Short Communication

Flavonoids and Colorectal Cancer in Italy

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Abstract

Because of their several biological activities, flavonoids may have an important role in explaining the protective effects of vegetables, fruit, and, possibly, tea against cancer. The potential relation between flavonoids and colorectal cancer risk was investigated using data from a multicentric Italian case-control study, including 1,953 cases of colorectal cancers (1,225 colon cancers and 728 rectal cancers) and 4,154 hospital controls admitted for acute nonneoplastic diseases. We have applied recently published data on the composition of foods and beverages, in terms of six principal classes of flavonoids, on dietary information collected through a validated food-frequency questionnaire. Odds ratios (OR) were estimated by multiple logistic regression models, including terms for sex, age, study center, family history of colorectal cancer, education, alcohol consumption, body mass index, physical activity, and energy intake. A reduced risk of colorectal cancer was found for increasing intake of isoflavones (OR, 0.76, for the highest versus the lowest quintile, P_{trend} = 0.001), anthocyanidins (OR, 0.67, P_{trend} < 0.001), flavones (OR, 0.78, P_{trend} = 0.004), and flavonols (OR, 0.64, P_{trend} < 0.001). No significant association was found for flavan-3-ols (OR, 0.98), flavanones (OR, 0.96), and total flavonoids (OR, 0.97). The estimates did not substantially differ for colon and rectal cancers, as well as in strata of sex, age, and body mass index. The findings of this large study provide support for an inverse association of selected classes of flavonoids with colorectal cancer risk. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1555–8)

Introduction

Flavonoids are a group of over 5,000 compounds contained in vegetables, fruit, and beverages of plant origin (1). They have several biological activities that include antimutagenic, antiproliferative, and antioxidant effects, as well as involvement in cell signaling, cell cycle regulation, and angiogenesis (2, 3). Consequently, flavonoids may have an important role in explaining the favorable effects of vegetables, fruit, and, possibly, tea against cancer (4-6). Two reviews (2, 7) of epidemiologic studies of flavonoid intake and cancer risk concluded that there is modest evidence that flavonoids are inversely associated with cancer risk, and that the evidence is more convincing for the flavonol quercetin and lung cancer.

Four cohort studies investigated the relation between flavonoids and colorectal cancer and gave inconsistent results. The Iowa Women's Health study (8), on a cohort of 34,651 postmenopausal women, including 132 rectal and 635 colon cancers, found an inverse association between intake of catechin (a flavan-3-ols) and rectal cancer incidence [odds ratio (OR), 0.55, 95% confidence intervals (CI), 0.32-0.95 for the highest versus the lowest quintile], but not for colon cancer (OR, 1.10; 95% CI, 0.85-1.44). In the Finnish α-Tocopherol, β-Carotene Study cohort (9) of 27,110 male smokers, including 133 colorectal cancer, there was a borderline direct association with intake of the sum of flavonols and flavones (OR, 1.70; 95% CI, 1.00-2.70). No significant associations were found in a Dutch case-cohort study (10) of 3,726 subjects, including 603 cases, with respect to flavonols and the flavone luteolin (OR, 0.97; 95% CI, 0.71-1.32). Similarly, a Finnish cohort (11, 12) of about 10,000 men and women, examined at two different times, with 72 and 90 colorectal cancers, respectively, found no association with single compounds of flavonols and flavanones (OR, 0.74; 95% CI, 0.32-1.68; ref. 11) and total flavonoids (computed as the sum of flavonols, flavanones and flavones; OR, 0.84; 95% CI, 0.43-1.64; ref. 12). Thus, the epidemiologic evidence is still inconclusive, also because most studies included a small number of cases or analyzed the effects of total flavonoids or single compounds only. Moreover, reliable data on the flavonoid content of foods has become available only recently (13, 14), and flavonoids have been categorized in six classes (iisoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols), according to their chemical structure and biological activity.

The aim of this article is to investigate the relation between different classes of flavonoids and colorectal cancer using data from a large multicentric case-control study of colon and rectum cancer conducted in Italy (15).

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Materials and Methods

A case-control study of colorectal cancer has been conducted between January 1992 and June 1996 in six Italian areas: the provinces of Pordenone, Gorizia, Forlì, and Latina; and the urban areas of Milan, Genoa, and Naples (15).

