Fruit and vegetable consumption and cancer risk with a focus on flavonoids and proanthocyanidins: an overview of italian studies

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Summary
We considered the relations between flavonoids, proanthocyanidins, and cancer risk, by reviewing data from a network of multicentric Italian case-control studies including about 10,000 incident, histologically confirmed cancer cases, and over 16,000 controls. Odds ratios (ORs) for the highest versus the lowest quintiles of six major classes of flavonoids and proanthocyanidins were estimated by logistic regression models, including major confounding factors, and energy intake. Total flavonoids (OR, 0.56), flavanones (OR, 0.51) and flavonols (OR, 0.62) were inversely related to oral cancer, and together with flavanols, to laryngeal cancer (ORs, 0.60, 0.60, 0.32 and 0.64, respectively). Flavanones were inversely related to esophageal cancer (OR, 0.38). Inverse relations were found with colorectal cancer for anthocyanidins (OR, 0.67), flavonols (OR, 0.64), flavones (OR, 0.78), and isoflavones (OR, 0.76). We found inverse associations with colorectal cancer for monomers and dimers proanthocyanidins (OR, 0.82), and polymers with three or more mers (OR, 0.74). Inverse relations with breast cancer were reported for flavones (OR, 0.81) and flavonols (OR, 0.80). Flavonols (OR, 0.63) and isoflavones (OR, 0.51) were inversely associated to ovarian cancer. No association was found with prostate cancer. Renal cancer was inversely related with flavonols (OR, 0.69) and flavones (OR, 0.68).

KEY WORDS: *Flavonoids, Cancer, Diet, Phytoestrogens, Risk.*

Introduction

A diet rich in vegetables and fruits has been associated with the reduced risk of various common cancers, particularly of the respiratory and digestive tracts (1). With specific focus to a network of Italian case-control studies conducted since the early 1990's (Figures 1 and 2), vegetable intake was inversely related to the risk of several common epithelial cancers: the odds ratios (OR) for digestive tract neoplasms ranged between 0.3 and 0.8 for the highest compared with the lowest levels of vegetable intake. Less consistent inverse relations were observed for some hormone-related neoplasms, such as breast and ovary. High fruit intake was associated to reduced ORs of cancers of the upper digestive tract, stomach, colorectum, and Non-Hodgkin's lymphomas. No material effect, however, was observed for fruit intake on neoplasms of the breast, the female genital tract or the prostate (2). For digestive tract cancers, population-attributable risks for low intake of vegetables and fruit ranged between 15 and 40% (3). Flavonoids belong to a vast group of polyphenols that

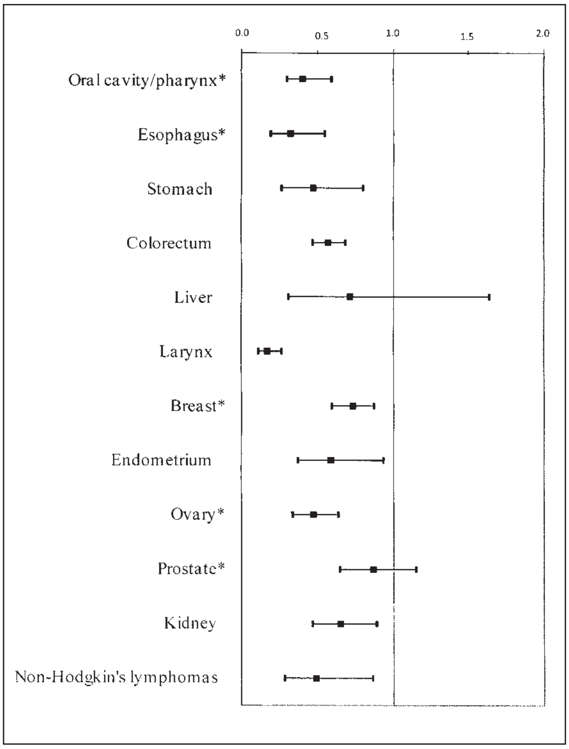

Figure 1. Odds ratios and 95% confidence intervals of selected cancers for the highest vs the lowest levels of vegetable consumption. Italy, 1991-2005.
** Raw vegetables.*

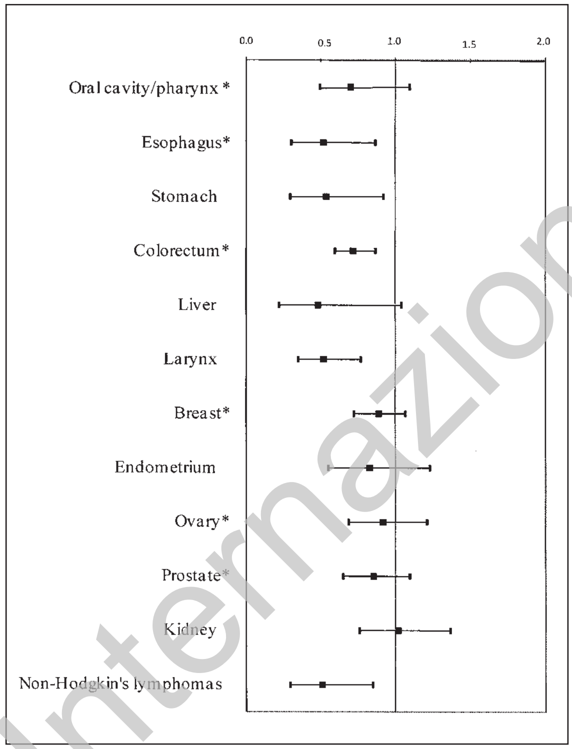

Figure 2. Odds ratios and 95% confidence intervals of selected cancers for the highest vs the lowest levels of fruit consumption. Italy, 1991-2005.
** Non-citrus fruit.*

