Dietary catechins in relation to coronary heart disease death among postmenopausal women

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Catechins, one of the major groups of flavonoids, are bioactive compounds present in a variety of plant foods and beverages. Experimental data suggest that they might prevent chronic diseases in humans. We studied whether the intake of catechins was inversely associated with the risk of coronary heart disease death in a prospective study of postmenopausal women from Iowa. Between 1986 and 1998, 767 of 34,492 participants initially free of cardiovascular diseases died from coronary heart disease. There was a strong inverse association between the intake of (+)-catechin and (−)-epicatechin and coronary heart disease death, which was somewhat attenuated after multivariate adjustment (risk ratios from lowest to highest quintile: 1.00, 0.95, 0.97, 0.77, 0.76). This inverse association was most pronounced in women at low risk of coronary heart disease (non-smokers, free of diabetes mellitus and cardiovascular diseases). A high intake of "gallates," catechins typical of tea, was not associated with coronary heart disease death. Of the major catechin sources, apples and wine were inversely associated with coronary heart disease death. Our data suggest that preventive effects might be limited to certain types of catechins, or that these are indicators of other dietary components or a healthy lifestyle in general. (EPIDEMIOLOGY 2001;12: 668–675)

Keywords: antioxidants, catechins, cohort studies, coronary heart disease, diet, flavonoid, postmenopausal women, tea.

Catechins are bioactive flavonoids present in a variety of plant foods and beverages. *In vitro* and animal experiments suggest they might help to prevent chronic diseases.[1] Catechins may reduce low density lipoprotein (LDL) oxidation by quenching free radicals, chelating metals, or recycling other antioxidants.[2–5] Catechins also have been shown to interfere with the inflammatory process[6] and to reduce thrombosis.[7,8] Recently, we reported a strong inverse association between the intake of catechins and risk of coronary heart disease (CHD) mortality.[9] Epidemiologic studies on tea, a major catechin source, and cardiovascular disease risk have provided inconsistent results.[10–13] We wanted to test the hypothesis that catechin intake is inversely associated with the risk of CHD death, independent of the catechin source.

Levels of oxidative stress are known to be elevated in pathological states such as diabetes mellitus. In the human body, enzymic antioxidant defense systems are operative; dietary antioxidants may be necessary mostly to supplement these systems in subjects with elevated levels of oxidative stress.[14] Epidemiologic studies have suggested that the protective effects of flavonoids may be limited to subjects who are at high CHD risk.[10,15] Our secondary objective was therefore to assess whether a high intake of catechins was more strongly associated with CHD death in subjects who smoked at baseline or had prevalent diabetes mellitus or cardiovascular diseases, compared with apparently healthy, low risk, subjects.

Subjects and Methods

STUDY POPULATION

In January 1986, a 16-page survey was sent to a random sample of 99,826 women, 55–69 years of age, who had a valid Iowa driver's license. 41,836 women who returned the questionnaire were enrolled in this prospective cohort study. We excluded women from the analyses if they were not postmenopausal at baseline (N = 569), if they left ≥30 items blank on the food frequency questionnaire (N = 2782), or if they had improbably high (≥5,000 Kcal) or low (<600

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Kcal) energy intakes (N = 538). Also, women who reported having cardiovascular diseases at baseline, defined as having been told by a doctor that they had suffered a heart attack or had angina or other heart disease (N = 4115), were excluded from all analyses, except for analyses concerning women at high risk. This exclusion left 34,492 women for analysis; owing to missing co-variates this number was reduced to 32,857 in the multivariate analysis. We considered women to be at high risk of death from CHD if they reported at baseline that they had been told by a doctor they had diabetes mellitus (yes or unsure) or were taking hypoglycemic medication (N = 1991); had suffered a heart attack or had angina or other heart disease (N = 3713); or were smoking at the time of the baseline examination (N = 5177). Numbers excluded are not mutually exclusive.

Data Collection

The baseline questionnaire included a 127-item semi-quantitative food frequency questionnaire.[16] Although this questionnaire was not validated for its ability to assess catechin intake, Feskanich and co-authors[17] assessed the ability of the questionnaire to determine the intake of foods compared with a 28-day diet record among male health professionals. Correlation coefficients for the main sources of catechins were: 0.77 for tea, 0.70 for apples, 0.45–0.83 for chocolate containing foods, and 0.83 for red and 0.78 for white wine. Moreover, no important dietary sources of catechins were omitted. We weighted catechin contents of questionnaire items that referred to more than one food, eg "fresh apples or pears," using US food disappearance data for the year 1986.[18] We used data on catechin contents of Dutch foods and beverages,[19,20] supplemented with analyses of US tea, apples, chocolate, beans, and lentils from the same laboratory in the Netherlands. Catechin contents of US foods were similar to comparable Dutch foods, except for US apples, which tended to have higher catechin levels than those from the Netherlands.

