Flavonoids and the Risk of Oral and Pharyngeal Cancer: A Case-Control Study from Italy

Marta Rossi,[1] Werner Garavello,[1,3] Renato Talamini,[4] Eva Negri,[1] Cristina Bosetti,[1] Luigino Dal Maso,[4] Pagona Lagiou,[5] Alessandra Tavani,[1] Jerry Polesel,[4] Luigi Barzan,[6] Valerio Ramazzotti,[7] Silvia Franceschi,[8] and Carlo La Vecchia[1,2]

[1]Istituto di Ricerche Farmacologiche ''Mario Negri'', Milan, Italy; [2]Istituto di Statistica Medica e Biometria ''G.A. Maccacaro'', Università degli Studi di Milano, Milan, Italy; [3]Clinica Otorinolaringoiatrica, DNTB, Università Milano-Bicocca, Monza, Italy; [4]Unità di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (PN), Italy; [5]Department of Hygiene and Epidemiology, University of Athens Medical School, Goudi, Athens, Greece; [6]Divisione di Otorinolaringoiatria, Ospedale ''S. Maria degli Angeli'', Pordenone, Italy; [7]Servizio Integrato di Epidemiologia e Sistemi Informativi, Istituto Nazionale Tumori ''Regina Elena'', Rome, Italy; and [8]International Agency for Research on Cancer, Lyon, France

Abstract

The intake of flavonoids has been inversely related to the risk of various common neoplasms, but scanty data exist on oral and pharyngeal cancer. We used data from a case-control study conducted in Italy between 1992 and 2005 to examine the relationship between flavonoid intake and oral and pharyngeal cancer risk. The study included 805 cases with incident, histologically confirmed oral and pharyngeal cancer, and 2,081 hospital controls admitted for acute, nonneoplastic conditions. We have applied data on food and beverage content of six major classes of flavonoids, on dietary information collected through a validated food-frequency questionnaire. The odds ratios (OR) were calculated using multiple logistic regression models, conditioned on study center, sex, and age. After adjustment for education, tobacco, alcohol, body mass index, and non–alcohol energy intake, ORs for the highest versus the lowest quintile of intake were 0.51 [95% confidence intervals (95% CI), 0.37-0.71] for flavanones, 0.62 (CI, 0.43-0.89) for flavonols, and 0.56 (95% CI, 0.40-0.78) for total flavonoids. No significant association emerged for isoflavones (OR, 0.90), anthocyanidins (OR, 0.86), flavan-3-ols (OR, 0.84), and flavones (OR, 0.75). 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 nonsignificant. None of the associations were significant after further allowance for vitamin C, probably on account of the high collinearity between these compounds. (Cancer Epidemiol Biomarkers Prev 2007;16(8):1621–5)

Introduction

Tobacco smoking and alcohol drinking are the two major risk factors for oral and pharyngeal cancer in developed countries (1, 2), but a role of diet has also been reported (3, 4). In particular, fruit and vegetable consumption has been associated with a reduced risk of this neoplasm (5, 6), but it is still unclear which components of vegetables and fruits may account for this inverse relation. Flavonoids—a large number of polyphenolic compounds ubiquitously present in foods and beverages of plant origin (7)—have shown antioxidant, and possibly antimutagenic and antiproliferative properties (8-10). Thus, they have been hypothesized to be responsible for the favorable effects of fruit and vegetables against various common neoplasms, mainly cancers of the respiratory (11-17) and digestive tracts (18-21).

With reference to oral and pharyngeal cancer, only one case-control study, conducted in Uruguay (13) has investigated this issue and found a risk below unity for the highest versus the lowest tertile of flavonoid intake [odds ratio (OR), 0.8, 95% confidence interval (95% CI), 0.5-1.4]. To examine the role of flavonoids on the risk of oral and pharyngeal cancer, we considered data from a large multicentric case-control study of oral and pharyngeal cancer conducted in Italy.

