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FOOD GROUPS AND RISK OF COLORECTAL CANCER IN ITALY

Silvia FRANCESCHI[1]*, Adriano FAVERO[1], Carlo LA VECCHIA[2,3], Eva NEGRI[2], Ettore CONTI[4], Maurizio MONTELLA[5], Attilio GIACOSA[6], Oriana NANNI[7] and Adriano DECARLI[3,8]

[1]*Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano (PN), Italy*
[2]*Istituto di Ricerche Farmacologiche "Mario Negri," Milan, Italy*
[3]*Istituto di Statistica Medica e Biometria, Università di Milano, Milan, Italy*
[4] *Servizio di Epidemiologia e Oncogenesi, Istituto Regina Elena, Rome, Italy*
[5]*Istituto Tumori "Fondazione Pascale," Naples, Italy*
[6]*Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy*
[7]*Istituto Oncologico Romagnolo, Ospedale Pierantoni, Forlì, Italy*
[8]*Istituto Nazionale Tumori, Milan, Italy*

The proportion of colorectal cancer attributed to dietary habits is high, but several inconsistencies remain, especially with respect to the influence of some food groups. To further elucidate the role of dietary habits, 1,225 subjects with cancer of the colon, 728 with cancer of the rectum and 4,154 controls, hospitalized with acute non-neoplastic diseases, were interviewed between 1992 and 1996 in 6 different Italian areas. The validated food-frequency questionnaire included 79 questions on food items and recipes, categorised into 16 food groups. After allowance for non-dietary confounding factors and total energy intake, significant trends of increasing risk of colorectal cancer with increasing intake emerged for bread and cereal dishes (odds ratio [OR] in highest *vs.* lowest quintile = 1.7), potatoes (OR = 1.2), cakes and desserts (OR = 1.1), and refined sugar (OR = 1.4). Intakes of fish (OR = 0.7), raw and cooked vegetables (OR = 0.6 for both) and fruit other than citrus fruit (OR = 0.7) showed a negative association with risk. Consumption of eggs and meat (white, red or processed meats) seemed uninfluential. Most findings were similar for colon and rectum, but some negative associations (*i.e.,* coffee and tea, and fish) appeared stronger for colon cancer. Our findings lead us to reconsider the role of starchy foods and refined sugar in light of recent knowledge on the digestive physiology of carbohydrates and the insulin/colon cancer hypothesis. The beneficial role of most vegetables is confirmed, with more than 20% reduction in risk of colorectal cancer from the addition of one daily serving. *Int. J. Cancer* 72:56–61, 1997.

The proportion of colorectal cancer avoidable by changes in diet is thought to be high, probably one of the highest among cancer sites. It was estimated to be in the order of 90% by Doll and Peto in 1981 and 70%, with a lower limit of 50%, by Willett in 1994 (Nelson, 1996). Research on diet and colon cancer has concentrated, with respect to food groups, on vegetables and fruit (Potter, 1996), red meat (Willett *et al.,* 1990; Giovannucci *et al.,* 1994; Goldbohm *et al.,* 1994) and dairy products (Kampman *et al.,* 1994; Kearney *et al.,* 1996). In the search for the mechanism(s) responsible of inter-country and inter-individual variations in risk, some food constituents (*e.g.,* fiber and animal fat, Giovannucci, 1995), micronutrients and minerals (*e.g.,* calcium and vitamin D, Kampman *et al.,* 1994; Kearney *et al.,* 1996; folate, Giovannucci, 1995; ascorbate and carotenoids, Ferraroni *et al.,* 1994) were particularly investigated.

The present multicentre case-control study was undertaken in Italy to elucidate the role of recent diet in the development of cancer of the colon and rectum. This approach provides original information on a southern European population where dietary and life-style habits and awareness of diet-related health issues are different from those in North America and northern Europe, where most other investigations have been conducted.

Our analysis concerns the evaluation of individual food items or food groups and, therefore, avoids some problems inherent to analyses of nutrient intake (*e.g.,* inaccuracy and incompleteness of food-composition tables). It does not preclude, however, adjustment for total energy intake in order to assess the issue of dietary composition rather than absolute intake and to allow for over- or under-reporting. Furthermore, it offers an advantage from a preventive viewpoint since results with respect to food groups are more easily translatable than those on nutrients into dietary recommendations.

MATERIAL AND METHODS

A case-control study of cancer of the colon and rectum has been conducted between January 1992 and June 1996 in 6 Italian areas: the provinces of Pordenone and Gorizia in north-eastern Italy; the urban areas of Milan and Genoa and the provinces of Forlì, in the north; and Latina and the urban area of Naples in the south.

Cases were subjects with histologically confirmed colorectal cancer diagnosed no longer than 1 year prior to the interview and no previous diagnoses of cancer at other sites. Overall, 1,225 subjects with cancer of the colon (688 men and 537 women, median age 62, range 19–74, years) and 728 with cancer of the rectum and recto-sigmoid junction (437 men and 291 women, median age 62, range 23–74, years) were included (Table I).

Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment areas of cases for acute, non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases or to long-term modifications of diet. They included 2,073 men and 2,081 women aged 19–74 years (median age 58) belonging to the following diagnostic categories: traumas, mostly fractures and sprains (27%); other orthopaedic disorders, such as low back pain and disc disorders (24%); acute surgical conditions (18%); eye diseases (24%); and other miscellaneous diseases, such as ear, nose, throat, skin and dental conditions (7%). Controls were younger than cases (Table I) since they were collected within the framework of a multi-site case-control study including cancer sites with an age distribution different from that of cancer of the colon-rectum (*e.g.,* breast). Thus, we allowed carefully for the age unbalance in statistical analyses.

Because most areas studied are not covered by cancer registries, it was not possible to estimate the proportion of colorectal cancer patients interviewed. However, the hospitals included in our study have most of the diagnostic and therapeutic facilities available in the areas (except for the urban areas of Milan, Genoa and Naples) and therefore have a high proportion of colorectal cancer cases referred to them. On average, about 4% of cases and controls

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*Correspondence to: Servizio di Epidemiologia, Centro di Riferimento Oncologico, Via Pedemontana Occ., 33081 Aviano (PN), Italy. Fax: 39(434)659222. e-mail: franceschis@ets.it

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TABLE I – DISTRIBUTION OF 1,225 CASES OF COLON CANCER, 728 OF RECTAL CANCER AND 4,154 CONTROLS[1] BY SEX, AGE GROUP, CENTER, YEARS OF EDUCATION, PHYSICAL ACTIVITY AND TOTAL ENERGY INTAKE: ITALY, 1992–1996

Characteristic	Cancer cases		Controls, number (%)
	Colon, number (%)	Rectum, number (%)	
Sex			
Male	688 (56)	437 (60)	2,073 (50)
Female	537 (44)	291 (40)	2,081 (50)
Age group (yr)			
<40	55 (4)	26 (4)	347 (8)
40–49	114 (9)	67 (9)	732 (18)
50–59	321 (26)	197 (27)	1,244 (30)
60–69	518 (42)	306 (42)	1,356 (33)
≥70	217 (18)	132 (18)	475 (11)
Center			
Pordenone/Gorizia	401 (33)	216 (30)	1,358 (33)
Milan	262 (21)	226 (31)	1,082 (26)
Genoa	152 (12)	73 (10)	498 (12)
Forlì	65 (5)	29 (4)	247 (6)
Naples	117 (10)	76 (10)	387 (9)
Rome/Latina	228 (19)	108 (15)	582 (14)
Education (yr)			
<7	621 (51)	422 (58)	2,276 (55)
7–11	331 (27)	181 (25)	1,156 (28)
≥12	267 (22)	122 (17)	693 (17)
χ^2_2	48.66[3]	0.41	
Physical activity (at the workplace)			
Low	444 (36)	231 (32)	1,378 (33)
Medium	451 (37)	258 (35)	1,476 (36)
High	330 (27)	239 (33)	1,299 (31)
χ^2_2	42.59[3]	1.40	
Total energy intake (quintiles)			
I	210 (17)	144 (20)	865 (21)
II	244 (20)	133 (18)	845 (20)
III	270 (22)	144 (20)	805 (19)
IV	249 (20)	144 (20)	830 (20)
V	252 (21)	163 (22)	809 (19)
χ^2_4	11.08[3]	3.39	

[1]Some figures do not add up to the total because of some missing values.–[2]Compared to the control group, adjusted for age, sex and centre.–[3]$p < 0.05$.

invited to participate in the study during hospital stay refused to be interviewed.

The same structured questionnaire and coding manual were used in each centre, and all interviewers were centrally trained and routinely supervised. Data checking for consistency and reliability also was conducted centrally. The questionnaire included information on socio-demographic characteristics, such as education and occupation, lifetime smoking and alcohol-drinking habits, physical activity, anthropometric measures at various ages, a problem-oriented personal medical history and family history of cancer. Menstrual and reproductive history and history of use of oral contraceptives, hormone replacement treatment and female hormones for other indications also were recorded in women. Dietary habits were investigated through a validated food-frequency consumption section, whose average duration was 40 min.

Food-frequency questionnaire

The interviewer-administered food-frequency questionnaire (FFQ) was developed to assess subjects' habitual diet, including total energy. Average weekly frequency of consumption of specific foods or food groups, as well as complex recipes (including the most common ones in the Italian diet) during the 2 years prior to cancer diagnosis or hospital admission (for controls) was elicited. Intakes lower than once a week but at least once a month were coded as 0.5 per week, whereas foods eaten less than once per month were coded as 0.

The FFQ included 79 foods, food groups or recipes grouped into 6 sections: (*i*) bread and cereal dishes (first courses); (*ii*) meat and foods used as meat substitutes in meals in Italy (second courses); (*iii*) vegetables (side dishes); (*iv*) fruit; (*v*) sweets, desserts and soft drinks; (*vi*) milk, coffee, tea and artificial sweeteners. Another section dealt with alcoholic beverage consumption. At the end of some sections, one or two summary questions were included concerning all food items or dishes of a certain type (*e.g.*, any type of meat). Several questions aimed at assessing fat intake pattern were also included.