Case Ascertainment

The women were followed annually through the State Health Registry of Iowa, which collects information on deaths in Iowa. Deaths were also reported in response to follow-up questionnaires mailed in 1987, 1989, 1992, and 1997. For non-responders not found in the Health Registry, the occurrence and causes of death were obtained from the National Death Index. Coding of the underlying cause of death followed the ninth Revision of the International Classification of Diseases.[21] Underlying ICD-codes 410–414 and 429.2 were taken as CHD.

Data Analysis

We defined total catechin as the sum of six major catechins: (+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate. We created two subgroups of catechins, the first one reflecting catechins derived mainly or solely from tea (the sum of (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate), further referred to as "gallates," and the second one reflecting catechins derived mainly from sources other than tea (the sum of (+)-catechin and (−)-epicatechin). We calculated the intake of catechins, "gallates" and the sum of (+)-catechin and (−)-epicatechin for each woman and stratified by quintiles of intake. We adjusted all baseline means of dietary characteristics for total energy intake using linear regression.

We combined foods that contained catechins to form six groups: tea, apples and pears, chocolate, wine, legumes, and fruits other than apples or pears. We combined items by converting each individual's response to an item into milligrams of catechins per day, and taking the sum of these values. Values for all groups except tea were based on more than one food frequency questionnaire item. Apples combined the items "fresh apples or pears" and "applesauce"; chocolate combined "chocolate," "candy bars," "cookies," "brownies," and "cake"; wine combined "red wine" and "white wine"; legumes combined "beans or lentils" and "fava beans"; and other fruits combined "raisins or grapes," "peaches, apricots or plums," "strawberries," "blueberries," "other fruit juices," and several fruits that were not included on the printed questionnaire, but were reported in an "other foods" category as eaten at least once a week.

We calculated the follow-up time for each participant from completion of the baseline questionnaire until the day of death or December 31, 1998, whichever came first. We estimated risk ratios (RRs) of death from CHD by Cox proportional hazards analysis, using the SAS procedure PHREG (SAS, release 6.12, SAS Institute, North Carolina, USA). We adjusted the initial analyses for age and total energy intake only. We adjusted the multivariate models also for marital status, educational attainment, self-reported high blood pressure, self-reported diabetes mellitus, body mass index, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy, use of vitamin supplements, alcohol intake, and intake of whole grains, saturated fatty acids, polyunsaturated fatty acids, cholesterol, dietary vitamin C, vitamin E, folate, and carotene.

Results

The average intake of catechins in this population of 34,492 postmenopausal women was 25.4 mg/day (standard deviation: 32.0). The intake ranged from 0 (24 participants) to 278 mg/day. As shown in Table 1, catechin intake was associated with a healthy lifestyle.

After 13 years of follow-up (422,648 person-years) 767 participants had died from CHD. Table 2 shows age and energy-adjusted RRs of CHD death by quintiles of intake of catechins, of (+)-catechin plus (−)-epicatechin, and of "gallates." Total catechin intake tended to be inversely associated with CHD mortality, although after the second quintile the RRs did not decrease much further. There was a strong inverse association between

TABLE 1. Baseline Characteristics by Quintiles of Catechin Intake for 34,492, Cardiovascular Disease-Free, Postmenopausal Women, 1986, Iowa Women's Health Study

