

## Consumption of Foods Rich in Flavonoids Is Related to a Decreased Cardiovascular Risk in Apparently Healthy French Women<sup>1</sup>

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**ABSTRACT** A high consumption of flavonoids may lower cardiovascular risk through their antioxidant capacity. This study evaluated the relation between consumption of foods rich in flavonoids and estimated cardiovascular risk. A cross-sectional analysis was performed in 1286 women and 1005 men of the SU.VI.MAX Study (an 8-y trial evaluating the effect of antioxidant supplementation on the incidence of major chronic diseases). Dietary intakes were estimated using six 24-h dietary records collected during the year between the clinical measurement of blood pressure, weight and height and the biological measurement of total serum cholesterol and fasting plasma glucose. The relation between flavonoid rich food consumption and cardiovascular risk factors was evaluated with analyses of covariance and the effect on cardiovascular risk with logistic regression analyses. In women, flavonoid-rich food consumption was inversely related to systolic blood pressure ( $P = 0.005$ ). No relation between risk factors and flavonoid-rich food consumption was seen in men. Women in the highest tertile of flavonoid-rich food consumption were at lower risk for cardiovascular disease [odds ratio (OR): 0.31; 95%CI: 0.14, 0.68], whereas a positive tendency was seen in men (OR: 1.38; 95%CI: 0.96, 2.00). These results indicate that in women, a high consumption of flavonoid-rich foods may prevent cardiovascular disease. *J. Nutr.* 134: 923–926, 2004.

**KEY WORDS:** • flavonoids • cardiovascular risk • blood pressure • blood lipids • body mass index

The development of cardiovascular diseases, a major public health problem, has been suggested to be closely related to

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antioxidant status and oxidative stress due to free radicals (1). Dietary intake or biological status of several vitamins and minerals with antioxidant properties has often been found to be associated with the risk of cardiovascular disease, and many prospective studies have shown a possible protective effect of these nutrients (2). Antioxidant properties are also seen in flavonoids, microconstituents that are the most abundant antioxidants in our diet (3). They are also among the most potent plant antioxidants (3), and antioxidant properties of certain flavonoids are 4 times larger than that of vitamin E, for example (4). Many different types of flavonoids can be found in plant foods, with a single plant often containing >1 type of polyphenolic molecule. Flavonoids are part of a group of molecules with similar structure (polyphenols) and are divided in several classes: flavonols, flavanols, flavones, flavanones, anthocyanidins, and isoflavones (5). Several prospective studies observed a lower cardiovascular risk with a high intake of certain flavonoids (6–8). Although some food composition data are available for flavonoids, especially on the USDA website, none are available in France. Because the amount of flavonoids in products of plant origin depends highly on the surroundings, it is difficult to apply such data collected in one country to foods from another. There is therefore currently no accurate information available to estimate the exact total dietary intake of flavonoids in France.

Dietary sources rich in flavonoids include apples, onions, red wine, chocolate, red fruits, citrus fruits, and tea (9–12). To evaluate the hypothesis that flavonoid intake is inversely related to cardiovascular risk, we investigated the relation between consumption of flavonoid-rich foods and cardiovascular risk factors and estimated cardiovascular risk in a large French population.

### SUBJECTS AND METHODS

**Subjects.** Subjects were participants in the SU.VI.MAX study, a randomized, double-blind, placebo-controlled, primary-prevention trial evaluating the effect of daily antioxidant supplementation (vitamin C, vitamin E,  $\beta$ -carotene, selenium, and zinc) at nutritional doses on the incidence of cancer and ischemic heart disease. The cohort consisted of 35- to 60-y-old women (mean  $\pm$  SD, 46.4  $\pm$  6.7 y) and 45- to 60-y-old men (51.1  $\pm$  4.7 y) at baseline in 1994; none of the participants used vitamin supplements other than those under study. Subjects were invited to participate by a multimedia campaign in the whole of France. Potential subjects received detailed information on the study and performed a self-test of acceptability of the daily supplement. In total, 13,077 subjects were included and were followed up for 8 y. Details on recruitment and study design are described elsewhere (13). A clinical examination and a biological examination were alternately done every 2 y. For the present analyses, those subjects, who completed at least six 24-h dietary records in the year between the clinical examination, during which weight, height and blood pressure were measured, and the biological examination, during which blood sampling was performed, and for whom all variables of interest were available, were included (1286 women and 1005 men).

The SU.VI.MAX Study was approved by the ethical committee for studies on human subjects (CCPPRB no. 706) of Paris-Cochin Hospital, and the "Comité National Informatique et Liberté" (CNIL no. 334641), which advocates that all medical information remain confidential and anonymous.