are widely distributed in all foods of plant origin such as vegetables, fruit, tea and wine (4, 5). As several flavonoids have antioxidant properties, as well as antimutagenic and antiproliferative properties in vitro (6-8), these compounds have been investigated for possible inverse associations with chronic diseases, including various types of cancer (9-12), and may explain at least in part, the protective effect of vegetable and fruit against cancer. The availability of detailed and reliable food composition tables for flavonoids published by the US Department of Agriculture on their 6 major classes (flavanols, flavanones, flavonols, flavones, anthocyanidins and isoflavones) (13, 14), and, more recently, on a class of polymers of flavanols called proanthocyanidins (15), has allowed epidemiological studies to further investigate the role of flavonoids in cancer etiology from the early 2000's. Intake of various flavonoids has been inversely related to the risk of cancers of the upper aerodigestive tract (16), digestive tract (17, 18), breast (19, 20), and urogenital tract (21, 22). No epidemiological study has systematically investigated the relation of dietary proanthocyanidins by their degree of polymerization with cancer risk.

We investigated flavonoids - and for colorectal cancer, proanthocyanidins - in relation to the risk of various neoplasms in a series of case-control studies conducted in Italy (23), which included 805 cancers of the oral cavity and pharynx, 743 of the esophagus, 460 of the larynx, 1,953 of the colorectum, 2,569 of the breast, 1,031 of the ovary, 1,294 of the prostate, and 767 of the kidney.

Material and Methods

We have been conducting a series of case-control studies in various regions of Italy since the early 1990s (23). These studies included a total of 9,622 cancer cases and 16,050 controls. Cases were individuals admitted to hospitals with incident, histologically confirmed cancer, and controls were patients with no history of cancer admitted to the same hospitals for acute, nonneoplastic conditions. Centrally trained interviewers administered a standard questionnaire to cases and controls during their hospital stay. The questionnaire included personal and socio-demographic characteristics, anthropometric measures, and lifesty-

Table 1. Primary contributors to flavonoid and proanthocyanidin intake among controls. Italy, 1991-2005.

	Principal flavonoid and proanthocyanidin food sources		
	1	**2**	**3**
Flavonoids			
Flavanols	Tea (50%)	Apples and pears (20%)	Wine (15%)
Flavanones	Citrus fruit (88%)	Fruit juice (11%)	
Flavonols	Apples and pears (16%)	Fennels (16%)	Mixed vegetable salad (12%)
Anthocyanidins	Wine (46%)	Strawberries and cherries (37%)	Onions (7%)
Flavones	Spinaches and Swiss chards (29%)	Vegetable and bean soups (17%)	Tea (15%)
Isoflavones	Soya milk (45%)	Soya (21%)	Vegetable and bean soups (12%)
Total of the above flavonoids	Citrus fruit (28%)	Tea (22%)	Apples and pears (11%)
Proanthocyanidins			
Monomers	Wine (54%)	Apples and pears (18%)	Tea (7%)
Dimers	Wine (50%)	Apples and pears (26%)	Peaches, apricots and prunes (7%)
Trimers	Apples and pears (47%)	Wine (13%)	Peaches, apricots and prunes (10%)
4-6mers	Apples and pears (45%)	Wine (14%)	Vegetable and bean soups (11%)
7-10mers	Apples and pears (48%)	Wine (13%)	Vegetable and bean soups (12%)
> 10 mers	Apples and pears (32%)	Vegetable and bean soups (16%)	Grape (13%)
Total proanthocyanidins	Apples and pears (35%)	Wine (24%)	Vegetable and bean soups (11%)

Table 2. Odds ratios[a] (OR) and 95% confidence intervals (CI) among 805 cases of oral cavity and pharyngeal cancer and 2081 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1992-2005 (from [33]).

	Quintile of intake					χ^2 trend
	1[b]	**2**	**3**	**4**	**5**	**(p-value)**
Flavanols (mg)						
Upper cutpoint	*23.3*	*40.3*	*59.4*	*99.6*	-	
OR	1	1.06	0.85	0.77	0.84	2.05
(95% CI)		(0.76-1.48)	(0.60-1.20)	(0.54-1.09)	(0.60-1.18)	(0.15)
Flavanones (mg)						
Upper cutpoint	*10.2*	*28.6*	*36.2*	*67.0*	-	
OR	1	0.90	0.70	0.61	0.51	22.03
(95% CI)		(0.68-1.18)	(0.52-0.94)	(0.45-0.83)	(0.37-0.71)	(<0.001)
Anthocyanidins (mg)						
Upper cutpoint	5.3	13.4	20.9	33.2	-	
OR	1	0.89	0.70	0.66	0.86	2.32
(95% CI)		(0.63-1.25)	(0.49-1.01)	(0.47-0.94)	(0.60-1.22)	(0.13)
Flavonols (mg)						
Upper cutpoint	*13.9*	*18.2*	*23.2*	*29.9*	-	
OR	1	0.92	0.80	0.65	0.62	9.33
(95% CI)		(0.66-1.28)	(0.57-1.12)	(0.46-0.92)	(0.43-0.89)	(0.002)
Flavones (mg)						
Upper cutpoint	*0.3*	*0.4*	*0.5*	*0.7*	-	
OR	1	1.02	0.74	0.95	0.75	3.22
(95% CI)		(0.76-1.36)	(0.54-1.00)	(0.69-1.29)	(0.55-1.04)	(0.073)
Isoflavones (mg)						
Upper cutpoint	*14.7*	*19.4*	*24.7*	*32.5*	-	
OR	1	1.05	1.06	0.89	0.90	0.92
(95% CI)		(0.78-1.42)	(0.78-1.44)	(0.65-1.23)	(0.64-1.26)	(0.34)
Total flavonoids (mg)						
Upper cutpoint	*83.5*	*117.9*	*151.8*	*204.0*	-	
OR	1	0.77	0.64	0.63	0.56	11.92
(95% CI)		(0.56-1.06)	(0.46-0.89)	(0.45-0.87)	(0.40-0.78)	(0.001)