Materials and Methods

The present analyses are based on data from a case-control study of oral and pharyngeal cancer conducted from 1992 to 2005 in the provinces of Pordenone in northeastern Italy, Rome and Latina in central Italy (6), and the greater Milan area in northern Italy. In previous publications (6), data from the Milan center was not included because the collection of data from this center started and ended later. However, the same questionnaire and selection criteria were used in all centers. Cases were 805 patients (659 men and 146 women; median age 58 years, range 22-78 years) admitted to major teaching and general hospitals in the study areas, with incident, histologically confirmed cancer of the oral cavity (406 cases) and of the pharynx (399 cases), diagnosed ≤1 year before the interview. Cancers of the lip, salivary glands, and nasopharynx were not included. Controls were 2,081 subjects (1,302 men and 779 women; median age 58 years, range 19-79 years) admitted to the same hospitals as cases for a wide spectrum of acute, nonneoplastic conditions, unrelated to known risk factors for oral and pharyngeal cancer, and not associated with long-term dietary modifications. Controls were frequency-matched with cases according to study center, sex, and 5-year age groups. To compensate for the rarity of oral and pharyngeal cancer in women, a control-to-case ratio of ∼5 was chosen for women, as opposed to ∼2 for men. Of these, 25% were admitted for traumas, 30% for other orthopedic disorders, 19% for surgical conditions, 9% for eye diseases, and 17% for miscellaneous

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Requests for reprints: Marta Rossi, Laboratorio di Epidemiologia, Istituto di Ricerche Farmacologiche ''Mario Negri'', Via La Masa 19, 20156, Milan, Italy. Phone: 390-23901-4541; Fax: 390-23320-0231. E-mail: mrossi@marionegri.it

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Table 1. Distribution of 805 oral cavity and pharyngeal cancer cases and 2,081 controls according to center, sex, age and selected other covariates (Italy, 1992-2005)

	Cases (%)	Controls (%)
Center		
Pordenone	494 (61.4)	1,053 (50.6)
Milan	207 (25.7)	590 (28.4)
Rome	104 (12.9)	438 (21.0)
Sex		
Male	659 (81.9)	1,302 (62.6)
Female	146 (18.1)	779 (37.4)
Age (y)		
<50	164 (20.4)	502 (24.1)
50-59	270 (33.5)	630 (30.3)
60-69	286 (35.5)	698 (33.5)
70-79	85 (10.6)	251 (12.1)
Range (median)	22-78 (58)	19-79 (58)
Education (y)		
<7	496 (61.6)	1,152 (55.4)
7-11	215 (26.7)	590 (28.4)
≥12	89 (11.1)	338 (16.3)
Missing	5 (0.6)	1 (0.0)
Smoking habit*		
Never smoker	102 (12.7)	881 (42.3)
Ex-smoker †	220 (27.3)	646 (31.0)
Current smoker		
1-19 cigarettes/d	222 (27.6)	334 (16.0)
≥20 cigarettes/d	260 (32.3)	217 (10.4)
Missing	1 (0.1)	3 (0.1)
Alcohol consumption (drinks/d)		
<4	264 (32.8)	1,482 (71.2)
4 to <9	247 (30.7)	484 (23.3)
≥9	290 (36.0)	110 (5.3)
Missing	4 (0.5)	5 (0.2)
BMI (kg/m^2)		
<20	450 (55.9)	846 (40.7)
20 to <25	279 (34.7)	941 (45.2)
≥25	68 (8.4)	283 (13.6)
Missing	8 (1.0)	11 (0.5)
Non−alcohol energy intake (quintiles)		
I (low)	153 (19.0)	417 (20.0)
II	157 (19.5)	416 (20.0)
III	138 (17.1)	415 (20.0)
IV	171 (21.2)	416 (20.0)
V	186 (23.1)	417 (20.0)

*One cigar is equivalent to three cigarettes, 1 g of pipe tobacco is equivalent to one cigarette.
† Ex-smokers were subjects who had stopped smoking for at least 1 y.

various other illnesses. Less than 5% of both cases and controls contacted refused to participate.

Cases and controls were interviewed during their hospital stay by trained interviewers using a structured questionnaire. This included information on sociodemographic characteristics, lifestyle habits, such as tobacco smoking and alcohol drinking, anthropometric measures, personal medical history, and family history of cancer.

The subjects' usual diet during the 2 years before cancer diagnosis or hospital admission (for controls) was assessed using a reproducible (22) and valid (23) food-frequency questionnaire, which included 78 foods and beverages, as well as a range of the most common Italian recipes. Subjects were asked to indicate their average weekly frequency of consumption for each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. To estimate total energy intake, an Italian food composition database was used, complemented with other sources when needed (24, 25). The food and beverage contents of six classes of flavonoids (i.e., isoflavones, anthocyanidins, flavan-3-ols, flavanones, flavones, and flavonols) were estimated on the basis of information obtained from the U.S. Department of Agriculture databases (26, 27), and supplemented by data from other sources (28-30). The major flavonoids included in these classes were genistein and daidzein for isoflavones; cyanidin and malvidin for anthocyanidins; catechin, epicatechin, gallocatechin, and epigallocatechin for flavan-3-ols; hesperitin and narigerin for flavanones; apigenin and luteolin for flavones; and quercetin, myricetin, and kaempferol for flavonols. Total flavonoids were calculated by summing up the six classes of flavonoids. Quintiles based on the control distribution were computed both directly on the flavonoids, and on the residuals of the regression of flavonoids on total energy (31). Because both analyses yielded similar results, only the former estimates are presented.