**Dietary assessment.** Subjects kept a 24-h record every 2 mo, for a total of 6 records/y. They kept the record randomly for 2 weekend days and 4 weekdays/y, so that each day of the week was covered in all seasons for the mean intake of all participants. Information was collected using the Minitel Telematic Network. The Minitel is a small terminal widely used in France as an adjunct to the telephone. At the beginning of the study, participants received free of charge a tiny central processing unit specifically developed for the study and loaded with specialized software that allows subjects to fill out the computerized dietary record off-line and to transmit data during brief telephone connections. An instruction manual for codification of foods guided the participants during the completion of the records. The manual contains photographs showing portions in 3 sizes with the possibility of 2 in-between portion sizes and 2 outliers, giving a total of 7 choices available to indicate the consumed portion. Photos of portion sizes were previously validated using 780 subjects in a pilot study (14).

**Measurements.** Weight and height were measured with subjects in underwear, and BMI was calculated by dividing weight by height squared ( $\text{kg}/\text{m}^2$ ). Blood pressure was measured 1 time for each arm using a standard mercury sphygmomanometer in subjects who had been lying down for 10 min. The mean of these 2 measurements was taken for analyses. Information on smoking habits was obtained by means of a questionnaire. Blood samples were obtained in vacutainer tubes (Becton Dickinson) from participants who had been fasting for 12 h. Plasma glucose and serum total cholesterol were measured with a DAX Technicon analyzer using oxidase enzymatic methods (Bayer Diagnostics). Laboratory quality assurance included analysis of serum from standard pools with each run and, if available, international standards. All biochemical measurements were centralized and performed in a single laboratory (Institut inter-Régional pour la Santé, La Riche, France). These measurements were performed in the first 2 y of the study.

**Data analyses.** Intakes of energy, total fat, SFA and fiber were calculated using a computerized food composition table derived from the CIQUAL data base (15).

The consumption of the flavonoid-rich foods, chocolate, apple,

red fruit, citrus fruit, wine, onions, and tea, was calculated by taking the mean intake of the 6 dietary records in y 2 of the study, expressed in g/d. We then calculated the total consumption of each food to investigate a possible global effect. The sum was divided into tertiles.

Cardiovascular risk was estimated according to the risk charts developed by the Second Joint Task Force of European and other Societies on Coronary Prevention (16). Subjects at risk for cardiovascular disease were defined when their estimated risk of having a cardiovascular event in the next 10 y was  $\geq 10\%$ .

Means  $\pm$  SD were calculated for cardiovascular risk factors and flavonoid-rich food intake and compared between women and men using either *t* test or  $\chi^2$  test where appropriate. Differences were considered significant when  $P < 0.05$ . Differences in cardiovascular risk factors were compared between groups with ANOVA. A test for trend was applied for the different categories of consumption. Data on serum-fasting glucose were log-transformed to obtain normal distributions. Logistic regression analyses, adjusted for age, smoking, SFA, fiber, and energy intake, were used to evaluate whether the consumption of flavonoid-rich foods was associated with being at risk for cardiovascular disease. Other nutrients related to cardiovascular disease and the intervention status were not related to the sum of flavonoid-rich food intake, and could therefore not confound the relation examined.

## RESULTS

As expected, cardiovascular risk factors were higher in men than in women (Table 1). There was little difference between genders with respect to intake of flavonoid-rich foods, except for the consumption of wine, which was higher in men and the consumption of tea, which was higher in women. In women, systolic blood pressure declined with a higher intake of flavonoid-rich foods (Table 2). Although there was a tendency for a similar relation between consumption of flavonoid-rich foods and BMI and fasting glucose, these relations were not

