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Flavonoids and risk of squamous cell esophageal cancer

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The relation between 5 classes of flavonoids (flavanones, flavan-3-ols, flavonols, flavones and anthocyanidines) and esophageal cancer was investigated using data from a case-control study conducted between 1992 and 1997 in 3 areas of northern Italy. The study included 304 cases (275 men, 29 women) with a first diagnosis of squamous-cell carcinoma of the esophagus and 743 controls (593 men, 150 women) with no history of cancer, admitted for acute illnesses, unrelated to tobacco and alcohol consumption, to major hospitals of the areas under surveillance. Dietary habits were investigated using a validated food frequency questionnaire. Odds ratios (ORs) and 95% confidence intervals (CI) were computed after allowance for age, sex, study centre, years of education, alcohol drinking, tobacco smoking, body mass index and energy intake. An inverse association emerged between flavanone intake and esophageal cancer risk (OR = 0.38 for the highest vs. the lowest quintile, 95% CI = 0.23–0.66). The inverse relation between flavanones and esophageal cancer tended to be stronger in those who drank ≥6 drinks/day. In conclusion, this study suggests that flavanone intake is inversely associated with esophageal cancer risk and may account, with vitamin C, for the protective effect of fruit, especially citrus fruit, on esophageal cancer.

Key words: flavonoids; squamous cell esophageal cancer; flavanones; case-control study; risk factors

Flavonoids are a large group of compounds contained in foods and beverages of plant origin, which cannot be synthesized by humans.[1,2] As several flavonoids have antioxidant properties, as well as antimutagenic and antiproliferative properties in vitro,[3–5] these compounds have been investigated for possible inverse associations with chronic diseases, including various types of cancer,[6–11] and may explain at least in part, the protective effect of vegetable and fruit against cancer.[12,13] Over 4,000 different flavonoids have been described, and they have been grouped into 6 classes, *i.e.* flavanones, flavan-3-ols, flavonols, flavones, anthocyanidines and isoflavones.[14] Until recently, the lack of a comprehensive nutritional database has however hindered a thorough epidemiological investigation of their role in cancer prevention.

As concerns esophageal cancer, several studies have reported a protective effect of fruit and vegetables.[15,16] To our knowledge, only 2 studies have investigated the relation between flavonoids and esophageal cancer risk, showing conflicting results. A case-control study from Uruguay,[17] including 66 esophageal cancer cases (of unspecified histology), found an inverse association between flavonoids and esophageal cancer risk [odds ratio (OR) = 0.4 for the highest vs. the lowest tertile, 95% confidence interval, CI, 0.3–0.6]; while another study, conducted in China,[18] on a cohort that had generated 42 esophageal cancer cases (mostly squamous cell carcinomas) reported no association between urinary polyphenol markers deriving from tea and esophageal cancer risk.

To further analyse the relation of flavonoid intake with esophageal cancer risk, we considered the dietary intake of 5 classes of flavonoids using data from a large multicentric case-control study of esophageal cancer conducted in Italy.

Material and methods

A case-control study of cancer of the esophagus was conducted between 1992 and 1997 in the provinces of Milan, Pordenone and Padua in northern Italy.[15] Cases were individuals admitted to the major teaching and general hospitals in the areas under study with incident, histologically confirmed squamous cell cancer of the esophagus, diagnosed not earlier than 1 year before the interview and with no history of cancer at other sites. A total of 304 individuals were enrolled, 275 men and 29 women, whose median age was 60 years (range 39–77). Controls were patients admitted to the same hospitals as the cases for a wide spectrum of acute, non-neoplastic conditions, not related to smoking or alcohol consumption, nor to long-term modification of diet. Controls were frequency-matched to cases on age (5-year groups), sex, year of interview and area of residence. To compensate for the rarity of esophageal cancer in women, a control-to-case ratio of about 5 was chosen for females, as opposed to about 2 for males. The control group comprised 743 subjects, 593 men and 150 women, whose median age was 60 years, ranging from 36 to 77. Twenty-nine percent of the controls were admitted for traumas, 36% for other orthopaedic disorders, 12% for acute surgical conditions and 23% for miscellaneous other illnesses. Less than 5% of both cases and controls contacted refused to participate.