Satisfactory reproducibility (Franceschi *et al.*, 1993, 1995) and validity (Decarli *et al.*, 1996) of the FFQ have been reported. Spearman correlation coefficients (r) for intake frequency of various foods ranged from 0.35 (chicken or turkey, boiled) to 0.80 (table sugar). Most coefficients were between 0.60 and 0.80 (mean $r = 0.59$).

Statistical analysis

Food items and recipes were categorised into 16 food groups, *i.e.*, milk (5 questions), coffee and tea (4 questions), bread and cereal dishes (14 questions), eggs (2 questions), poultry (2 questions), red meat (beef, veal and pork, 8 questions), processed meats (3 questions), fish (3 questions), cheese (5 questions), raw vegetables (4 questions), cooked vegetables (9 questions), potatoes (2 questions), citrus fruit (2 questions), other fruit (8 questions), cakes and desserts (7 questions) and refined sugar (including honey and candies, 4 questions), as in Franceschi *et al.* (1995). Some recipes were allocated to 2 food groups (half frequency each). For instance, pizza was apportioned into both bread and cereal dishes and cheese. The sum of the weekly frequency of intake of food items and recipes included in the same group was approximately distributed into quintiles based on the entire study population. The use of artificial sweeteners was assessed in 2 groups (never/ever users). With respect to vegetables and fruit, diversity was defined as the number of different types of vegetable and fruit eaten on average at least weekly.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed, using unconditional multiple logistic regression models (Breslow and Day, 1980). All regression equations included terms for age in quinquennia, study centre, years of education (<7/7–11/≥12), level of physical activity (low, medium, high) at the workplace (since the level of recreational physical activity was generally low and unrelated to cancer risk), and quintile of total energy intake (<1,642, 1,642–2,002, 2,003–2,350, 2,351–2,826, ≥2,827 kcal). Inclusion in the models of other variables, such as total number of servings of any food per week, alcohol consumption, body mass index, family history of colorectal cancer and, in women, parity and age at first birth, did not materially modify any of the estimates. Tests for trend for intake quintiles of food groups were based on the likelihood ratio test between the models with and without a linear term for each food or food group.

Intake frequency of each food group was introduced as a continuous variable. In these models, colon and rectal cancers were examined separately, and the unit of measurement for each food group was set at 7 per week. Hence, the model with the continuous coefficient gives an estimate of the OR relative to an increase of 1 average serving per day. For sugar, this corresponded to 4 teaspoons. To investigate deviation from linearity, the likelihood-ratio test between models with and without a further quadratic term for the examined food group was used. The quadratic term did not improve the model fit, except for bread and cereal dishes (colon) and processed meats and cooked vegetables (rectum).

All analyses were performed separately for males and females and for individuals below age 50 years and those aged 50 or above (not shown). The interaction terms between food group intake and sex or age were calculated by means of the Wald χ^2 test with 1 degree of freedom.

RESULTS

After allowance for age, sex and centre, patients with cancer of the colon, but not rectum, were significantly more educated than controls (Table I). They also reported significantly lower levels of physical activity at the workplace. With respect to total energy, only cases of colon cancer showed significantly higher intake.

Table II shows the upper limit of intake quintiles of each food group and the corresponding energy-adjusted ORs. Intakes of eggs, poultry, red meat, processed meats, cheese and citrus fruit were not significantly related to cancer risk. A significant trend of increasing risk with increasing intake emerged for bread and cereal dishes (OR in highest as compared to lowest quintile = 1.7), potatoes (OR = 1.2), cakes and desserts (OR = 1.1) and refined sugar (OR = 1.4).

Four food groups seemed to exert a significant protection against colorectal cancer: fish (OR in highest as compared to lowest quintile = 0.7), raw and cooked vegetables (OR = 0.6 for both) and fruit other than citrus fruit (OR = 0.7). Milk and coffee and tea showed negative associations of borderline significance.

ORs for an intake increase of 1 serving per day of each examined food group are shown in Table III, separately for cancers of the colon and rectum and all colorectal cancer. Most findings were similar for the 2 subsites. For all vegetables combined, one more serving per day gave an OR of 0.7 (95% CI 0.7–0.8) for colon cancer and 0.8 (95% CI 0.7–0.9) for rectal cancer. However, significantly lowered risks for coffee and tea and fish were restricted to colon cancer, while poultry meat intake was positively associated with rectal cancer. Use of artificial sweeteners was associated with ORs of 0.9 (95% CI 0.7–1.1) for colon cancer and 0.8 (95% CI 0.6–1.0) for rectal cancer (not shown).