ORs and the corresponding 95% CIs were calculated using conditional multiple logistic regression models (32), conditioned on to study center, sex, and age. All the regression models included terms for years of education, tobacco smoking, alcohol drinking, body mass index (BMI), and non−alcohol energy intake. In additional models, terms for fruit and vegetable consumption, as well as for selected micronutrients, were added. The flavonoids were entered in the model as quintiles of intake or as continuous variables, with the measurement unit set at 1 SD of the distribution of the controls.

Results

Table 1 gives the distribution of 805 cases and 2,081 controls according to center, age, sex, and selected other covariates. By design, the proportion of women was higher in controls than in cases, and the age distribution was similar in cases and controls. Cases were slightly less educated, reported a significantly higher tobacco and alcohol consumption, and tended to have a lower BMI, and a higher non−alcohol energy intake than controls.

Table 2. Distribution of 805 oral cavity and pharyngeal cancer cases and 2,081 controls according to intake quintile of six classes of flavonoids (Italy, 1992-2005)

Flavonoids	Mean (SD)*	Quintile of intake				
		1	2	3	4	5
Isoflavones (μg)						
Upper cutpoints †	24.8 (13.8)	14.7	19.4	24.7	32.5	—
Cases		174	173	172	154	132
Controls		416	417	415	416	417
Anthocyanidins (mg)						
Upper cutpoints †	21.9 (21.0)	5.3	13.4	20.9	33.2	—
Cases		139	98	79	106	383
Controls		416	416	417	415	417
Flavan-3-ols (mg)						
Upper cutpoints †	65.4 (60.0)	23.3	40.3	59.4	99.6	—
Cases		131	118	118	171	267
Controls		417	416	415	417	416
Flavanones (mg)						
Upper cutpoints †	38.8 (32.8)	10.2	28.6	36.2	67.0	—
Cases		261	191	132	126	95
Controls		416	417	416	417	415
Flavones (mg)						
Upper cutpoints †	0.5 (0.3)	0.30	0.41	0.52	0.67	—
Cases		214	176	138	142	135
Controls		417	416	416	416	416
Flavonols (mg)						
Upper cutpoints †	22.5 (10.7)	13.9	18.2	23.2	29.9	—
Cases		129	143	150	163	220
Controls		416	417	416	416	416
Total flavonoids (mg)						
Upper cutpoints †	149.2 (85.1)	83.5	117.9	151.8	204.0	—
Cases		161	120	103	150	271
Controls		416	416	417	415	417

*Mean intake and SD among controls.
† For the quintile of intake of the control distribution.

Table 3. ORs* and 95% CIs for 805 oral cavity and pharyngeal cancer cases and 2,081 controls, according to intake quintile of six classes of flavonoids (Italy, 1992-2005)

Flavonoids	Quintile of intake, OR (95% CI)					χ^2 trend (*P* value)	Continuous OR †
	1 ‡	2	3	4	5		
Isoflavones	1	1.05 (0.78-1.42)	1.06 (0.78-1.44)	0.89 (0.65-1.23)	0.90 (0.64-1.26)	0.92 (0.34)	0.96 (0.86-1.07)
Anthocyanidins	1	0.89 (0.63-1.25)	0.70 (0.49-1.01)	0.66 (0.47-0.94)	0.86 (0.60-1.22)	2.32 (0.13)	1.02 (0.93-1.12)
Flavan-3-ols	1	1.06 (0.76-1.48)	0.85 (0.60-1.20)	0.77 (0.54-1.09)	0.84 (0.60-1.18)	2.05 (0.15)	1.01 (0.92-1.10)
Flavanones	1	0.90 (0.68-1.18)	0.70 (0.52-0.94)	0.61 (0.45-0.83)	0.51 (0.37-0.71)	22.03 (<0.001)	0.78 (0.69-0.87)
Flavones	1	1.02 (0.76-1.36)	0.74 (0.54-1.00)	0.95 (0.69-1.29)	0.75 (0.55-1.04)	3.22 (0.073)	0.96 (0.86-1.06)
Flavonols	1	0.92 (0.66-1.28)	0.80 (0.57-1.12)	0.65 (0.46-0.92)	0.62 (0.43-0.89)	9.33 (0.002)	0.80 (0.71-0.91)
Total flavonoids	1	0.77 (0.56-1.06)	0.64 (0.46-0.89)	0.63 (0.45-0.87)	0.56 (0.40-0.78)	11.92 (0.001)	0.92 (0.84-1.01)

*Estimates from logistic regression models, conditioned on sex, age, study center, and adjusted for tobacco smoking, alcohol drinking, education, BMI, and non–alcohol energy intake.
† Estimated for an increment of intake equal to 1 SD.
‡ Reference category.