A structured questionnaire was administered by trained interviewers to the subjects during their hospital stay. Cases and controls were interviewed by the same interviewers and under similar conditions. The questionnaire included information on personal medical history, socio-demographic characteristics, anthropometric measures and life-style habits, including tobacco smoking and alcohol drinking. In particular, weekly number of the 5 most common alcoholic beverages or groups of beverages was investigated; 1 drink corresponded to ~125 ml of wine, 330 ml of beer and 30 ml of hard liquor (*i.e.* about 12–15 g of ethanol). A validated and reproducible food frequency questionnaire (FFQ) was used to assess the patients' usual diet in the 2 years before diagnosis or hospital admission,[19,20] including 78 foods or food groups, plus questions specifically aimed at assessing fat intake and general dietary practices.[15] Selected nutrients and energy intake were computed using an Italian food composition database, appropriately checked and supplemented with other published data.[21] Food and beverage content of 5 classes of flavonoids (*i.e.*, flavanones,

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TABLE I – DISTRIBUTION OF 304 CASES OF SQUAMOUS CELL CANCER OF THE ESOPHAGUS (275 MEN AND 29 WOMEN) AND 743 CONTROLS (593 MEN AND 150 WOMEN) ACCORDING TO SELECTED VARIABLES IN NORTHERN ITALY, 1992–1997

	Cases				Controls			
	Men		Women		Men		Women	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Age (years)								
<50	26	9.5	3	10.3	63	10.6	15	10.0
50–55	43	15.6	4	13.8	94	15.8	20	13.3
55–59	59	21.5	6	20.7	122	20.6	30	20.0
60–64	56	20.4	6	20.7	116	19.6	30	20.0
65–69	51	18.5	6	20.7	112	18.9	30	20.0
≥70	40	14.5	4	13.8	86	14.5	25	16.7
Education (years)								
<7	196	71.3	21	72.4	356	60.0	100	66.7
7–11	59	21.4	6	20.7	154	26.0	35	23.3
≥12	20	7.3	2	6.9	83	14.0	15	10.0
Smoking habit[a]								
Never smoking	19	6.9	14	50.0	139	23.4	106	70.7
Ex smoker	105	38.2	4	14.2	270	45.5	17	11.4
Current smoker								
<15 cigarettes/day	32	11.6	5	17.9	72	12.2	14	9.3
15–24 cigarettes/day	79	28.7	5	17.9	84	14.2	8	5.3
≥25 cigarettes/day	40	14.6	–	–	28	4.7	5	3.3
Alcohol consumption habit								
0–20 drinks/week	15	5.5	19	65.5	203	34.2	136	90.7
21–34 drinks/week	47	17.1	4	13.8	172	29.0	10	6.7
35–55 drinks/week	57	20.7	5	17.2	114	19.2	3	2.0
56–83 drinks/week	84	30.5	1	3.5	68	11.5	–	–
≥84 drinks/week	72	26.2	–	–	36	6.1	1	0.6
Non alcohol energy intake (quintiles)								
I	68	24.7	3	10.3	106	17.9	32	21.3
II	58	21.1	4	13.8	115	19.4	32	21.3
III	57	20.7	5	17.3	116	19.6	32	21.3
IV	48	17.5	5	17.3	127	21.4	30	20.1
V	44	16.0	12	41.3	129	21.7	24	16.0

[a]The sum does not add up to the total because of some missing values.

flavan-3-ols, flavonols, flavones and anthocyanidines) was obtained from the US Department of Agriculture,[9,22] supplemented by data from other sources.[23–25] Major flavonoids included in these classes are hesperitin and narigerin for flavanones, epicatechin and catechin for flavan-3-ols, quercetin, myricetin and kaempferol for flavonols, apigenin and luteolin for flavones, and cyanidin and malvidin for anthocyanidines. In this population, anthocyanidines were derived from wine and red fruits; flavan-3-ols from tea, wine and fruit; flavanones from citrus fruit, flavones from cooked vegetables; and flavonols from various common vegetables, fruit and wine. Given the low consumption of soy beans and other pulses in this population, isoflavone intake could not be reliably estimated.