[a] *Estimates from logistic regression models, conditioned on sex, age, study centre, and adjusted for education, alcohol consumption, tobacco smoking, body mass index, and non-alcohol energy intake.* [b] *Reference category.*

Table 3. Odds ratios[a] (OR) and 95% confidence intervals (CI) among 304 cases of squamous cell cancer of the esophagus and 743 controls, according to daily intake quintile of five classes of flavonoids and total flavonoids. Italy, 1992-1997 (from [34]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*32.6*	*49.4*	*72.8*	*109.1*	-	
OR	1	1.03	0.72	0.89	1.06	0.08
(95% CI)		(0.55-1.96)	(0.38-1.37)	(0.48-1.64)	(0.58-1.94)	(0.77)
Flavanones (mg)						
Upper cutpoint	*6.4*	*19.7*	*33.9*	*58.8*	-	
OR	1	0.42	0.59	0.56	0.38	8.47
(95% CI)		(0.26-0.67)	(0.36-0.97)	(0.34-0.92)	(0.23-0.66)	(0.004)
Anthocyanidins (mg)						
Upper cutpoint	*8.1*	*18.2*	*30.2*	*41.2*	-	
OR	1	0.60	0.56	0.41	0.84	0.45
(95% CI)		(0.29-1.24)	(0.29-1.13)	(0.22-0.79)	(0.46-1.54)	(0.50)
Flavonols (mg)						
Upper cutpoint	*15.9*	*20.4*	*25.4*	*31.9*	-	
OR	1	1.02	0.76	0.55	0.68	3.54
(95% CI)		(0.59-1.76)	(0.43-1.32)	(0.30-0.98)	(0.38-1.24)	(0.060)
Flavones (mg)						
Upper cutpoint	*0.3*	*0.4*	*0.5*	*0.7*	-	
OR	1	0.87	1.31	0.78	0.97	0.02
(95% CI)		(0.52-1.44)	(0.81-2.11)	(0.45-1.36)	(0.57-1.67)	(0.88)
Total flavonoids (mg)						
Upper cutpoint	*96.5*	*127.7*	*166.2*	*217.4*	-	
OR	1	1.29	0.78	0.81	0.99	0.23
(95% CI)		(0.72-2.33)	(0.42-1.42)	(0.45-1.46)	(0.55-1.79)	(0.63)

[a] *Estimates from multiple logistic regression models adjusted for age, sex, study centre, education, alcohol consumption, tobacco smoking, body mass index and energy intake.* [b] *Reference category.*

le habits, including tobacco smoking and alcohol consumption. A reproducible (24) and valid (25) food frequency questionnaire (FFQ) was used to assess the patients' usual diet in the 2 years preceding diagnosis (for cases) or hospital admission (for controls). The FFQ included the average weekly consumption of 78 food items or food groups and beverages. Intakes lower than once a week, but at least once per month were coded as 0.5 per week.

We developed a standardized method based on food composition tables in terms of flavonoids and proanthocyanidins in order to translate the frequency of consumption of each food item of the FFQ into average daily intakes of flavonoids and proanthocyanidins, taking into account the portion size of each item food. For the six major classes of flavonoids, i.e., flavanols, flavanones, flavonols, anthocyanidins, flavones, and isoflavones, we used food composition data published by the US Department of Agriculture (USDA) (13, 14), further integrated with other sources when needed (26-28). Major flavonoids included in the six classes were epicathechin and catechin for flavanols, hesperetin and naringerin for flavanones, quercetin for flavonols, cyanidin and malvidin for anthocyanidins, apigenin and luteolin for flavones, and daidzein and genistein for isoflavones. In our control population, flavanols came mainly from tea, apples, pears and wine; flavanones from oranges and other citrus fruits; flavonols from apples, pears and various common vegetables; anthocyanidins from wine, strawberries, cherries and onions; flavones from cooked vegetables and tea; and isoflavones from soya and bean soups (Table 1).

For proanthocyanidins, data from the USDA became available more recently (15). Since analytical technology did not allow quantification of these compounds according to their type linkage (e.g., procyanidins, prodelphinidins, etc.), but only according to their degree of polymerization, the USDA food composition tables were in terms of six classes of proanthocyanidins, i.e., monomers, dimers, trimers, 4-6 mers,