Cases were subjects with histologically confirmed colorectal cancer diagnosed no longer than 1 year before the interview

and no previous diagnoses of cancer. Overall, 1,225 subjects with cancer of the colon (688 men and 537 women, median age 62 years, range 19-74 years) and 728 with cancer of the rectum or recto-sigmoid junction (437 men and 291 women, median age 62 years, range 23-74 years) were included (15).

Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment areas of cases for acute and nonneoplastic 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 years); 27% were admitted for traumas, 24% for other orthopedic disorders, 18% for acute surgical conditions, and 31% for eye and other miscellaneous diseases (15). About 4% of subjects invited to participate in the study refused.

The same structured questionnaire and coding manual were used in each center, and interviewers were centrally trained. The questionnaire included information on socio-demographic characteristics, lifetime smoking and alcohol-drinking habits, physical activity, anthropometric measures, a problem-oriented personal medical history, and family history of cancer.

Food-Frequency Questionnaire. A reproducible (16) and valid (17) food-frequency questionnaire was used to assess the patients' usual diet during the 2 years before cancer diagnosis or hospital admission, including 78 foods or food groups, as well as complex recipes, plus questions aimed at assessing fat intake and general dietary habits. The average weekly consumption of each item was recorded.

Energy was computed using an Italian food composition database, supplemented with other published data (18). We obtained food and beverage content in terms of six subclasses of flavonoids (isoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols) according to the data recently published by the U.S. Department of Agriculture (13, 14), further integrated with other sources (19). Major flavonoids were genistein and daidzein for isoflavones, cyanidin and malvidin for anthocyanidines, epicatechin and catechin for flavan-3-ols, hesperitin and narigerin for flavanones, apigenin and luteolin for flavones and quercetin, myricetin and kaempferol for flavonols.

Statistical Analysis. We computed ''calorie-adjusted'' flavonoid intakes using the residual method suggested by Willett and Stampfer (20). The calorie-adjusted flavonoids were categorized into approximate quintiles based on the controls distribution, and the corresponding OR and 95% CI were estimated using unconditional multiple logistic regression models (21). All models included terms for sex, age (5-year categories), study center, family history of colorectal cancer, education (<7, 7-11, ≥12 years), alcohol consumption (quartiles), body mass index (quintiles), and occupational physical activity (low, medium, high). Moreover, calorie-adjusted flavonoids were entered as continuous variables, with a measurement unit equal to the difference between the upper cutpoints of the 4th and 1st quintile. Tests for trend were based on the likelihood ratio test between models with and without a linear term for each class of flavonoids. We also fitted models across strata of sex, age, and body mass index. Further adjustment for other potential confounders yielded similar results.

Polytomous logistic regression was used to estimate separate ORs for colon and rectum cancer and to test for heterogeneity between the two sites (22).

Table 1. ORs and 95% CIs of 1,953 cases with colorectal cancer and corresponding 4,154 controls, according to energy-adjusted classes of flavonoids (Italy, 1992-1996)