All food groups which showed significant associations with one or both cancer sites were included in the same multiple logistic equations, to allow for a mutual confounding effect. All retained their significant trends in risk except fruit, whose intake was

TABLE II – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI)[1] ACCORDING TO INTAKE QUINTILE OF FOOD GROUPS AMONG 1,953 CASES OF COLORECTAL CANCER AND 4,154 CONTROLS: ITALY, 1992–1996

Food group	Intake quintile					χ^2_1 (trend)
	1	2	3	4	5	
Milk						
Upper limit (servings/week)	0.0	3.5	7.0	10.3		
OR (95% CI)	1	1.03 (0.86–1.23)	1.01 (0.86–1.18)	0.94 (0.77–1.13)	0.83 (0.68–1.01)	3.81
Coffee and tea						
Upper limit (servings/week)	6.5	13.5	20.5	27.5		
OR (95% CI)	1	0.96 (0.78–1.18)	0.85 (0.69–1.03)	0.98 (0.80–1.20)	0.79 (0.64–0.98)	3.60
Bread and cereal dishes						
Upper limit (servings/week)	19.3	23.8	29.3	37.8		
OR (95% CI)	1	1.09 (0.91–1.32)	1.20 (0.99–1.45)	1.19 (0.97–1.46)	1.69 (1.36–2.10)	19.05[2]
Eggs						
Upper limit (servings/week)	0.0	0.5	1.0	2.0		
OR (95% CI)	1	1.14 (0.94–1.39)	1.16 (0.97–1.38)	1.08 (0.91–1.28)	0.92 (0.75–1.14)	0.47
Poultry						
Upper limit (servings/week)	0.5	1.0	2.0	3.0		
OR (95% CI)	1	1.26 (1.06–1.51)	1.18 (1.00–1.41)	0.99 (0.81–1.22)	1.26 (1.00–1.57)	0.22
Red meat						
Upper limit (servings/week)	2.3	3.5	4.8	6.3		
OR (95% CI)	1	0.98 (0.83–1.17)	1.12 (0.94–1.34)	1.00 (0.83–1.21)	1.14 (0.93–1.39)	1.45
Processed meats						
Upper limit (servings/week)	1.0	2.0	3.0	4.0		
OR (95% CI)	1	1.21 (1.03–1.42)	1.06 (0.89–1.26)	1.24 (1.02–1.49)	1.02 (0.84–1.24)	0.13
Fish						
Upper limit (servings/week)	0.5	1.0	1.5	2.5		
OR (95% CI)	1	0.97 (0.81–1.17)	0.95 (0.78–1.17)	0.81 (0.68–0.98)	0.72 (0.59–0.88)	15.32[2]
Cheese						
Upper limit (servings/week)	2.4	3.5	4.7	6.2		
OR (95% CI)	1	1.15 (0.97–1.37)	0.99 (0.83–1.18)	0.91 (0.76–1.09)	0.99 (0.82–1.19)	1.48
Raw vegetables						
Upper limit (servings/week)	4.0	6.8	9.0	12.0		
OR (95% CI)	1	0.92 (0.78–1.10)	0.84 (0.71–1.00)	0.72 (0.60–0.87)	0.59 (0.48–0.71)	32.40[2]
Cooked vegetables						
Upper limit (servings/week)	2.9	4.2	5.4	7.3		
OR (95% CI)	1	0.87 (0.73–1.03)	0.72 (0.60–0.86)	0.65 (0.54–0.78)	0.57 (0.47–0.69)	43.06[2]
Vegetables (all)						
Upper limit (servings/week)	8.4	11.6	14.5	18.1		
OR (95% CI)	1	0.98 (0.82–1.16)	0.72 (0.60–0.85)	0.64 (0.53–0.77)	0.57 (0.47–0.69)	50.55[2]
Potatoes						
Upper limit (servings/week)	0.5	1.0	2.0	3.0		
OR (95% CI)	1	1.16 (0.97–1.39)	1.21 (1.03–1.43)	1.26 (1.03–1.54)	1.20 (0.96–1.51)	4.35[3]
Citrus fruit						
Upper limit (servings/week)	1.0	3.4	4.0	7.0		
OR (95% CI)	1	0.93 (0.78–1.10)	0.84 (0.71–1.00)	0.89 (0.74–1.06)	1.02 (0.85–1.22)	0.06
Other fruit						
Upper limit (servings/week)	7.2	10.8	14.0	19.0		
OR (95% CI)	1	0.87 (0.73–1.04)	0.70 (0.58–0.83)	0.74 (0.62–0.89)	0.72 (0.60–0.87)	15.00[2]
Cakes and desserts						
Upper limit (servings/week)	0.7	2.1	4.5	8.5		
OR (95% CI)	1	0.90 (0.75–1.07)	1.01 (0.84–1.21)	1.20 (1.01–1.44)	1.13 (0.93–1.37)	6.14[3]
Refined sugar						
Upper limit (servings/week)	7.5	20.5	30.5	48.5		
OR (95% CI)	1	1.35 (1.13–1.62)	1.24 (1.03–1.48)	1.33 (1.10–1.60)	1.43 (1.19–1.73)	10.09[2]

[1]Adjusted for age, sex, centre, education, physical activity and total energy intake.–[2]$p < 0.01$.–[3]$p < 0.05$.