Table 4. Odds ratios[a] (OR) and 95% confidence intervals (CI) among 460 cases of laryngeal cancer and 1088 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1992-2000 (from [35]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*31.2*	*50.2*	*72.9*	*110.4*	-	
OR	1	0.63	0.57	0.49	0.64	3.26
(95% CI)		(0.40-1.01)	(0.35-0.91)	(0.31-0.77)	(0.41-0.99)	(0.071)
Flavanones (mg)						
Upper cutpoint	*7.7*	*20.8*	*33.7*	*49.2*	-	
OR	1	0.55	0.54	0.39	0.60	10.53
(95% CI)		(0.38-0.81)	(0.37-0.80)	(0.26-0.59)	(0.41-0.89)	(0.001)
Anthocyanidins (mg)						
Upper cutpoint	*8.6*	*18.8*	*30.7*	*41.1*	-	
OR	1	1.21	1.05	0.51	0.77	2.14
(95% CI)		(0.71-2.06)	(0.60-1.83)	(0.30-0.89)	(0.46-1.30)	(0.14)
Flavonols (mg)						
Upper cutpoint	*16.8*	*22.1*	*26.8*	*33.7*	-	
OR	1	0.53	0.49	0.30	0.32	24.61
(95% CI)		(0.34-0.82)	(0.31-0.75)	(0.19-0.48)	(0.20-0.52)	(<0.001)
Flavones (mg)						
Upper cutpoint	0.3	0.4	0.5	0.7	-	
OR	1	0.76	0.80	0.58	0.76	2.52
(95% CI)		(0.50-1.14)	(0.53-1.20)	(0.38-0.89)	(0.50-1.15)	(0.11)
Isoflavones (mg)						
Upper cutpoint	*14.7*	*19.8*	*25.1*	*32.6*	-	
OR	1	1.23	0.87	0.67	0.73	6.41
(95% CI)		(0.82-1.85)	(0.57-1.33)	(0.43-1.03)	(0.47-1.14)	(0.011)
Total flavonoids (mg)						
Upper cutpoint	*95.5*	*132.1*	*168.0*	*221.8*	-	
OR	1	0.62	0.56	0.57	0.60	3.55
(95% CI)		(0.39-0.99)	(0.36-0.88)	(0.36-0.89)	(0.38-0.94)	(0.060)

[a] *Estimates from multiple logistic regression models adjusted for age, sex, study centre, education, alcohol consumption, tobacco smoking, body mass index, occupational physical activity and non-alcohol energy intake.* [b] *Reference category.*

7-10 mers, > 10 mers (15). Given the high correlation between some classes of proanthocyanidins, we further combined monomers and dimers, as well as polymers with three or more mers, and also studied total proanthocyanidins. In our data, the major sources of combined monomers and dimers of proanthocyanidins were wine, apples or pears, peaches, apricots or prunes, whereas major sources of proanthocyanidins with three or more mers were apples or pears, wine, vegetables or bean soup (Table 1). Other main sources are chocolate, pulses and grape.

Energy intake was computed using an Italian food composition database, integrated with others published data (29, 30).

We derived the ORs and the corresponding 95% confidence intervals (CIs), by unconditional multiple logistic regression models (31) including terms for study centre, sex, age (in quinquennia, categorically), education (<7, 7-11, ≥ 12 years, categorically), as well as other major recognized confounding factors for each cancer of interest. These included alcohol consumption, tobacco smoking and body mass index (BMI) for upper aerodigestive tract neoplasms; alcohol consumption, BMI, occupational physical activity, family history of colorectal cancer for colorectal cancer; alcohol consumption and parity for breast cancer; alcohol consumption, parity, oral contraceptives and family history of ovarian and/or breast cancer for ovarian cancer; BMI and family history of prostate cancer for prostate cancer; alcohol consumption, tobacco smoking, BMI, occupational physical activity, and family history of kidney cancer for renal cell carcinomas. Adjustment for energy intake was performed entering the term in the model (with or without energy from alcohol intake) and

Table 5. Odds ratios[a] (OR) and 95% confidence intervals (CI) among 1953 cases of colorectal cancer and 4154 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1992-1996 (from [40]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*25.02*	*48.79*	*48.79*	*78.29*	-	
OR	1	0.75	0.75	0.79	0.98	0.11
(95% CI)		(0.63-0.91)	(0.62-0.90)	(0.65-0.95)	(0.82-1.18)	(0.74)
Flavanones (mg)						
Upper cutpoint	*12.86*	*27.94*	*38.25*	*62.9*	-	
OR	1	0.88	0.89	0.80	0.96	0.62
(95% CI)		(0.74-1.05)	(0.75-1.07)	(0.67-0.96)	(0.81-1.15)	(0.43)
Anthocyanidins (mg)						
Upper cutpoint	*9.15*	*14.88*	*20.55*	*29.06*	-	
OR	1	0.81	0.78	0.64	0.67	20.02
(95% CI)		(0.68-0.96)	(0.65-0.93)	(0.53-0.77)	(0.54-0.82)	(<0.001)
Flavonols (mg)						
Upper cutpoint	15.3	18.27	21.62	26.9	-	
OR	1	0.80	0.77	0.74	0.64	21.09
(95% CI)		(0.67-0.95)	(0.64-0.91)	(0.62-0.88)	(0.54-0.77)	(<0.001)
Flavones (mg)						
Upper cutpoint	*0.30*	*0.40*	*0.50*	*0.65*	-	
OR	1	0.82	0.72	0.76	0.78	8.38
(95% CI)		(0.69-0.98)	(0.61-0.86)	(0.64-0.91)	(0.65-0.93)	(0.004)
Isoflavones (mg)						
Upper cutpoint	*16.22*	*20.88*	*25.66*	*32.96*	-	
OR	1	0.86	0.79	0.77	0.76	10.81
(95% CI)		(0.72-1.02)	(0.66-0.94)	(0.65-0.92)	(0.63-0.91)	(0.001)
Total flavonoids (mg)						
Upper cutpoint	*86.23*	*112.73*	*138.93*	*180.49*	-	
OR	1	0.90	0.79	0.81	0.97	0.45
(95% CI)		(0.75-1.08)	(0.66-0.94)	(0.67-0.97)	(0.81-1.16)	(0.50)

[a] *Estimates from multiple logistic regression models adjusted for age, sex, study centre, education, alcohol consumption, body mass index, physical activity, family history of colorectal cancer and energy intake, according to the residual model.* [b] *Reference category.*

using the residual method (32). Because both analyses yielded similar results, only the former estimates generally were presented. Flavonoids and proanthocyanidins were entered in the models as quintiles of the distribution of controls. Tests for trend for quintiles were based on the likelihood ratio test between the models with and without a linear term for flavonid (or proanthocyanidin) quintile.