OR and the corresponding 95% CI were estimated using unconditional multiple logistic regression models.[26] The core model included terms of age, sex, study centre, years of education, alcohol drinking, tobacco smoking, body mass index (BMI) and energy intake.

Results

Table I gives the distribution of 304 cases of squamous cell cancer of the esophagus and 743 controls according to selected variables by gender. By design, cases and controls had similar age distribution. Cases were less educated than controls and reported significantly higher tobacco and alcohol consumption. Non-alcohol energy intake was lower among male cases than among male controls, whereas it was higher in female cases than in the corresponding control group.

Table II shows the median daily intake of 5 classes of flavonoids and total flavonoids among controls and the ORs of esophageal cancer, according to quintiles of intake and for a continuous increment. The median daily intake was 23.7 mg for anthocyanidins, 60.7 mg for flavan-3-ols, 33.5 mg for flavanones, 0.4 mg for flavones, 22.3 mg for flavonols, and 146.3 mg for total flavonoids. A significant inverse relation with esophageal cancer risk was found for flavanones (OR, 0.38, for the highest versus the lowest quintile; *p*-trend, 0.004). No meaningful association emerged for other classes of flavonoids, including anthocyanidins (OR, 0.84), flavan-3-ols (OR, 1.06), flavones (OR, 0.97), as well as total flavonoids (OR, 0.99). A borderline significant trend in risk was found for flavonols (OR, 0.68; *p*-trend, 0.060), which however, declined after allowance for vegetables consumption (OR, 0.81; *p*-trend, 0.246). Within flavonols, kaempferol was inversely but non significantly related to esophageal cancer. The OR across subsequent quintiles of kaempferol were 0.90, 0.66, 0.61 and 0.67 ($\chi^2_{1,}$ 3.78; *p*-trend, 0.052). The continuous value was 0.97.

After allowance for fruit intake, the association of flavanones with esophageal cancer remained inverse, though non significantly (OR = 0.79, 95% CI, 0.58–1.08). Similarly, allowing for vitamin C the OR of flavanone intake changed from 0.38 (95% CI, 0.23–0.66) to 0.55 (95% CI, 0.27–1.12). After exclusion of flavonoids derived from wine (65% of anthocyanidins, 30% of flavan-3-ols and 12% of flavonols), the continuous ORs for an increment equal to the difference between the 80th and 20th percentile became 0.93 (95% CI, 0.77–1.13) for anthocyanidins, 1.11 (95% CI, 0.97–1.26) for flavan-3-ols and 0.82 (95% CI, 0.65–1.03) for flavonols.

In Table III the relation between flavonoids and esophageal cancer risk was analyzed in strata of alcohol drinking and tobacco smoking. In spite of the many tests performed, and hence the possibility of false-positive findings, the estimates were generally consistent across strata of alcohol and tobacco. However, the inverse relation between flavanone intake and esophageal cancer risk was stronger in subjects who drank ≥6 drinks/day (continuous OR = 0.49, 95% CI, 0.32–0.75) (*p*-value for interaction = 0.05). For flavonols, a non significant inverse relation was found for current smokers (OR, 0.75; 95% CI, 0.54–1.03), and for moderate drinkers (OR, 0.73; 95% CI, 0.49–1.08). The interaction term was significant in strata of alcohol intake. When stratified analyses

TABLE II – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) OF 304 CASES WITH SQUAMOUS CELL CANCER OF THE ESOPHAGUS AND CORRESPONDING 743 CONTROLS, ACCORDING TO INTAKE QUINTILES OF SELECTED FLAVONOIDS. ITALY, 1992–1997