TABLE III – ODDS RATIOS AND CORRESPONDING 95% CONFIDENCE INTERVALS[1] AMONG 1,225 CASES OF COLON CANCER, 728 OF RECTAL CANCER AND 4,154 CONTROLS FOR AN INTAKE INCREASE OF ONE SERVING OF EACH FOOD GROUP PER DAY: ITALY, 1992–1996

Food group	Odds ratio (95% confidence interval)		
	Colon cancer	Rectal cancer	Both
Milk	0.96 (0.89–1.03)	0.92 (0.84–1.01)	0.95 (0.89–1.01)
Coffee and tea	0.96 (0.92–1.00)	0.99 (0.94–1.04)	0.97 (0.94–1.00)
Bread and cereal dishes	1.11 (1.06–1.16)	1.10 (1.05–1.15)	1.11 (1.07–1.15)
Eggs	0.85 (0.60–1.20)	1.30 (0.90–1.87)	1.00 (0.77–1.31)
Poultry	0.91 (0.63–1.30)	1.57 (1.03–2.41)	1.12 (0.83–1.51)
Red meat	1.06 (0.85–1.32)	1.16 (0.88–1.52)	1.09 (0.90–1.31)
Processed meats	1.08 (0.87–1.36)	0.78 (0.57–1.06)	0.97 (0.79–1.18)
Fish	0.42 (0.28–0.64)	0.72 (0.44–1.18)	0.53 (0.37–0.75)
Cheese	0.96 (0.80–1.15)	0.99 (0.79–1.25)	0.97 (0.83–1.13)
Raw vegetables	0.75 (0.67–0.84)	0.83 (0.73–0.95)	0.79 (0.72–0.86)
Cooked vegetables	0.61 (0.51–0.72)	0.69 (0.56–0.84)	0.65 (0.56–0.74)
Vegetables (all)	0.74 (0.68–0.81)	0.81 (0.73–0.90)	0.77 (0.72–0.83)
Potatoes	1.31 (0.93–1.86)	1.29 (0.86–1.95)	1.31 (0.98–1.75)
Citrus fruit	1.09 (0.98–1.23)	0.94 (0.80–1.09)	1.03 (0.94–1.14)
Other fruit	0.95 (0.90–1.01)	0.89 (0.82–0.96)	0.93 (0.88–0.98)
Cakes and desserts	1.01 (0.94–1.09)	1.04 (0.95–1.14)	1.02 (0.96–1.09)
Refined sugar	1.10 (1.02–1.19)	1.13 (1.03–1.23)	1.11 (1.05–1.19)

[1]Adjusted for age, sex, centre, education, physical activity and total energy intake.

positively correlated to vegetable intake (correlation coefficient = 0.19). Several stratified analyses of food intake by age group, level of education and body mass index did not disclose any significant interaction or effect modification. The results were consistent in the 6 different study areas; *e.g.*, for the highest intake quintile of bread and cereal dishes OR varied from 1.2 to 1.9. In no area was a significant risk trend seen for red meat.

ORs in men and women were comparable for all food groups, with the exception of bread and cereal dishes and potatoes, where the association was significantly more marked in, but not restricted to, women. For cancer of the colon, ORs in the highest as compared to the lowest intake quintile of bread and cereal dishes were 1.4 (95% CI 1.0–2.0) in men and 2.1 (95% CI 1.4–3.2) in women. Corresponding results for cancer of the rectum were 1.3 (95% CI 0.8–2.0) and 1.8 (95% CI 1.0–3.0), respectively.

With respect to hot beverages, coffee, but not tea, was inversely related to cancer of the colon. Type of recipe (*i.e.*, pasta or rice with butter or oil, tomato sauce or meat sauce) seemed uninfluential on the positive association with bread and cereal dishes. In this group, only high intake of pizza conferred a significant protection against cancer of the colon (OR = 0.8, 95% CI 0.7–1.0). Among different types of red and processed meat, none was associated with colorectal cancer risk. Also, individual habits with respect to trimming meat fat or eliminating chicken skin did not modify ORs. Our questionnaire included 5 types of deep-fried food (eggs, chicken, beef, fish and potatoes). None conferred an increased risk of colon or rectal cancer, but fried fish was significantly protective against colon cancer (OR = 0.8, 95% CI 0.6–0.9).

The inverse association with vegetable intake was similar not only for raw and cooked vegetables but also for almost all vegetables examined. ORs around 0.5 for the highest as compared to the lowest intake quintile were found for green peas and beans, lettuce-like salad and raw (colon) and cooked (rectum) carrots. Among individual types of fruit, high intakes of apples and pears, kiwi, peaches, apricots and prunes were significantly protective, whereas cooked fruit intake was positively associated to cancer risk. Among different dairy products, only high intake of skimmed milk was associated with a significant (40%) risk reduction.

Finally, risks by approximate tertile of diversity in the intake of vegetables and fruit are presented in Table IV. Consumption of many different types of vegetable and fruit seemed to exert a significant protection against both colon and rectal cancers. Allowance for total number of servings of vegetables and fruit, however, eliminated the favourable effect of diversity for rectal cancer and reduced that for colon cancer. The colon cancer OR in individuals who reported 8 or more different types of vegetables per week, as compared to less than 6, increased from 0.6 to 0.8 (95% CI 0.6–1.0).