Cancers at the upper digestive tract

The study of oral and pharyngeal cancer (Table 2) showed that total flavonoids were inversely related to the risk of this neoplasm (33). The ORs for the highest versus the lowest quintile of all classes of flavonoid intake were below unity. The OR was 0.51 (95% confidence interval, CI, 0.37-0.71) for flavanones, 0.62 (95% CI, 0.43-0.89) for flavonols, and 0.56 (95% CI, 0.40-0.78) for total flavonoids. No significant association emerged for other classes of flavonoids. The ORs were consistent across strata of age, sex, education, body mass index, tobacco and alcohol. After allowance for vegetable and fruit consumption, the inverse relations with total flavonoids and flavanones remained significant, whereas that with flavonols became non significant. None of the associations was significant after further allowance for vitamin C, probably on account of the high co-linearity between these compounds.

In the study on esophageal cancer (Table 3), only flavanones were inversely associated with cancer risk (OR, 0.38, 95% CI, 0.23-0.66) (34). The inverse relation tended to be stronger in subjects who drank ≥ 6 drinks of alcoholic beverages per day. After allowance for fruit

Table 6. Odds ratio[a] (OR) and 95% confidence intervals (CI) among 2,569 cases of breast cancer and 2,588 controls, according to daily intake quintile of six classes of flavonoids. Italy, 1991-1994 (from [46]).

	Quintile of intake					χ^2 trend
	1[b]	**2**	**3**	**4**	**5**	**(p-value)**
Flavanols (mg)						
Upper cutpoint	*18.1*	*30.3*	*44.1*	*79.7*	-	
OR[c]	1	0.98	0.80	1.01	0.86	1.28
(95% CI)		(0.82-1.18)	(0.66-0.98)	(0.83-1.23)	(0.71-1.05)	(0.26)
Flavanones (mg)						
Upper cutpoint	*11.5*	*29.1*	*37.7*	*62.2*	-	
OR[c]	1	1.19	1.11	1.15	0.95	0.48
(95% CI)		(1.00-1.43)	(0.92-1.33)	(0.96-1.38)	(0.79-1.15)	(0.49)
Anthocyanidins (mg)						
Upper cutpoint	*3.7*	*7.9*	*14.3*	*20.5*	-	
OR[c]	1	1.03	1.16	1.11	1.09	0.76
(95% CI)		(0.86-1.25)	(0.95-1.40)	(0.90-1.37)	(0.87-1.36)	(0.38)
Flavonols (mg)						
Upper cutpoint	*12.6*	*16.4*	*21.5*	*29.9*	-	
OR[c]	1	0.81	1.00	0.82	0.80	3.52
(95% CI)		(0.67-0.98)	(0.83-1.21)	(0.67-1.00)	(0.66-0.98)	(0.06)
Flavones (mg)						
Upper cutpoint	0.2	0.3	0.5	0.6	-	
OR[c]	1	0.94	0.97	0.86	0.81	5.41
(95% CI)		(0.79-1.13)	(0.81-1.17)	(0.71-1.04)	(0.66-0.98)	(0.02)
Isoflavones (µg)						
Upper cutpoint	*13.4*	*19.0*	*25.2*	*34.7*	-	
OR[c]	1	1.05	1.00	1.02	1.05	0.08
(95% CI)		(0.87-1.27)	(0.83-1.22)	(0.84-1.24)	(0.86-1.29)	(0.78)

[a] *Estimates from multiple logistic regression models including terms for age, study center, education, parity, alcohol consumption and non-alcohol energy intake.* [b] *Reference category.*

intake or vitamin C, the association of flavanones with esophageal cancer remained inverse, though non significantly, suggesting that flavanone may explain, together with vitamin C, the protective effect of citrus fruits on esophageal cancer.

In the study on laryngeal cancer (Table 4), significant inverse relations were found for flavanols (OR, 0.64), flavanones (OR, 0.60), flavonols (OR, 0.32), and total flavonoids (OR, 0.60), although the overall trends in risk were significant only for flavanones and flavonols (35). The estimates persisted after controlling for vegetable, fruit, and vitamin C intake.

The Italian data are in agreement with those of a case control-study conducted in Uruguay that investigated the relation between diet and upper aerodigestive tract and reported inverse relations between flavonoids and oral, esophageal, and laryngeal cancer risk. No specific information on flavonoids are given in that study. More recently, in a population-based case-control study from the USA (36), inverse associations in white men were observed between anthocyanidin intake and esophageal adenocarcinoma, and isoflavone intake and esophageal squamous cell carcinoma. However, none of these associations remained significant after adjusting for dietary fiber. To our knowledge, no other study investigated the issue.

Flavanones, that were the class of flavonoids most strongly associated to the risk of neoplasms at the upper aerodigestive tract in these Italian studies, have been inversely related to gastric cancer in a Greek case-control study (17). This is of particular interest, given the similarities in risk factors between various neoplasms of the upper digestive and respiratory tract (mainly tobacco, alcohol, as well as a diet poor in vegetables and fruit) (37, 38), and gastric cancer, too (i.e., tobacco, lower social class and various indicators of a poor diet) (39). As also noted for esophageal and laryngeal cancers, the inverse relation between flavanones and stomach cancer was still persistent, although became weaker, after allowance for vitamin C (17, 34, 35).