	Median intake[a]	Quintiles of intake Quintiles of intake					χ^2(trend per quintile) *p*-value	Continuous[b]
		1	2	3	4	5		
Anthocyanidins (mg)								
Upper cutpoint	23.7	8.1	18.2	30.2	41.2	–		
Cases: Controls		38:148	23:149	34:148	53:150	156:148		
OR[c]		1[d]	0.60	0.56	0.41	0.84	0.45	1.23
(95% CI)			(0.29–1.24)	(0.29–1.13)	(0.22–0.79)	(0.46–1.54)	0.502	(0.96–1.59)
Flavan-3-ols (mg)								
Upper cutpoint	60.7	32.6	49.4	72.8	109.1	–		
Cases:Controls		33:148	40:150	47:148	83:148	101:149		
OR[c]		1[d]	1.03	0.72	0.89	1.06	0.08	1.22
(95% CI)			(0.55–1.96)	(0.38–1.37)	(0.48–1.64)	(0.58–1.94)	0.773	(1.02–1.46)
Flavanones (mg)								
Upper cutpoint	33.5	6.4	19.7	33.9	58.8	–		
Cases:Controls		105:148	55:149	55:148	50:150	39:148		
OR[c]		1[d]	0.42	0.59	0.56	0.38	8.47	0.73
(95% CI)			(0.26–0.67)	(0.36–0.97)	(0.34–0.92)	(0.23–0.66)	0.004	(0.53–0.99)
Flavones (mg)								
Upper cutpoint	0.4	0.3	0.4	0.5	0.7	–		
Cases:Controls		80:149	57:148	74:149	42:148	51:149		
OR[c]		1[d]	0.87	1.31	0.78	0.97	0.02	1.09
(95% CI)			(0.52–1.44)	(0.81–2.11)	(0.45–1.36)	(0.57–1.67)	0.877	(0.90–1.31)
Flavonols (mg)								
Upper cutpoint	22.3	15.9	20.4	25.4	31.9	–		
Cases:Controls		53:148	58:149	68:148	56:150	69:148		
OR[c]		1[d]	1.02	0.76	0.55	0.68	3.54	0.89
(95% CI)			(0.59–1.76)	(0.43–1.32)	(0.30–0.98)	(0.38–1.24)	0.060	(0.70–1.12)
Total Flavonoids (mg)								
Upper cutpoint	146.3	96.5	127.7	166.2	217.4	–		
Cases:Controls		35:148	46:149	46:149	66:149	111:148		
OR[c]		1[d]	1.29	0.78	0.81	0.99	0.23	1.17
(95% CI)			(0.72–2.33)	(0.42–1.42)	(0.45–1.46)	(0.55–1.79)	0.634	(0.95–1.44)

[a]Median intake among controls.–[b]Estimated for an increment of intake equal to the difference between the 80th and 20th percentile.–[c]Estimated using multiple logistic regression models adjusted for age, sex, study centre, education, alcohol consumption, tobacco smoking, body mass index and energy intake.–[d]Reference category.

TABLE III – ODDS RATIOS (OR)[a] OF SQUAMOUS CELL CANCER OF THE ESOPHAGUS AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) ACCORDING TO SELECTED FLAVONOIDS INTAKE ACROSS STRATA OF TOBACCO SMOKING AND ALCOHOL DRINKING. ITALY, 1992–1997

Flavonoids	OR[b] (95% CI)			
	Tobacco smoking		Alcohol intake (drinks/day)	
	Never + ex-smokers (106/563)[c]	Current Smokers (198/180)[c]	<6 (84/454)[c]	≥6 (220/289)[c]
Anthocyanidins	2.36[d] (1.46–3.83)	1.02[d] (0.77–1.37)	1.46 (0.60–3.51)	1.21 (0.92–1.60)
Flavan-3-ols	1.38 (1.00–1.91)	1.15 (0.92–1.45)	1.23 (0.86–1.76)	1.21 (0.97–1.50)
Flavanones	0.68 (0.37–1.24)	0.68 (0.48–0.99)	1.16[d] (0.74–1.82)	0.49[d] (0.32–0.75)
Flavones	1.23 (0.91–1.66)	1.00 (0.79–1.27)	1.13 (0.83–1.55)	1.07 (0.84–1.35)
Flavonols	1.22 (0.88–1.68)	0.75 (0.54–1.03)	0.73[d] (0.49–1.08)	1.03[d] (0.73–1.45)
Total Flavonoids	1.54 (1.05–2.27)	1.02 (0.78–1.32)	0.95 (0.53–1.72)	1.12 (0.89–1.43)