TABLE IV – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) ACCORDING TO DIVERSITY OF INTAKE OF VEGETABLES AND FRUIT AMONG 1,225 CASES OF COLON CANCER, 728 OF RECTAL CANCER AND 4,154 CONTROLS: ITALY, 1992–1996

Site	Food group	Diversity[1]	OR (95% CI)[2]	OR adjusted for number of servings (95% CI)[3]
Colon	Vegetables	≤5[4]	1	1
		6–7	0.76 (0.65–0.89)	0.85 (0.71–1.01)
		≥8	0.62 (0.52–0.73)	0.77 (0.62–0.95)
		χ^2_1 (trend)	31.61[5]	6.38[5]
	Fruit	≤3[4]	1	1
		4–5	0.90 (0.78–1.04)	0.93 (0.79–1.09)
		≥6	0.79 (0.64–0.98)	0.80 (0.63–1.01)
		χ^2_1 (trend)	4.97[5]	3.29
Rectum	Vegetables	≤5[4]	1	1
		6–7	0.70 (0.57–0.85)	0.77 (0.62–0.96)
		≥8	0.72 (0.58–0.88)	0.85 (0.65–1.09)
		χ^2_1 (trend)	11.80[5]	2.11
	Fruit	≤3[4]	1	1
		4–5	0.81 (0.68–0.97)	0.91 (0.75–1.12)
		≥6	0.79 (0.61–1.02)	0.94 (0.70–1.25)
		χ^2_1 (trend)	4.96[5]	0.36

[1]Number of food items in major FFQ sections consumed at least weekly.–[2]Estimates from multiple logistic regression equations including terms for age, sex, centre, education, physical activity and total energy intake.–[3]Same as above, plus total weekly servings of vegetables or fruit.–[4]Reference category.–[5]$p < 0.05$.

DISCUSSION

Our present study, one of the largest case-control investigations conducted on diet and cancer of the colon and rectum so far, identified a few protective food groups (*i.e.*, fish, vegetables and fruit) and others (*i.e.*, bread and pasta, potatoes, cakes and desserts and refined sugar) to be positively associated with cancer risk.

Our results agree, in large part, with previous epidemiological data, especially with respect to the inverse association between vegetable intake and risk of cancers of the colon (as emerging from at least 24 of 29 studies, Potter, 1996; Shannon *et al.*, 1996) and the rectum (Potter, 1996). It is not clear whether the anti-carcinogenic effect of vegetables depends on physiological mechanisms (*e.g.*, stool bulking, transit time, bile acid binding) and/or specific chemical substances (*e.g.,* anti-oxidants, phenols, flavonoids, isothiocyanates, indoles) (Potter, 1996). According to our data, however, protective factors in vegetables seem to be (*i*) thermo-resistant, given the similar protection from raw and cooked vegetables, and (*ii*) of different types or widely distributed, given the consistent protection from a wide range of vegetables, from green peas to raw tomatoes and carrots. However, the variety of vegetable types gave a moderate benefit beyond the advantage of high vegetable intake *per se.*

As in most previous work (Potter, 1996), high intake of fruit was less strongly protective than high intake of vegetables. Fruit, therefore, may lack some beneficial property of vegetables, including perhaps low-energy and low-sugar content.

With respect to the associations with the predominant sources of carbohydrates (bread and pasta, sugar), our present results are apparently at variance with etiological hypotheses generated by ecological observations. However, the strong inverse correlation between starch intake and colorectal cancer incidence worldwide largely depended upon findings from some developing countries (*e.g.,* China and India, Cassidy *et al.,* 1994). In several populations where cereal consumption is elevated, especially in Europe, South America and Asia, case-control investigations found that risk was higher in those individuals who reported higher consumption of rice (Haenszel *et al.,* 1973, 1980), bread and/or pasta (La Vecchia *et al.,* 1988; Bidoli *et al.,* 1992; Macquart-Moulin *et al.,* 1986; Benito *et al.,* 1990), starch or carbohydrates (Iscovich *et al.,* 1992; Zaridze *et al.,* 1993). In many case-control studies and most prospective investigations, these types of food were not reported individually (Potter, 1996).

Direct associations between colorectal cancer and intake of refined sugar and cakes have been reported in a dozen studies (Manousos *et al.,* 1983; La Vecchia *et al.,* 1993; Bostick *et al.,* 1994 and related references; Shannon *et al.,* 1996). The quantity of refined sugar in the diet can significantly influence gut function and the composition of bowel contents (La Vecchia *et al.,* 1993).

Taken together, these findings lead us to reconsider the role of starchy foods and sugar, also in the light of recent knowledge on the digestive physiology of dietary carbohydrates (Cummings and Englyst, 1995) and on the role of insulin resistance and hyperinsulinemia in the promotion of colon carcinogenesis (Giovannucci, 1995). It has been shown that the physical form of food, rather than the degree of polymerisation, is the major determinant of the digestion rate of both starch and sugars in the small intestine and, hence, their availability for a stool bulking effect and fermentation by the anaerobic flora of the colon (Cummings and Englyst, 1995). In particular, starch digestion in the small intestine is rapid and complete for bread and freshly cooked pasta, as it is traditionally consumed in Italy, whereas the resistant starch fraction is high for legumes and starchy foods when they are cooked and cooled. Glycemic overload, from either refined sugar or starch intake, produces a compensatory increase of blood insulin, which is an important growth factor of the human colonic mucosa and a mitogen of tumor cell growth *in vitro* (Giovannucci, 1995).