Table 7. Odds ratios[a] (OR) and corresponding 95% confidence intervals (CI) among 1,031 cases of ovarian cancer and 2,411 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1992-1999 (from [48]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*16.3*	*28.3*	*42.7*	*77.0*	-	
OR	1	0.81	0.73	0.92	0.89	0.23
(95% CI)		(0.62-1.05)	(0.55-0.96)	(0.71-1.19)	(0.67-1.17)	(0.63)
Flavanones (mg)						
Upper cutpoint	*12.2*	*31.3*	*36.6*	*67.0*	-	
OR	1	1.22	0.99	1.07	1.28	1.44
(95% CI)		(0.93-1.60)	(0.75-1.31)	(0.81-1.41)	(0.98-1.68)	(0.23)
Anthocyanidins (mg)						
Upper cutpoint	*3.5*	*7.4*	*12.3*	*19.4*	-	
OR	1	0.74	0.90	1.02	0.99	0.68
(95% CI)		(0.56-0.98)	(0.68-1.18)	(0.79-1.34)	(0.76-1.29)	(0.41)
Flavonols (mg)						
Upper cutpoint	*11.6*	*15.4*	*20.0*	*28.8*	-	
OR	1	0.78	0.65	0.88	0.63	6.89
(95% CI)		(0.60-1.01)	(0.50-0.85)	(0.67-1.14)	(0.47-0.84)	(0.009)
Flavones (mg)						
Upper cutpoint	*0.3*	*0.4*	*0.5*	*0.7*	-	
OR	1	0.91	0.95	0.87	0.79	2.62
(95% CI)		(0.70-1.19)	(0.73-1.24)	(0.66-1.15)	(0.60-1.04)	(0.11)
Isoflavones (mg)						
Upper cutpoint	*12.8*	*17.8*	*23.5*	*32.5*	-	
OR	1	1.12	0.93	0.85	0.51	19.51
(95% CI)		(0.87-1.45)	(0.71-1.21)	(0.64-1.12)	(0.37-0.69)	(<0.001)
Total flavonoids (mg)						
Upper cutpoint	*67.3*	*97.2*	*127.5*	*173.6*	-	
OR	1	1.03	0.94	0.80	1.07	0.12
(95% CI)		(0.80-1.34)	(0.72-1.24)	(0.61-1.06)	(0.82-1.40)	(0.72)

[a] *Estimates from multiple logistic regression models including terms for age, study centre, year of interview, education, parity, oral contraceptive use and family history of ovarian and/or breast cancer and energy intake, according to the residual model.* [b] *Reference category.*

Colorectal cancer

In the study on colorectal cancer (Table 5), a reduced risk was found for increasing intake of anthocyanidins (OR, 0.67, p-trend, 0.001), flavonols (OR, 0.64, p-trend < 0.001), flavones (OR, 0.78, p-trend, 0.004), and isoflavones (OR, 0.76, p-trend, 0.001) (40). The estimates did not substantially differ for colon and rectal cancers. After allowance for vegetables and fruit consumption, for dietary fiber, or for micronutrients previously associated to this tumor including vitamin C, the associations with flavonoids did not change by more than 10%.

A case-control study from Canada indicated an inverse association between dietary isoflavone intake and risk of colorectal cancer (41). In two prospective studies from Japan (42, 43), the intake of isoflavones was inversely associated with the risk of proximal colon cancer in men (42) and consumption of soy products (major sources of isoflavones) with the risk of colon cancer among women (43). No other consistent associations, however, were reported from these Japanese studies undertaken in a population characterized by a high consumption of isoflavone-rich foods (42, 43). A case-control study conducted in Sweden confirmed a significant decrease in risk of colorectal cancer for intake of anthocyanidins and flavonols (44), but there was no relation for isoflavones and flavones. Intake of flavonols was associated with colorectal cancer risk among normal weight women in the Netherlands Cohort Study (NLCS) (45). Associations for catechins were also found with the risk of rectal cancer in overweight men, and of colorectal cancer among normal weight women (45).

Table 8. Odds ratios[a] (OR) and corresponding 95% confidence intervals (CI) among 1294 cases of prostate cancer and 1451 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1991-2002 (from [54]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*29.9*	*47.6*	*67.8*	*102.1*	-	
OR	1	1.33	1.08	0.94	1.30	0.49
(95% CI)		(1.04-1.70)	(0.84-1.40)	(0.72-1.23)	(1.01-1.69)	(0.48)
Flavanones (mg)						
Upper cutpoint	*5.2*	*19.1*	*33.5*	*46.9*	-	
OR	1	1.10	1.06	1.00	0.96	0.35
(95% CI)		(0.86-1.40)	(0.82-1.36)	(0.78-1.29)	(0.75-1.23)	(0.56)
Anthocyanidins (mg)						
Upper cutpoint	*8.3*	*18.4*	*29.8*	*40.3*	-	
OR	1	1.13	1.20	1.18	1.18	1.49
(95% CI)		(0.88-1.45)	(0.94-1.54)	(0.91-1.52)	(0.91-1.53)	(0.22)
Flavonols (mg)						
Upper cutpoint	*15.1*	*19.8*	*24.0*	*30.7*	-	
OR	1	1.31	1.08	1.24	1.23	1.26
(95% CI)		(1.02-1.68)	(0.83-1.40)	(0.95-1.62)	(0.95-1.61)	(0.26)
Flavones (mg)						
Upper cutpoint	*0.2*	*0.3*	*0.4*	*0.6*	-	
OR	1	1.13	1.09	0.98	1.09	0.02
(95% CI)		(0.88-1.45)	(0.85-1.40)	(0.76-1.26)	(0.85-1.40)	(0.88)
Isoflavones (µg)						
Upper cutpoint	*14.7*	*19.8*	*24.8*	*32.2*	-	
OR	1	1.15	0.94	0.92	0.98	0.90
(95% CI)		(0.90-1.47)	(0.73-1.20)	(0.71-1.18)	(0.76-1.26)	(0.34)
Total flavonoids (mg)						
Upper cutpoint	*109.4*	*145.7*	*184.4*	*240.8*	-	
OR		1.32	0.97	1.13	1.20	0.59
(95% CI)		(1.06-1.64)	(0.76-1.23)	(0.88-1.44)	(0.92-1.58)	(0.44)

[a] *Estimates from multiple logistic regression models including terms for age, study centre, education, body mass index, family history of prostate cancer and total energy intake.* [b] *Reference category.*

Breast cancer

The study on breast cancer (Table 6) found a reduced risk of breast cancer for increasing intake of flavones (OR, 0.81, p-trend, 0.02), and flavonols (OR, 0.80, p-trend, 0.06) (46).

