologic follow-up study. Am. J. Clin. Nutr., *57:* 434–450, 1993.

9. La Vecchia, C., Negri, E., Decarli, A., D'Avanzo, B., Gallotti, L., Gentile, A., and Franceschi, S. A case-control study of diet and colo-rectal cancer in Northern Italy. Int. J. Cancer, *41:* 492–498, 1988.

10. Ferraroni, M., La Vecchia, C., D'Avanzo, B., Negri, E., Franceschi, S., and Decarli, A. Selected micronutrient intake and the risk of colorectal cancer. Br. J. Cancer, *70:* 1150–1155, 1994.

11. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research. I. The Analysis of Case-Control Studies. IARC Scientific Publ. No. 32. Lyon, France: IARC, 1980.

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