TABLE 1

General characteristics of the study population<sup>1</sup>

	Women	Men
<i>n</i>	1286	1005
Age, y	49.5 $\pm$ 6.6	54.5 $\pm$ 4.8*
Past smokers, <i>n</i> (%)	360 (28)	523 (52)*
Current smokers, <i>n</i> (%)	154 (12)	111 (11)
BMI, $\text{kg}/\text{m}^2$	22.8 $\pm$ 3.7	25.1 $\pm$ 2.9*
Systolic blood pressure, mmHg	121 $\pm$ 11	132 $\pm$ 11*
Diastolic blood pressure, mmHg	77 $\pm$ 11	88 $\pm$ 11*
Serum total cholesterol, mmol/L	5.75 $\pm$ 0.93	5.89 $\pm$ 0.93*
Fasting plasma glucose, mmol/L	5.35 $\pm$ 0.55	5.84 $\pm$ 0.93*
Saturated fatty acid, g/d	32.2 $\pm$ 11	41 $\pm$ 12.7
Fiber, g/d	15.8 $\pm$ 5.3	19.5 $\pm$ 6.4
Energy, MJ/d	7.2 $\pm$ 1.8	9.7 $\pm$ 2.1*
Chocolate, g/d	3.4 $\pm$ 6.6	3.7 $\pm$ 7.7
	7.5 $\pm$ 9.5 [487] <sup>2</sup>	6.3 $\pm$ 7.9 [703] <sup>2</sup>
Apple, g/d	54 $\pm$ 64.2	69.2 $\pm$ 85.1
	96.6 $\pm$ 86.4 [720] <sup>2</sup>	73.5 $\pm$ 64.7 [945] <sup>2</sup>
Red fruit, g/d	26 $\pm$ 35.9	28.5 $\pm$ 40.1
	51.3 $\pm$ 41.4 [559] <sup>2</sup>	43.7 $\pm$ 37.4 [766] <sup>2</sup>
Citrus fruit, g/d	62.1 $\pm$ 60.5	58.8 $\pm$ 70.5
	69.2 $\pm$ 71.6 [854] <sup>2</sup>	67.3 $\pm$ 60.2 [1186] <sup>2</sup>
Wine, mL/d	50 $\pm$ 78.5	158.6 $\pm$ 166.3*
	187.1 $\pm$ 165.2 [852] <sup>2</sup>	80.3 $\pm$ 86.4 [800] <sup>2</sup>
Onion, g/d	1.2 $\pm$ 2.7	1.4 $\pm$ 3.1
	4.4 $\pm$ 4.0 [317] <sup>2</sup>	3.68 $\pm$ 3.64 [418] <sup>2</sup>
Tea, mL/d	167.8 $\pm$ 253.3	84.4 $\pm$ 180.4*
	237 $\pm$ 235 [357] <sup>2</sup>	288 $\pm$ 275 [748] <sup>2</sup>
Sum of polyphenol-rich foods, g/d	404 $\pm$ 267	367 $\pm$ 288
	405 $\pm$ 268 [1002] <sup>2</sup>	365 $\pm$ 291 [1282] <sup>2</sup>

<sup>1</sup> Values are mean  $\pm$  SD or *n* (%). \* Different from women,  $P < 0.05$ .

<sup>2</sup> Nonconsumers excluded [*n*].

**TABLE 2**

*BMI, systolic blood pressure, total cholesterol, and fasting glucose according to tertile of flavonoid-rich food consumption in women and men<sup>1</sup>*

	BMI <sup>2</sup>	<i>P</i> for trend	Systolic blood pressure	<i>P</i> for trend	Total cholesterol	<i>P</i> for trend	Fasting glucose	<i>P</i> for trend
	<i>kg/m</i> <sup>2</sup>	<i>mmHg</i>	<i>mmol/L</i>					
Women								
Tertile								
1st	22.9 (22.5, 23.2)		120 (119, 122)		5.74 (5.64, 5.84)		5.34 (5.29, 5.39)	
2nd	22.4 (22.0, 22.9)		119 (117, 120)		5.69 (5.60, 5.79)		5.35 (5.30, 5.41)	
3rd	22.4 (22.0, 22.8)	0.08	118 (116, 119)	0.005	5.74 (5.64, 5.83)	0.95	5.28 (5.23, 5.33)	0.09
Men								
Tertile								
1st	25.0 (24.6, 25.4)		129 (127, 131)		5.83 (5.72, 5.94)		5.77 (5.68, 5.86)	
2nd	25.2 (24.8, 25.6)		129 (127, 131)		5.96 (5.85, 6.06)		5.73 (5.65, 5.82)	
3rd	25.1 (24.7, 25.4)	0.73	129 (127, 130)	0.96	5.89 (5.78, 6.00)	0.19	5.80 (5.71, 5.89)	0.64

<sup>1</sup> Values are means adjusted for age, smoking status, total fat, fiber, and energy intake (95% CI).

significant (*P* = 0.08–0.09). When wine was excluded from the total sum of flavonoid-rich foods because the alcohol in wine may have some adverse effects, fasting glucose, systolic blood pressure, and BMI were lowest in the highest tertile for flavonoid-rich food consumption (data not shown). No association was seen at all in men, irrespective of exclusion or inclusion of wine from the total sum of flavonoid-rich food consumption (Table 2).

Of the participants, 67 women and 586 men were at high risk for cardiovascular disease. Women in the upper tertile of flavonoid-rich food consumption had a lower risk of cardiovascular disease than women in the lowest tertile (Table 3). This decrease in risk was due mainly to the consumption of tea and chocolate, for which the odds ratios (ORs; 95% CI) of the upper tertile vs. the lowest were 0.46 (0.20, 0.98) and 0.39 (0.17, 0.86), respectively. In men, the association between consumption of flavonoid-rich foods and cardiovascular risk tended to be positive (*P* = 0.08; Table 3) and seemed due to wine intake only [OR for highest vs. lowest tertile when wine was excluded: 1.13 (0.77, 1.65)].