These findings are in agreement with those of a case-control study on breast cancer from Greece (20), which found a similar protective effect of flavones. A US case-control study on women (19) confirmed previous results on these Mediterranean populations. Most epidemiological studies also found that dietary phytoestrogens were inversely associated to breast cancer risk (47). The absence of any meaningful association with isoflavone intake in the Italian study may be due to the extremely limited intake of soya or soya products – and consequently of isoflavones- in the Italian population.

Ovarian cancer

The study on ovarian cancer (Table 7) found an inverse relation with ovarian cancer risk for flavonols (OR, 0.63; 95% CI, 0.47-0.84) and isoflavones (OR, 0.51; 95% CI, 0.37-0.69), with a significant trend in risk (48).

In line with these findings, intake of isoflavones was associated with a lower risk of ovarian cancer in a US cohort study (22), and in a Chinese case-control study (49). The evidence of an inverse association between isoflavones and ovarian cancer risk is supported by the observation that isoflavones have anti-estrogenic effects (5), and hence may inhibit the growth and proliferation of ovarian cell lines (50-52).

Another cohort study from the US reported a significant decrease in ovarian cancer incidence for subjects with a higher intake of flavonol kaempferol (53), in line with our results.

Table 9. Odds ratios[a] (OR) and 95% confidence intervals (CI) among 767 cases of renal cell carcinoma and 1534 controls, according to daily intake quintile of six classes of flavonoids and total flavonoids. Italy, 1992-2004 (from [57]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
Flavanols (mg)						
Upper cutpoint	*21.3*	*35.8*	*54.0*	*90.6*	-	
OR	1	1.15	1.09	0.91	0.77	4.02
(95% CI)		(0.87-1.52)	(0.80-1.47)	(0.66-1.26)	(0.56-1.06)	(0.045)
Flavanones (mg)						
Upper cutpoint	*9.6*	*22.5*	*33.9*	*57.8*	-	
OR	1	0.94	0.94	0.71	0.90	1.90
(95% CI)		(0.71-1.25)	(0.71-1.24)	(0.53-0.96)	(0.67-1.21)	(0.17)
Anthocyanidins (mg)						
Upper cutpoint	*5.5*	*11.6*	*19.7*	*32.4*	-	
OR	1	0.96	0.79	1.06	0.94	0.19
(95% CI)		(0.72-1.28)	(0.58-1.09)	(0.74-1.53)	(0.60-1.47)	(0.67)
Flavonols (mg)						
Upper cutpoint	*13.3*	*17.6*	*22.1*	*29.9*	-	
OR	1	0.89	0.76	0.88	0.69	4.05
(95% CI)		(0.68-1.19)	(0.57-1.03)	(0.65-1.19)	(0.50-0.95)	(0.044)
Flavones (mg)						
Upper cutpoint	*0.3*	*0.4*	*0.5*	*0.6*	-	
OR	1	1.05	0.87	0.86	0.68	7.37
(95% CI)		(0.80-1.39)	(0.65-1.16)	(0.64-1.15)	(0.50-0.93)	(0.007)
Isoflavones (mg)						
Upper cutpoint	*14.8*	*19.7*	*24.8*	*32.6*	-	
OR	1	0.86	0.81	0.77	0.76	3.48
(95% CI)		(0.65-1.14)	(0.61-1.08)	(0.57-1.03)	(0.56-1.03)	(0.062)
Total flavonoids (mg)						
Upper cutpoint	*80.6*	*109.1*	*139.4*	*180.9*	-	
OR	1	1.01	0.89	0.77	0.80	3.55
(95% CI)		(0.76-1.33)	(0.66-1.19)	(0.56-1.05)	(0.58-1.11)	(0.060)

[a] *Estimates from conditional logistic regression models, conditioned on sex, age, study centre, and adjusted for period of interview, education, alcohol consumption, tobacco smoking, body mass index, occupational physical activity, family history of kidney cancer, and total energy intake.* [b] *Reference category.*

Prostate cancer

In the study on prostate cancer (Table 8) no association between prostate cancer risk was found with any of the analyzed flavonoids (54).

Although some flavonoids showed a favourable effect against prostate cancer (55), the results from epidemiological studies are inconsistent. A recent prospective study from Japan found that isoflavone intake was associated with a decreased risk of localized prostate cancer (21), possibly explaining the much lower incidence of prostate cancer in Asian as compared to Western populations characterized by a low consumption of isoflavones rich foods as soya. In a case-control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study (56), higher plasma concentrations of isoflavone genistein, but not other isoflavones, were associated with lower risk of prostate cancer.

Renal cancer

The study on renal cell carcinoma (Table 9) showed that flavonols (OR, 0.69, 95% CI, 0.50-0.95) and flavones (OR, 0.68, 95% CI, 0.50-0.93) were inversely related to the risk of renal cancer (57). Allowance for vegetable and fruit consumption only partly explained the inverse relation with flavonoids.