Table 2 shows the distribution of oral and pharyngeal cancer cases and controls according to intake quintiles of the six classes of flavonoids, and the mean daily intake of the six classes of flavonoids and total flavonoids among controls. The mean daily intake was 24.8 μg for isoflavones, 21.9 mg for anthocyanidins, 65.4 mg for flavan-3-ols, 38.8 mg for flavanones, 0.5 mg for flavones, 22.5 mg for flavonols, and 149.2 mg for total flavonoids. In this population, isoflavones were derived mainly from vegetable or bean soups and pulses, anthocyanidins from wine and red fruits, flavan-3-ols from tea, wine, and fruits, flavanones from citrus fruit, flavones from green leafy vegetables, and flavonols from various fruits, wine, and common vegetables.

The ORs of oral and pharyngeal cancer according to quintile of intake of the six classes of flavonoids are given in Table 3. All the ORs for the highest versus the lowest quintile of intake were below unity. The OR was 0.51 for flavanones, 0.62 for flavonols, and 0.56 for total flavonoids. No significant association emerged for isoflavones, anthocyanidins, flavan-3-ols, and flavones. After allowance for fruit and vegetables, the OR became 0.60 (95% CI, 0.42-0.85) for flavanones, 0.94 (95% CI, 0.62-1.43) for flavonols, and 0.69 (95% CI, 0.49-0.98) for total flavonoids, whereas after allowance for vitamin C, the ORs changed to 1.01 (95% CI, 0.66-1.56), 0.95 (95% CI, 0.65-1.41), and 0.86 (95% CI, 0.60-1.24), respectively. However, models including flavanones, flavonols or total flavonoids, and vitamin C are difficult to interpret, given the high collinearity between these variables (*r* between 0.50 and 0.77). Likewise, the correlation of flavonols with fruit and vegetables was >0.5, again making the results from this model difficult to interpret. No substantial differences emerged in OR estimates when carotenoids and vitamin E were included in the model.

After the exclusion of flavonoids derived from wine, (which consist of 65% of anthocyanidin, 30% of flavan-3-ol, and 12% of flavonol intake), the ORs were not materially modified.

Table 4 shows the continuous ORs for flavanone and flavanol intake in separate strata of sex, age, education, BMI, tobacco smoking, and alcohol drinking. Risk patterns were consistent across the strata of these covariates. However, the inverse association between flavanones and oral and pharyngeal cancer was stronger in less educated subjects, and that of flavonols was stronger among never smokers and ex-smokers than in current smokers (*P* for heterogeneity, <0.05).

Table 4. ORs* and 95% CI for 805 oral cavity and pharyngeal cancer cases and 2,081 controls, according to flavanone and flavonol intake across strata of selected covariates (Italy, 1992-2005)

Covariate	Cases/controls †	OR ‡ (95% CI)	
		Flavanones	Flavonols
Sex			
Male	659/1,302	0.81 (0.72-0.92)	0.85 (0.74-0.97)
Female	146/779	0.65 (0.51-0.83)	0.68 (0.53-0.87)
Age (y)			
<60	434/1,132	0.78 (0.67-0.89)	0.78 (0.67-0.92)
≥60	371/949	0.78 (0.65-0.93)	0.83 (0.70-0.98)
Education (y)			
<7	496/1,152	0.68 (0.58-0.79)§	0.80 (0.69-0.93)
≥7	304/918	0.90 (0.77-1.05)	0.80 (0.68-0.95)
BMI (kg/m²)			
<20	450/8,461	0.83 (0.71-0.97)	0.79 (0.68-0.93)
≥20	347/1,224	0.73 (0.62-0.85)	0.81 (0.70-0.95)
Smoking habits			
Never/ex-smokers	322/1,527	0.74 (0.63-0.87)	0.70 (0.60-0.82)§
Current smokers	482/551	0.81 (0.70-0.95)	0.94 (0.79-1.10)
Alcohol consumption (drinks/d)			
<4	264/1,482	0.75 (0.64-0.89)	0.83 (0.70-0.99)
≥4	537/594	0.80 (0.69-0.92)	0.78 (0.67-0.92)

*Estimates from logistic regression models, conditioned on sex, age, study center, and adjusted for tobacco smoking, alcohol drinking, education, BMI, and non–alcohol energy intake.
† The sum may not add up to the total because of some missing values.
‡ Estimated for an increment of intake equal to 1 SD.
§ $P < 0.05$ at Wald χ^2_1 test for heterogeneity.