A dozen ecological studies have reported correlations of 0.7 or greater between the national average intake of meat, fat or animal protein and mortality or incidence of colorectal cancer (Potter, 1996). Other indicators of a country affluence seemed, however, to be equally good predictors of the disease mortality than dietary variables (Potter, 1996). The majority of case-control studies showed some positive association between various indicators of intake of meat or animal fat and colon cancer (Potter, 1996). Of the 4 largest prospective investigations on the topic, each dealing with approximately 200 colon cancers, one (Willett *et al.,* 1990) reported a significant positive association with animal fat and 2 (Willett *et al.,* 1990; Giovannucci *et al.,* 1994) with intake of red meat. Conversely, Bostick *et al.* (1994) and Goldbohm *et al.* (1994) showed no consistent associations for fat and meat, with the possible exception, in Goldbohm *et al.* (1994), of processed meats. Our study does not lend support to the possibility that meat, including red meat, processed meats and broiled or fried meat, may increase the risk of cancer of the colon or rectum. A lower meat intake in Italy as compared to the United States coupled with a higher intake of vegetable oils and fish can lead to a higher unsaturated/saturated fatty acid ratio (Franceschi *et al.,* 1995, 1996) and, possibly, improve insulin sensitivity (Giovannucci, 1995).

Elevated fish intake exerted a protective effect against colon cancer, as in a few previous studies (Haenszel *et al.,* 1980; Willett *et al.,* 1990; Caygill *et al.,* 1996). Several previous investigations suggested a protective role of milk or milk constituents (*i.e.,* calcium and vitamin D) on cancer of the colon. Only a moderate inverse relation emerged between dairy product intake and colon cancer risk, though our population had elevated cheese consumption which accounted for about 40% of calcium intake and over 30% of saturated fatty acid intake.

In several studies, such as the present one, high coffee consumption has been associated with about 30% decreases of cancer of the colon (Potter, 1996). Tea and other non-alcoholic beverages (*i.e.,* fruit juices and soft drinks) were uninfluential on colon cancer risk, but we had no sufficient data to test the hypothesis that high water intake may exert a favourable effect (Shannon *et al.,* 1996).

In conclusion, our data showed that cancer of the colon and cancer of the rectum (which has been far less often studied, Potter, 1996) largely share the same dietary determinants. Despite differences in the age and subsite distribution by gender (Potter, 1996), we also did not find strong reasons to consider the diet–colorectal cancer link qualitatively different in men and women.

Supplementing diet with vegetables, fruit and fish appears to be the practical implication of our as well as most previous epidemiological studies. One more serving per day of vegetables afforded in our study more than 20% protection from colorectal cancer. Conversely, the adverse effects of high intake of bread, pasta and refined sugar support the hypothesis of a role of glycemic overload and hyperinsulinemia in carcinogenesis. These issues should be reexamined with available epidemiological data if effective dietary recommendations on the intake of various sources of carbohydrates are to be given.

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REFERENCES

BENITO, E., OBRADOR, A., STIGGELBOUT, A., BOSCH, F.X., MULET, M., MUÑOZ, N. and KALDOR, J., A population-based case-control study of colorectal cancer in Mallorca. I. Dietary factors. *Int. J. Cancer,* **45,** 69–76 (1990).

BIDOLI, E., FRANCESCHI, S., TALAMINI, R., BARRA, S. and LA VECCHIA, C., Food consumption and cancer of the colon and rectum in north-eastern Italy. *Int. J. Cancer,* **50,** 223–229 (1992).

BOSTICK, R.M., POTTER, J.D., KUSHI, L.H., SELLERS, T.A., STEINMETZ, K.A., MCKENZIE, D.R., GAPSTUR, S.M. and FOLSOM, A.R., Sugar, meat and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control,* **5,** 38–52 (1994).

BRESLOW, N.E. and DAY, N.E., *Statistical methods in cancer research. Vol. I. The analysis of case-control studies,* IARC Scientific Publications **32,** International Agency for Research on Cancer, Lyon (1980).

CASSIDY, A., BINGHAM, S.A. and CUMMINGS, J.H., Starch intake and colorectal cancer risk: an international comparison. *Brit. J. Cancer,* **69,** 937–942 (1994).

CAYGILL, C.P.J., CHARLETT, A. and HILL, M.J., Fat, fish, fish oil and cancer. *Brit. J. Cancer,* **74,** 159–164 (1996).

CUMMINGS, J.H. and ENGLYST, H.N., Gastrointestinal effects of food carbohydrate. *Amer. J. clin. Nutr.,* **61**(Suppl.), 938S–945S (1995).

DECARLI, A., FRANCESCHI, S., FERRARONI, M., GNAGNARELLA, P., PARPINEL, M.T., LA VECCHIA, C., NEGRI, E., SALVINI, S., FALCINI, F. and GIACOSA, A., Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. *Ann. Epidemiol.,* **6,** 110–118 (1996).