	Mean* (SD)	Quintiles†					χ^2 (P_{trend})	Continuous‡
		1	2	3	4	5		
Isoflavones (μg)	25.4 (15.6)							
Upper cutpoint		14.4	19.6	25.2	33.9	—		
Cases		448	408	369	369	359		
OR§ (95% CI)		1‖	0.86 (0.72-1.02)	0.79 (0.66-0.94)	0.77 (0.65-0.92)	0.76 (0.63-0.91)	10.81 (0.001)	0.92 (0.86-0.99)
Anthocyanidins (mg)	20.0 (18.7)							
Upper cutpoint		5.3	11.5	19.4	31.7	—		
Cases		429	369	391	364	400		
OR§ (95% CI)		1‖	0.81 (0.68-0.96)	0.78 (0.65-0.93)	0.64 (0.53-0.77)	0.67 (0.54-0.82)	20.02 (<0.001)	0.86 (0.79-0.94)
Flavan-3-ols (mg)	57.4 (54.0)							
Upper cutpoint		20.8	34.4	51.7	88.5	—		
Cases		378	342	366	395	472		
OR§ (95% CI)		1‖	0.75 (0.63-0.91)	0.75 (0.62-0.90)	0.79 (0.65-0.95)	0.98 (0.82-1.18)	0.11 (0.736)	1.04 (0.98-1.10)
Flavanones (mg)	38.3 (31.8)							
Upper cutpoint		12.5	28.7	35.5	67.0	—		
Cases		436	378	399	347	393		
OR§ (95% CI)		1‖	0.88 (0.74-1.05)	0.89 (0.75-1.07)	0.80 (0.67-0.96)	0.96 (0.81-1.15)	0.62 (0.430)	0.99 (0.90-1.08)
Flavones (mg)	0.5 (0.3)							
Upper cutpoint		0.3	0.4	0.5	0.7	—		
Cases		456	388	358	364	387		
OR§ (95% CI)		1‖	0.82 (0.69-0.98)	0.72 (0.61-0.86)	0.76 (0.64-0.91)	0.78 (0.65-0.93)	8.38 (0.004)	0.91 (0.85-0.99)
Flavonols (mg)	21.6 (10.8)							
Upper cutpoint		13.2	17.3	22.0	28.5	—		
Cases		439	399	389	390	336		
OR§ (95% CI)		1‖	0.80 (0.67-0.95)	0.77 (0.64-0.91)	0.74 (0.62-0.88)	0.64 (0.54-0.77)	21.09 (<0.001)	0.87 (0.80-0.94)
Total flavonoids (mg)	137.8 (78.9)							
Upper cutpoint		75.3	108.5	141.6	191.1	—		
Cases		383	396	357	373	444		
OR§ (95% CI)		1‖	0.90 (0.75-1.08)	0.79 (0.66-0.94)	0.81 (0.67-0.97)	0.97 (0.81-1.16)	0.45 (0.500)	0.99 (0.92-1.07)

*Mean intake and SD among controls.
†Each quintile included 831 ± 1 controls.
‡Estimated for an increment of intake equal to the difference between the upper cutpoints of 4th and the 1st quintiles.
§Adjusted for age, sex, study center, family history of colorectal cancer, education, alcohol consumption, body mass index, occupational physical activity, and energy intake, according to the residual model.
‖Reference category.

Table 2. ORs and 95% CIs of 1,225 cases with colon cancer and 728 cases of rectum cancer and corresponding 4,154 controls, according to energy-adjusted classes of flavonoids (Italy, 1992-1996)

	Colon		Rectum		χ^2_1 heterogeneity*	
	OR 5 vs 1 quintile (95% CI)	OR continuous † (95% CI)	OR 5 vs 1 quintile (95% CI)	OR continuous † (95% CI)	χ^2 5 vs 1 (P)	χ^2_1 continuous † (P)
Isoflavones	0.70 (0.56-0.87)	0.88 (0.81-0.97)	0.81 (0.63-1.04)	0.96 (0.87-1.07)	0.62 (0.432)	1.75 (0.186)
Anthocyanidins	0.69 (0.54-0.89)	0.87 (0.79-0.96)	0.64 (0.48-0.86)	0.84 (0.74-0.96)	0.75 (0.387)	0.54 (0.462)
Flavan-3-ols	1.12 (0.90-1.39)	1.06 (0.98-1.13)	0.81 (0.62-1.06)	1.03 (0.94-1.11)	4.83 (0.028)	0.42 (0.517)
Flavanones	1.05 (0.85-1.29)	1.06 (0.95-1.18)	0.86 (0.66-1.11)	0.90 (0.78-1.03)	1.64 (0.201)	3.12 (0.077)
Flavones	0.77 (0.62-0.95)	0.91 (0.83-1.00)	0.78 (0.61-1.00)	0.92 (0.82-1.02)	0.04 (0.847)	2.30 (0.129)
Flavonols	0.65 (0.53-0.81)	0.89 (0.81-0.97)	0.63 (0.48-0.83)	0.81 (0.72-0.91)	0.03 (0.861)	1.41 (0.236)
Total flavonoids	1.08 (0.87-1.34)	1.04 (0.95-1.14)	0.83 (0.64-1.07)	0.93 (0.82-1.05)	3.10 (0.079)	2.53 (0.111)

NOTE: ORs were estimated using multiple logistic regression models adjusted for sex, age, study center, family history of colorectal cancer, education, alcohol consumption, body mass index, occupational physical activity, and energy intake, according to the residual model.
*Between colon and rectum.
†Estimated for an increment of intake equal to the difference between the upper cutpoints of 4th and the 1st quintiles.