A recent study showed an inverse association between the flavonol quercetin and renal cancer among smokers of the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study cohort (58), in line with our results.

Table 10. Odds ratios[a] (ORs) and 95% confidence intervals (CI) among 1953 cases of colorectal cancer and 4154 controls, according to daily intake quintile of six classes of proanthocyanidins, two their combinations and total proanthocyanidins. Italy, 1992-1996 (from [59]).

	Quintile of intake					χ^2 trend
	1[b]	2	3	4	5	(p-value)
≤ 2 mers (mg)						
Upper cutpoint	*41.2*	*67.9*	*98.5*	*147.3*	-	
OR		1.04	0.89	0.80	0.82	7.7
(95% CI)		(0.87-1.25)	(0.74-1.07)	(0.66-0.97)	(0.66-1.01)	(0.006)
Monomers (mg)						
Upper cutpoint	*16.9*	*28.5*	*42.4*	*64.9*	-	
OR		1.00	0.92	0.83	0.88	3.4
(95% CI)		(0.83-1.20)	(0.77-1.11)	(0.69-1.01)	(0.71-1.09)	(0.064)
Dimers (mg)						
Upper cutpoint	*24.1*	*39.3*	*56.0*	*82.2*	-	
OR		1.01	0.83	0.77	0.75	12.2
(95% CI)		(0.84-1.21)	(0.69-1.00)	(0.64-0.94)	(0.61-0.93)	(0.001)
≥3 mers (mg)						
Upper cutpoint	*149.7*	*207.3*	*265.6*	*348.0*	-	
OR		0.94	0.89	0.79	0.74	13.7
(95% CI)		(0.79-1.12)	(0.74-1.06)	(0.66-0.94)	(0.62-0.89)	(<0.001)
Trimers (mg)						
Upper cutpoint	*10.8*	*15.4*	*19.7*	*26.7*	-	
OR		0.96	0.84	0.78	0.84	7.5
(95% CI)		(0.81-1.15)	(0.70-1.00)	(0.65-0.93)	(0.70-1.00)	(0.006)
4-6mers (mg)						
Upper cutpoint	*38.1*	*53.5*	*68.4*	*91.2*	-	
OR		0.98	0.81	0.80	0.80	10.2
(95% CI)		(0.82-1.16)	(0.68-0.97)	(0.67-0.96)	(0.66-0.95)	(0.001)
7-10mers (mg)						
Upper cutpoint	*30.3*	*43.3*	*55.1*	*73.3*	-	
OR		0.96	0.84	0.79	0.79	10.2
(95% CI)		(0.81-1.15)	(0.70-1.00)	(0.66-0.95)	(0.66-0.95)	(0.001)
> 10 mers (mg)						
Upper cutpoint	*68.2*	*93.9*	*119.8*	*157.5*	-	
OR		0.91	0.88	0.76	0.69	19.1
(95% CI)		(0.76-1.08)	(0.74-1.05)	(0.63-0.91)	(0.58-0.83)	(<0.001)
Total proanthocyanidins (mg)						
Upper cutpoint	*202.5*	*284.2*	*364.9*	*486.6*	-	
OR		0.92	0.78	0.84	0.74	10.1
(95% CI)		(0.78-1.10)	(0.65-0.93)	(0.70-1.01)	(0.62-0.90)	(0.002)

[a] *Estimates from multiple logistic regression models including terms for age, sex, study centre, education, body mass index, family history of colorectal cancer, occupational physical activity, alcohol consumption and energy intake, according to the residual model.* [b] *Reference category.*

Proanthocyanidins and colorectal cancer

In another study on colorectal cancer, we investigated proanthocyandins in relation to the risk of this neoplasm (59). The ORs were below unity for all classes of proanthocyanidins (Table 10). The inverse associations appeared stronger for proanthocyanidins with higher degree of polymerization: the OR was 0.82 for monomers and dimers combined, 0.74 for polymers with three or more mers and 0.69 for polymers with ten or more mers. We found a significant inverse trend in risk with increasing intake for all class of proanthocyandins, except for monomers. The inverse associations appeared to be stronger for rectal than for colon cancer. Since proanthocyanidins yield anthocyanidins upon depolymerisation under acidic conditions (60) and were strongly correlated with these compounds and flavanols, we further adjustment for flavonoids and did not find substantially differences in the inverse relation between proanthocyanidins and colorectal cancer risk.

A recent case-control study from Scotland found an inverse association of colorectal cancer risk with the intake of single flavanols, including catechins and epicatechins, and procyanidins (polymers of (epi) catechin) (61). Studies in vitro and experimental animals suggest they have favorable effects on colorectal cancer (4, 62-68) and have larger antioxidant effects than flavanols (69, 70).

Conclusion

The data from this large network of Italian case-control studies allowed to investigate the potential effects of flavonoids and proanthocyanidins against cancer, on a population characterized by a diet rich in vegetables and fruit with regular wine consumption such as the Italian one (2). The findings provide support for an apparent protective role of flavanones on upper aerodigestive tract cancers (33-35), flavonols, anthocyanidins and proanthocyanidins on colorectal cancer (40, 59), flavonols and flavones on breast cancer (46), isoflavones on ovarian cancer (48), and flavonols on renal cancer (57). For most investigated neoplasms, adjustment for flavonoids reduced the strength of the inverse association between vegetables or fruit consumption and the risk of cancer, whereas allowance for vegetables and fruit consumption only moderately changed the observed associations with flavonoids. Misclassification may play a role, but it appears that a diet rich in vegetables and fruit does not alone account for the protections of flavonoids on the risk of several cancer sites, whereas the inverse relation of cancer with vegetables and fruit is not totally explained by flavonoid intake.

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