FERRARONI, M., LA VECCHIA, C., D'AVANZO, B., NEGRI, E., FRANCESCHI, S. and DECARLI, A., Selected micronutrient intake and the risk of colorectal cancer. *Brit. J. Cancer,* **70,** 1150–1155 (1994).

FRANCESCHI, S., FAVERO, A., DECARLI, A., NEGRI, E., LA VECCHIA, C., FERRARONI, M., RUSSO, A., SALVINI, S., AMADORI, D., CONTI, E., MONTELLA, M. and GIACOSA, A., Intake of macronutrients and risk of breast cancer. *Lancet,* **347,** 1351–1356 (1996).

FRANCESCHI, S., FAVERO, A., LA VECCHIA, C., NEGRI, E., DAL MASO, L., SALVINI, S., DECARLI, A. and GIACOSA, A., Influence of food groups and food diversity on breast cancer risk in Italy. *Int. J. Cancer,* **63,** 785–789 (1995).

FRANCESCHI, S., NEGRI, E., SALVINI, S., DECARLI, A., FERRARONI, M., FILIBERTI, R., GIACOSA, A., TALAMINI, R., NANNI, O., PANARELLO, G. and LA VECCHIA, C., Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. *Europ. J. Cancer,* **29A,** 1–10 (1993).

GIOVANNUCCI, E., Insulin and colon cancer. *Cancer Causes Control,* **6,** 164–179 (1995).

GIOVANNUCCI, E., RIMM, E.B., STAMPFER, M.J., COLDITZ, G.A., ASCHERIO, A. and WILLETT, W.C., Intake of fat, meat and fiber in relation to risk of colon cancer in men. *Cancer Res.,* **54,** 2390–2397 (1994).

GOLDBOHM, R.A., VAN DEN BRANDT, P.A., VAN'T VEER, P. BRANTS, H.A.M., DORANT, E., STURMANS, F. and HERMUS, R.J.J., A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res.,* **54,** 718–723 (1994).

HAENSZEL, W., BERG, J.W., SEGI, M., KURIHARA, M. and LOCKE, F.B., Large-bowel cancer in Hawaiian Japanese. *J. nat. Cancer Inst.,* **51,** 1765–1779 (1973).

HAENSZEL, W., LOCKE, F.B. and SEGI, M., A case-control study of large bowel cancer in Japan. *J. nat. Cancer Inst.,* **64,** 17–22 (1980).

ISCOVICH, J.M., L'ABBÉ, K.A., CASTELLETTO, R., CALZONA, A., BERNEDO, A., CHOPITA, N.A., JMELNITZKY, A.C., KALDOR, J. and HOWE, G.R., Colon cancer in Argentina. II: Risk from fibre, fat and nutrients. *Int. J. Cancer,* **51,** 858–861 (1992).

KAMPMAN, E., GOLDBOHM, R.A., VAN DEN BRANDT, P.A. and VAN'T VEER, P., Fermented dairy products, calcium and colorectal cancer in the Netherlands cohort study. *Cancer Res.,* **54,** 3186–3190 (1994).

KEARNEY, J., GIOVANNUCCI, E., RIMM, E.B., ASCHERIO, A., STAMPFER, M.J., COLDITZ, G.A., WING, A., KAMPMAN, E. and WILLETT, W.C., Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. *Amer. J. Epidemiol.,* **143,** 907–917 (1996).

LA VECCHIA, C., FRANCESCHI, S., DOLARA, P., BIDOLI, E. and BARBONE, F., Refined-sugar intake and the risk of colorectal cancer in humans. *Int. J. Cancer,* **55,** 386–389 (1993).

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).

MACQUART-MOULIN, G., RIBOLI, E., CORNÉE, J., CHARNAY, B., BERTHEZÈNE, P. and DAY, N., Case-control study on colorectal cancer and diet in Marseilles. *Int. J. Cancer,* **38,** 183–191 (1986).

MANOUSOS, O., DAY, N.E., TRICHOPOULOS, D., GEROVASSILIS, F., TZONOU, A. and POLYCHRONOPOULOU, A., Diet and colorectal cancer: a case-control study in Greece. *Int. J. Cancer,* **32,** 1–5 (1983).

NELSON, N.J., Is chemoprevention overrated or underfunded? *J. nat. Cancer Inst.,* **88,** 947–949 (1996).

POTTER, J.D., Nutrition and colorectal cancer. *Cancer Causes Control,* **7,** 127–146 (1996).

SHANNON, J., WHITE, E., SHATTUCK, A.L. and POTTER, J.D., Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol. Biomarkers Prev.,* **5,** 495–502 (1996).

WILLETT, W.C., STAMPFER, M.J., COLDITZ, G.A., ROSNER, B.A. and SPEIZER, F.E., Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *New Engl. J. Med.,* **323,** 1664–1672 (1990).

ZARIDZE, D., FILIPCHENKO, V., KUSTOV, V., SERDYUK, V. and DUFFY, S., Diet and colorectal cancer: results of two case-control studies in Russia. *Europ. J. Cancer,* **29A,** 112–115 (1993).