[a]Estimated using multiple logistic regression models adjusted for sex, age, study centre, education, alcohol consumption, tobacco smoking, body mass index and energy intake.–[b]Estimated for an increment of intake equal to the difference between the 80th and 20th percentile.–[c]Cases/controls.–[d]$p < 0.05$ at wald χ^2_1 test for heterogeneity.

were made for the categorical model, the ORs for the highest quintile of flavanones were 0.44 among non smokers, 0.34 among current smokers, 0.70 among moderate drinkers and 0.18 among heavy drinkers. Corresponding values for flavonols were 1.68, 0.40, 0.55 and 0.61. The interaction terms were not significant for these models.

Discussion

Our results rely on a large dataset and are in broad agreement with those reported from two earlier smaller investigations. In fact, an inverse association was found between flavonoids and esophageal cancer risk in a case-control study conducted in Uruguay.[17] Another study from China reported no association between urinary polyphenol markers deriving from tea and esophageal cancer risk, including epigallocatechin, epicatechin and their metabolites, which belong to flavan-3-ols, unrelated to esophageal cancer risk in our study too.[18] The contribution of tea to flavonoid intake was too small in this population to investigate the issue.

Flavonoids have been considered as possible mediators of the protective effect of vegetables and fruit against cancer.[6–11,27] In particular, a Greek study[8] found that among the major classes of

flavonoids, only flavanones were inversely associated with cancer of the stomach, similar to our results.

The use of hospital controls has been widely debated and several strengths and weaknesses should be considered.[28] Dietary information, even when explicitly referring to the past, can be influenced by recent diagnosis of cancer. However, the information collected referred to the habitual diet in the 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 unrelated to major changes in diet and other life-style factors. Moreover, the same interview setting and catchment areas for cases and controls, and the almost complete participation rate, are reassuring. Among other strengths of the study, there are the large dataset, the high and variable intake of fruit and vegetables in this population, the satisfactory reproducibility and validity of the FFQ,[19–20] and the ability to control for total energy intake and other major recognized confounding factors. Among the limitations of this study, there are the questions concerning the adaptability of U.S. flavonoid food composition dataset to the Italian diet, and the fact that the questionnaire was not specifically designed to investigate flavonoids. Moreover, it is difficult to evaluate the precision 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 geological, climatic and meteorological factors. These limitations may apply particularly to flavones, whose intake derives essentially form aromatic herbs. More in general, limitations in the food composition database may well underestimate the absolute flavonoid intake and, if anything, lead an attenuation of the real associations.

Alcohol is a strong risk factor for squamous cell esophageal cancer,[29] and can interact with diet in several ways. The presence of some classes of flavonoids in red wine, in a population in which wine is the major source of alcohol, may create misleading associations, although all our estimates were adjusted for alcohol drinking. In fact, the apparent direct association of anthocyanidins and flavan-3-ols with esophageal cancer vanished when we excluded flavonoids derived from wine consumption (65% of anthocyanidin and 30% of flavan-3-ol intake).

Since citrus fruit accounts for 90% of flavanone intake, our findings suggest that flavanones may play a role in explaining the protective effect of citrus fruit on esophageal cancer. Other compounds contained in citrus fruit, like vitamin C, may also provide protection against esophageal cancer.[15,30] Adjustment for vitamin C reduced the strength of the association between flavanones and esophageal cancer. However, the strong correlation between vitamin C and flavanones (Spearman-r = 0.67) makes it difficult to distinguish between their effects.

This study shows some inverse moderate relation between flavonols and esophageal cancer, particularly in current smokers and non or moderate drinkers. This is at least in part consistent with previous studies, which reported that flavonols had a favourable effect in the risk of several neoplasms, mainly of the digestive and respiratory tract,[11,31–34] where they could prevent damage to the mucosa, including damage because of oxidative stress resulting from tobacco smoking.

In conclusion, this study suggests that flavanone intake is inversely associated with esophageal cancer risk and may account, with vitamin C, for the protective effect of fruit, especially citrus fruit, on esophageal cancer.[15,18,35]

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