Results

Table 1 gives the mean daily intake of six classes of flavonoids and total flavonoids among controls, and the ORs of colorectal cancer according to quintile of intake. The mean daily intake was 25.4 μg for isoflavones, 20.0 mg for anthocyanidins, 57.4 mg for flavan-3-ols, 38.3 mg for flavanones, 0.5 mg for flavones, 21.6 mg for flavonols, and 137.8 mg for total flavonoids. A significant inverse relation with colorectal cancer was observed for isoflavones (OR, 0.76; 95% CI, 0.63-0.91 for the highest versus the lowest quintile), anthocyanidins (OR, 0.67; 95% CI, 0.54-0.82), flavones (OR, 0.78; 95% CI, 0.65-0.93), and flavonols (OR, 0.64; 95% CI, 0.54-0.77). Further adjustment for fruit and vegetable intake did not materially modify these associations: the OR became 0.77 (95% CI, 0.64-0.92) for isoflavones, 0.78 (95% CI, 0.61-0.99) for anthocyanidins, 0.80 (95% CI, 0.66-0.96) for flavones, and 0.76 (95% CI, 0.62-0.92) for flavonols. No significant association emerged for flavan-3-ols (OR, 0.98), flavanones (OR, 0.96), and total flavonoids (OR, 0.97).

The continuous ORs for an increment equal to the difference between the upper cutpoint of the fourth and the first quintile were 0.92 for isoflavones, 0.86 for anthocyanidins, 1.04 for flavan-3-ols, 0.99 for flavanones, 0.91 for flavones, 0.87 for flavonols, and 0.99 for total flavonoids.

In Table 2, we analyzed the relation between flavonoids and cancer of the colon and rectum separately. The estimates did not differ substantially with respect to the ones for colorectal cancer, and the heterogeneity terms were not significant.

Table 3 shows the ORs for the continuous terms, in separate strata of sex, age (<60, ≥60 years), and body mass index (<25, ≥25 kg/m^2). Interaction test confirmed that risk patterns were generally consistent across strata.

Discussion

The present study examined the relation of six classes of flavonoids (isoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols) and total flavonoids with colorectal cancer. Total flavonoids were not associated with colorectal cancer; however, we found an inverse association for isoflavones, anthocyanidins, flavones, and flavonols.

To our knowledge, no other epidemiologic study investigated the role of isoflavones and anthocyanidins on colorectal cancer, whereas with respect to the remaining classes, our data are not completely in agreement with some previous studies. However, most previous investigations examined the effects of selected compounds only rather than the classes of flavonoids that we considered (8-12).

Flavonoids have several important biological functions, which may be related to cancer risk. *In vitro* and animal model systems showed that they influence signal transduction pathways, stimulate apoptosis, and inhibit inflammation and proliferation in human cancer cell lines. Selected flavonoids may also increase transcription of phase II detoxifying enzymes involved in the clearance of procarcinogenic substances (2, 23).

Table 3. ORs and 95% CIs of 1,953 cases with colorectal cancer and corresponding 4,154 controls, according to energy-adjusted classes of flavonoids in strata of sex, age, and body mass index (Italy, 1992-1996)

	OR* (95% CI)								
	Sex (cases:controls)			Age (cases:controls)			Body mass index, kg/m^2 (cases:controls)		
	Male (1,125:2,073)	Female (828:2,081)	P †	<60 (780:2,323)	≥60 (1,173:1,831)	P †	<25 (890:1,907)	≥25 (1,063:2,247)	P †
Isoflavones	0.90 (0.81-1.00)	0.94 (0.85-1.04)	0.545	0.95 (0.86-1.06)	0.91 (0.83-1.00)	0.457	0.97 (0.88-1.07)	0.90 (0.81-0.99)	0.339
Anthocyanidins	0.90 (0.82-0.98)	0.74 (0.62-0.88)	0.048	0.86 (0.77-0.97)	0.88 (0.80-0.98)	0.763	0.92 (0.82-1.04)	0.85 (0.77-0.94)	0.244
Flavan-3-ols	1.09 (1.01-1.18)	0.98 (0.90-1.07)	0.059	1.04 (0.95-1.13)	1.06 (0.99-1.15)	0.660	1.09 (1.01-1.18)	1.02 (0.94-1.10)	0.232
Flavanones	0.97 (0.86-1.11)	1.00 (0.88-1.14)	0.752	0.96 (0.84-1.09)	1.00 (0.87-1.13)	0.678	1.01 (0.88-1.15)	0.95 (0.84-1.07)	0.499
Flavones	0.91 (0.82-1.01)	0.92 (0.82-1.03)	0.944	0.88 (0.78-0.99)	0.97 (0.88-1.07)	0.200	0.96 (0.86-1.07)	0.90 (0.81-1.00)	0.375
Flavonols	0.88 (0.79-0.98)	0.85 (0.76-0.95)	0.676	0.87 (0.78-0.97)	0.90 (0.81-0.99)	0.678	0.87 (0.78-0.97)	0.90 (0.82-1.00)	0.500
Total flavonoids	1.04 (0.94-1.15)	0.93 (0.82-1.05)	0.158	0.97 (0.87-1.09)	1.03 (0.93-1.14)	0.485	1.06 (0.95-1.19)	0.95 (0.86-1.05)	0.146