Discussion

In this study, certain classes of flavonoids, in particular, flavanones and flavonols, are related to the risk of oral and pharyngeal cancer. However, given the collinearity among food components found in fruit and vegetables, we were unable to separate the independent role of fruit and vegetables, vitamin C, and flavonoids. Our findings are in agreement with those of another case-control study from Uruguay (13), which found an OR below unity for flavonoids, although the estimate was not significant. To our knowledge, no other study investigated this issue.

Among the strengths of the study are the large sample size, the high and variable consumption and diversity of fruits and vegetables in this Mediterranean population (33), the use of a reproducible (22) and valid (23) food-frequency questionnaire, and the proper allowance for non–alcohol energy intake, as well as for other major confounding factors, including tobacco smoking and alcohol drinking (34). In this data set, information on tobacco smoking was satisfactory reproducible (with 94% of overlapping of responses for smoking habits; ref. 35) and that on alcohol drinking was reproducible and valid ($r > 0.75$ in both sexes; ref. 36). After the exclusion of flavonoids derived from wine, the estimated ORs did not show substantial change.

Among the limitations of the present study are the inherent problems related to the food composition data, which, in the case of flavonoids, may not be able to satisfactorily reflect the variability in content attributable to factors such as crop conditions, sunlight, and temperature. Other open questions are the adaptability of U.S. Department of Agriculture flavonoid food composition tables to the Italian diet, and the fact that the dietary questionnaire was not specifically designed to investigate flavonoid intake. Although total flavonoid intake may have been underestimated in our study, these limitations should not have affected the comparisons between cases and controls. Dietary recall of cases can be influenced by recent diagnosis of cancer. However, the information collected refers to the habitual diet at least 2 years before diagnosis or hospital admission. The dietary habits of hospital controls may differ from those of the general population, but only patients admitted to the hospital for acute conditions, not related to major changes in diet and other lifestyle factors, were included. Recall bias in the intake of flavonoids should also be limited, as awareness of a link between vegetable and fruit consumption and oral and pharyngeal cancer risk in Italy is not widely known. Moreover, the same interview setting and catchment areas for cases and controls, and the almost complete participation, are reassuring against any strong selection bias.

Flavonoids have been considered as possible mediators of the favorable effect of vegetables and fruit against cancer (37). In this study, total flavonoid consumption, which is composed mainly of flavan-3-ols (43%), flavanones (26%), anthocyanidins (15%), and flavonols (15%), showed an inverse association with oral and pharyngeal cancer that remained significant after adjustment for fruit and vegetable consumption.

Flavanones have been related to gastric cancer in a Greek case-control study (19) and to esophageal and laryngeal cancer in two Italian studies (14, 21), and the favorable effect persisted after adjustment for vitamin C, which mainly derives from citrus fruits, which are also the main sources of flavanones in these populations. However, in our study, the inverse association of flavanones with oral and pharyngeal cancer became nonsignificant after adjustment for intake of vitamin C. This may reflect, however, the strong collinearity between flavanones and vitamin C in the Italian diet ($r = 0.77$). In contrast, allowance for vitamin E and carotenoids did not materially change the results.

Flavonols, which are derived from various fruit and vegetables, have been inversely associated with the risk of several neoplasms, mainly of the digestive tract, including the stomach and colorectum, in two case-control studies conducted, respectively, in Greece and Italy (12, 18), of the larynx (14) and kidney (38) in Italy, of the breast in Italy and in the U.S. (39, 40), of the lung in two Finnish cohort investigations (11, 16), and of the urinary system, including the prostate, in a Finnish cohort study (16).

No relation was found between isoflavones and oral and pharyngeal cancer. This may be due to the low consumption of the major sources of isoflavones including beans, soy, and soy products in the Italian diet. Similar consideration also hold for flavones, whose intake is derived from the consumption of tea, which is limited in this population.

The inverse relations between flavonoids and oral and pharyngeal cancer were consistent across strata of sex, age, education, BMI, tobacco smoking, and alcohol drinking. However, the inverse association of flavonols was stronger in never/ex-smokers than in current smokers. There is no clear biological explanation for this apparent heterogeneity. Given the many tests done, an effect of chance alone is plausible. Alternatively, the different effects in smokers and nonsmokers can be related to the different effects of various food components or different baseline risks in these two groups.

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