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BRIEF COMMUNICATION

High Intake of Specific Carotenoids and Flavonoids Does Not Reduce the Risk of Bladder Cancer

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Abstract: *An analysis of a previously completed Spanish multicentric case-control study of bladder cancer was carried out using new available data on the contents in foods of specific carotenoids (α-carotene, β-carotene, lutein, and lycopene) and flavonoids (quercetin, kaempferol, myricetin, and luteolin) to investigate the relationship of these phytochemicals with bladder cancer. The study included 497 cases first diagnosed with bladder cancer, 547 neighborhood controls, and 566 hospitals controls, matched by gender, age, area of residence, and hospital. Usual food intake was estimated using a dietary history questionnaire administered by trained interviewers. None of the specific carotenoids and none of the specific flavonoids have been found to be significantly associated with bladder cancer risk in this analysis. The adjusted odds ratios for subjects in the highest quartile of intake with respect to subjects in the lowest quartile were 1.36 (95% confidence interval = 0.94–1.95) for total carotenoid intake and 1.23 (95% confidence interval = 0.85– 1.79) for total flavonoid intake. The result of this study does not support the hypothesis that intake of specific carotenoids and flavonoids is protective against bladder cancer risk.*

The few epidemiological studies that have focused on the role of the diet in bladder cancer risk suggest that high fruit and vegetable intake probably protects against bladder cancer (1). A large number of potentially anticarcinogenic agents are found in these foods, including carotenoids and flavonoids, but knowledge of the specific components that are responsible for their anticarcinogenic effect is still poor, and the evidence of the effect of carotenoids is considered insufficient (1). Until recently, the effect on cancer risk of specific carotenoids and nonnutritive components such as flavonoids, with potentially anticarcinogenic properties, has been difficult to assess because of the lack of food composition tables to estimate their content in foods.

An analysis of a previously completed Spanish multicentric case-control study of bladder cancer (2) was carried out using new available data on the contents in foods of specific carotenoids (β-carotene, α-carotene, lutein, and lycopene) and flavonoids (quercetin, kaempferol, myricetin, and luteolin) to investigate the independent effect of these phytochemicals on bladder cancer risk. The study included 497 cases first diagnosed with bladder cancer during the period 1983–1986, 547 neighborhood controls, and 566 hospital controls, matched by gender, age, area of residence, and hospital. Usual food intake was estimated using a dietary history questionnaire administered by trained interviewers, which has been validated in Spain (3). The average intake of 60 different groups of food and drinks was recorded, including the main sources of carotenoids, retinol, vitamin C, and specific flavonoids, with the exception of onion, one source of quercetin. Data on composition of specific carotenoids in foods were obtained from a Spanish food composition table (4), and composition in specific flavonoids was obtained from the analyses performed in fruits, vegetables, fruit juices, wines, and tea infusions by Hertog and co-workers (5,6). Carotenoids and flavonoids are pigments that have common mechanisms of action, like antioxidant effects, but carotenoids are fat-soluble compounds not detected in urine, whereas flavonoids are water soluble. Although there are no hypotheses concerning a local/topical effect of carotenoids, all that is known implies effects via the blood; the availability of carotenoids and flavonoids in the urinary bladder may be different, then they were analyzed separately.

Intake of specific carotenoids tended to be higher in cases than in controls, whereas flavonoid intake was similar in both groups (Table 1). In a multivariate model adjusted for several potential confounders, no association was found between intake of any of the studied specific carotenoids and flavonoids and the risk of bladder cancer. The adjusted odds ratios for subjects in the highest quartile of intake with re-

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Table 1. Daily Specific Carotenoid and Flavonoid Consumption Among Bladder Cancer Cases and Controls and Odds Ratios and 95% Confidence Intervals

	Cases[a] (n = 495)	Controls[a] (n = 1,112)	Odds Ratios[b,c] Q1	Q2	Q3	Q4	P Value (for trend)
Carotenoids, g/day							
α-Carotene	425.9 ± 701.5	391.6 ± 488.1	1.00	0.82 (0.6–1.2)	1.11 (0.7–1.7)	0.87 (0.5–1.5)	0.80
β-carotene	2,334.5 ± 2,191.2	2,182.3 ± 1,808.4	1.00	1.10 (0.7–1.7)	0.87 (0.5–1.5)	1.62 (0.8–3.2)	0.29
Lycopene	887.2 ± 1,357.6	817.3 ± 1,115.7	1.00	0.88 (0.6–1.3)	0.82 (0.6–1.2)	0.80 (0.5–1.2)	0.28
Lutein	1,524.7 ± 1,911.6	1,442.8 ± 1,827.3	1.00	1.11 (0.8–1.6)	1.34 (0.9–2.0)	0.87 (0.5–1.5)	0.84
Flavonoids, mg/day							
Quercetin	4.8 ± 3.2	4.8 ± 3.3	1.00	1.45 (1.0–2.1)	0.98 (0.7–1.4)	1.21 (0.8–1.9)	0.94
Kaempferol	0.97 ± 1.15	1.03 ± 1.18	1.00	1.21 (0.8–1.8)	1.52 (1.0–2.3)	1.35 (0.9–2.1)	0.11
Myricetin	0.23 ± 0.35	0.21 ± 0.34	1.00	0.97 (0.7–1.4)	0.82 (0.6–1.2)	0.82 (0.6–1.2)	0.20
Luteolin	0.39 ± 1.34	0.38 ± 1.29	1.00	1.37 (0.9–2.0)	1.14 (0.7–1.8)	0.95 (0.6–1.4)	0.40

a: Values are means ± SD; *n*, number of cases or controls.

b: Odds ratios were adjusted for smoking status (never-smokers, former smokers, current smokers), total pack-years smoked, occupational exposure (no/yes), total energy intake (by residual method), vitamin E intake, saturated fatty acid intake, and intake of other specific carotenoids or other specific flavonoids. Values in parentheses are 95% confidence intervals.

c: Quartiles of nutrient intake (Q1, Q2, Q3, and Q4) were based on quartile distribution among control group, with lowest quartile as reference category.

spect to subjects in the lowest quartile were 1.36 (95% confidence interval = 0.94–1.95) for total carotenoid intake and 1.23 (95% confidence interval = 0.85–1.79) for total flavonoid intake.

In the previous analysis of this study, no association was found between bladder cancer risk and consumption of vegetables, fruits, vitamin C, vitamin E, and carotene. None of the specific carotenoids and none of the specific flavonoids have been found to be significantly associated with bladder cancer risk in this analysis. As far as we know, only a prospective study conducted in Finland (7), with a small sample size, analyzed the association between flavonoid intake and bladder cancer and showed no association. The majority of studies have focused on retinol and β-carotene, showing inconsistent results (1). Only a case-control study investigated the effect of other carotenoids; it showed that low plasma levels of lycopene could be associated with bladder cancer risk (8). Selection bias is unlikely to be present in this study, since no differences between hospital and neighborhood controls were observed regarding their dietary consumption (9). Flavonoid composition of foods was estimated using data from analyses performed in Dutch foods because of the absence of Spanish data. This could affect reliability of absolute estimates of intake but not the estimated measures of association. On the other hand, cooking practices do not affect flavonoid composition of foods, since flavonoids are fairly stable (6). The estimated average intake of flavonoids in this study was much lower than the intake of 23 mg/day observed in the Dutch population (6), where tea is the main source (48%) of flavonoid intake. The low consumption of tea in Spain could explain in part the difference in total flavonoid intake between these two populations. In conclusion, this study does not support the hypothesis that intake of specific carotenoids and flavonoids is protective against bladder cancer risk.

Acknowledgments and Notes

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