**DISCUSSION**

The results of this study showed that the consumption of flavonoid-rich foods such as apples, tea, chocolate, onions,

citrus fruit, and red fruit is inversely associated with cardiovascular risk factors as well as with estimated cardiovascular risk in women. No such relation was seen in men.

The cross-sectional design of this study does not allow conclusions on causality; dietary habits may have changed as a result of the diagnosis of cardiovascular risk. It may well be that the difference between men and women with respect to the effect of flavonoid-rich food consumption on the risk of cardiovascular disease may be explained by this phenomenon. The women who were categorized as being at risk were all in the 10–20% risk category for cardiovascular disease in the next 10 y, whereas 72 of the men were in the 20–40% category. This means that the men at risk had a relatively high risk and were probably aware of that risk; a high blood pressure, a high total cholesterol or serum-triglycerides, or type II diabetes may have been diagnosed and treated, which may have changed their dietary behavior. Because the risk in the women was still relatively low, probably also due to the fact that they were younger, their disease may not yet have been diagnosed, and they did not alter unfavorable dietary habits. The fact that women present with atypical symptoms and are less likely to have adequate primary prevention (17) underlines this hypothesis. Unfortunately, no data in our study are available to evaluate diagnosis of these factors; therefore, this explanation remains hypothetical, although it seems unlikely that women would change their dietary habits for the worse if they also were aware of their higher risk.

Furthermore, dietary data used were collected in the year before blood sampling, but after weight, height, and blood pressure were measured because we presumed it would be reflected in both measurements. When these data were compared with dietary data collected by the same means in the year before clinical examination (before measurement of blood pressure, weight, and height) no difference was observed in the intakes between the 2 y of data collection (data not shown), which justifies the selection of 1 study sample only.

To evaluate flavonoid intake, the sum in grams of flavonoid-rich foods was taken, even though some foods were consumed in small quantities (such as chocolate and onions), whereas others, especially beverages such as tea and red wine, were consumed in larger quantities. The intake of flavonoid-rich foods tended to cluster, i.e., subjects who had a high tea consumption, for example, also had a high fruit and vegetable intake (18). It is clear though that the type of flavonoid differs among foods and it may be that one type has a stronger effect

**TABLE 3**

*Odds ratios (OR) for the effect of flavonoid-rich food consumption according to tertile on cardiovascular risk in men and women<sup>1</sup>*

	Total subjects <i>n</i>	Subjects at risk <i>n</i>	OR	95% CI
Women	1286	67		
Tertile				
1st	428	28	1	
2nd	423	23	0.81	0.40, 1.60
3rd	435	16	0.31	0.14, 0.68
Men	1005	586		
Tertile				
1st	335	184	1	
2nd	328	190	1.04	0.73, 1.47
3rd	342	212	1.38	0.96, 2.00

<sup>1</sup> Adjusted for age, smoking, fiber, SFA, and energy intake.



than another; however, no valid data exist to prove this. Furthermore, when we analyzed each food separately, we observed similar relations between the foods and the cardiovascular risk factors (data not shown). This was especially the case for fasting glucose, which is in line with the findings from an *in vitro* study showing that tea flavonoids may repress hepatic glucose production (19). Supplementation with cocoa for 6 wk, however, did not affect blood glucose in a study including 25 healthy volunteers (20).

Several studies included measurement of total cholesterol when evaluating the possible beneficial effects of tea or tea flavonoids intake (21–26), but only one observed a decrease in total cholesterol after the consumption of 5 servings of tea for 3 wk (21). In addition, studies evaluating the effect of other flavonoid-rich fruit sources such as orange juice or chocolate, did not observe an effect on total cholesterol (20,27). Only supplementation with a flavonoid-rich licorice extract resulted in a decrease in total cholesterol, but that study was performed in hypercholesterolemic patients (28). Our results are in line with the intervention studies that did not show an effect of flavonoids on total cholesterol.

In 2000, Moline et al. (29) proposed that flavonoids may have hypotensive effects, but few studies have evaluated this hypothesis. Duffy et al. (26) did not observe an effect on blood pressure in coronary artery disease patients who drank 900 mL tea/d for 4 wk. However, 12 wk of supplementation with a pine bark extract rich in flavonoids decreased systolic blood pressure in 24 older subjects (30). The effect on blood pressure may depend on the specific flavonoid evaluated. In the latter study, a decrease in BMI was observed, which is in line with the results of our study.

In conclusion, a diet rich in flavonoid-rich foods, except wine, may be useful in the prevention of cardiovascular disease in women. These results must be confirmed in studies using detailed information on precise flavonoid intake when they become available and, in the future, by intervention studies evaluating cardiovascular risk markers.

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