NOTE: ORs were estimated using multiple logistic regression models adjusted for sex, age, study center, family history of colorectal cancer, education, alcohol consumption, body mass index, occupational physical activity, and energy intake, according to the residual model.
*Estimated for an increment of intake equal to the difference between the upper cutpoints of 4th and the 1st quintiles.
†P values of the χ^2_1 test of interaction.

The strengths and weaknesses of hospital-based case-control studies (21) should be considered in evaluating our results. Among the limitations are the questions concerning the adaptability of U.S. flavonoid food composition data to the Italian diet, and the fact that the questionnaire was not specifically designed to investigate flavonoids. To our knowledge, no studies using biomarkers of flavonoid intake have been conducted to date. Thus, it is difficult to evaluate, in this as well as other studies, the imprecision of exposure measurement due, among others, to the variation of the food quantities in the recipes and the variability in plant flavonoid content attributable to several factors, such as sunlight and heat. Dietary habits can be influenced by recent diagnosis of cancer or by the fact that the disease process would have been well under way during the reference period of the food-frequency questionnaire (2 years before the diagnosis or hospital admission). The dietary habits of hospital controls may differ from those of the general population, but we took great care to include only patients admitted to hospital for acute conditions not related to major changes in diet and other lifestyle factors. Moreover, the same interview setting and catchment areas for cases and controls, and the almost complete participation rate are reassuring. Among the strengths of this study are the uniquely large data set, the high intake of fruit and vegetables in this population, the satisfactory reproducibility and validity of the food-frequency questionnaire (16, 17), and the ability to control for total energy intake and other major potential confounding factors.

The Italian population has a high and varied consumption of vegetables and fruit (24), which has been associated with a reduced risk of colorectal cancer (15, 25). Although the causality of this association is still debated, it has been suggested that some bioactive compounds in fruit and vegetables, and, among these, flavonoids, account for this association.

The correlations of the various classes of flavonoids with fruit ranged between 0.04 and 0.56, and that with total vegetables between 0.03 and 0.25. Adjustment for isoflavones, flavones, or flavonols reduced the strength of the inverse association between vegetables consumption and colorectal cancer, whereas adjustment for flavonols only reduced the association with fruit. Conversely, allowance for fruit and vegetables consumption changed only weakly, if at all, the observed associations with flavonoids. This suggests that, on one side, a diet rich in fruit and vegetables does not alone account for the observed protections, at least for some classes, and, on the other side, the relation with fruit and vegetables is not totally explained by flavonoid intake.

Similarly, allowance for vitamin C, vitamin E, carotenoids, folate, fiber, and macronutrient intake did not modify the estimated ORs by >10%. In this population, vegetables or bean soup (37%) and pulses (12%) were the major sources for isoflavones; wine (65%) and red fruits (22%) for anthocyanidins; spinach or chards (27%), vegetables or bean soup (19%) and tea (14%) for flavones; and apples or pears (18%) and wine (12%) for flavonols. The lack of association for flavanones, deriving from citrus fruit (90%), is in accordance with previous results from this study (15), which did not find a relation between citrus fruit and colorectal cancer risk. We did not consider flavonoids deriving from tea separately because tea consumption was too limited in this population.

In conclusion, we found that some classes of flavonoids, in particular isoflavones, anthocyanidins, flavones, and flavonols, significantly decreased the risk of colorectal cancer and could account, at least in part, for the protective effect of vegetable and fruit consumption against colorectal cancer in this population.

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