	Catechin Intake Quintile				
	1	2	3	4	5
Flavonoid intake					
Total catechins (mg/d)*	3.6 (1.6)†	8.8 (1.3)	14.9 (2.2)	24.8 (5.2)	74.8 (42.3)
(+)-catechin	1.4 (0.7)	2.5 (0.9)	3.6 (1.2)	4.5 (2.2)	6.1 (3.1)
(−)-epicatechin	1.9 (0.9)	5.1 (1.7)	8.9 (3.0)	11.2 (4.2)	18.1 (10.0)
(+)-gallocatechin	0.0 (0.1)	0.1 (0.1)	0.2 (0.2)	0.6 (0.5)	3.5 (2.6)
(−)-epigallocatechin	0.0 (0.1)	0.1 (0.2)	0.2 (0.3)	1.0 (0.8)	5.5 (4.1)
(−)-epicatechin gallate	0.2 (0.4)	0.6 (0.7)	1.1 (1.5)	4.3 (3.5)	23.9 (17.9)
(−)-epigallocatechin gallate	0.1 (0.3)	0.4 (0.5)	0.8 (1.1)	3.2 (2.6)	17.7 (13.3)
Flavonols + flavones (mg/d)	5.3 (3.4)	7.8 (4.2)	10.7 (4.6)	14.5 (6.5)	31.3 (15.5)
Demographics					
Age (y)	61.3 (4.2)	61.5 (4.2)	61.4 (4.1)	61.7 (4.2)	61.6 (4.2)
Education (% > high school)	34.0	38.7	41.5	42.8	43.2
Anthropometry					
Body mass index (kg/m^2)	26.8 (5.1)	27.0 (5.1)	27.0 (5.0)	26.9 (5.0)	26.9 (5.1)
Waist-to-hip ratio	0.843 (0.092)	0.836 (0.084)	0.833 (0.085)	0.834 (0.083)	0.836 (0.084)
Self-reported illness					
Diabetes mellitus (%)	5.7	5.5	5.8	5.4	6.5
Hypertension (%)	34.8	34.8	34.1	34.2	34.2
Cardiovascular diseases (%)‡	10.4	10.0	9.3	9.5	9.4
Lifestyle behaviors					
Current smoker (%)	25.1	16.7	12.1	10.4	11.8
Pack-years of smoking	14.2 (20.8)	9.7 (17.7)	7.8 (16.0)	7.0 (15.4)	8.0 (16.6)
Vitamin supplement use (%)	29.8	32.7	34.1	34.9	32.9
Alcohol (% never drinkers)	52.5	53.9	54.5	53.4	57.1
Physical activity (% engaging in moderate to high activity)	42.6	50.6	56.3	58.7	55.0
Hormone replacement therapy (% ever)	37.7	37.8	38.5	38.2	38.5
Diet§					
Energy intake (kcal/d)	1,526 (492.4)	1,715 (541.5)	1,845 (584.6)	1,973 (638.5)	1,946 (649.2)
Alcohol intake (g/d)	5.9	4.0	3.3	2.9	3.2
Saturated fat intake (g/d)	25.6	24.6	23.8	23.2	23.4
Polyunsaturated fat intake (g/d)	12.1	12.1	12.1	12.0	12.0
Cholesterol intake (mg/d)	286	276	273	267	268
Whole grain intake (servings/wk)	10.0	11.0	11.7	12.1	11.8
Dietary vitamin C intake (mg/d)	133	149	161	167	163
Dietary vitamin E intake (mg/d)	7.6	8.1	8.5	8.7	8.6
Dietary folate intake (μg/d)	286	301	314	322	336
Dietary carotenoid intake (IU/d)	7,419	8,610	9,482	10,085	9,831

* Sum of: (+)-catechin, (−)-epicatechin, (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate.
† Values are means (standard deviation) or percentages where indicated.
‡ Includes women with self-reported cardiovascular diseases at baseline, N = 38,205.
§ All diet means, except energy intake, were adjusted for total energy intake.

TABLE 2. Risk Ratios of Coronary Heart Disease (CHD) Death by Quintiles of Catechin Intake for 34,492, Cardiovascular Disease-Free, Postmenopausal Women

	Catechin Intake Quintile				
	1	2	3	4	5
Total catechins					
Median intake (range) mg/day	3.7 (0, 6.3)	8.7 (6.3, 11.2)	14.8 (11.2, 18.5)	23.5 (18.5, 36.8)	52.7 (36.8, 277.7)
CHD deaths	186	143	148	140	150
Person-years	83,563	84,599	84,885	84,975	84,626
CHD death rate/1000 person-years	2.23	1.69	1.74	1.65	1.77
RR (95% CI)*	1.00	0.73 (0.58, 0.90)	0.74 (0.60, 0.92)	0.66 (0.53, 0.83)	0.73 (0.59, 0.91)
RR (95% CI) multivariate†	1.00	0.80 (0.63, 1.00)	0.86 (0.69, 1.09)	0.83 (0.66, 1.06)	0.85 (0.67, 1.07)
Sum of (+)-catechin and (−)-epicatechin‡					
Median intake (range) mg/day	3.2 (0, 4.8)	7.0 (4.8, 8.8)	10.4 (8.8, 12.8)	15.9 (12.8, 18.6)	23.1 (18.6, 124.8)
CHD deaths	184	162	147	130	144
Person-years	83,691	84,518	84,734	84,881	84,823
CHD death rate/1000 person-years	2.20	1.92	1.74	1.53	1.70
RR (95% CI)	1.00	0.86 (0.69, 1.07)	0.76 (0.60, 0.96)	0.64 (0.50, 0.82)	0.65 (0.50, 0.85)
RR (95% CI) multivariate	1.00	0.95 (0.76, 1.20)	0.97 (0.76, 1.24)	0.77 (0.60, 1.00)	0.76 (0.58, 1.03)
"Gallates"‡§					
Median intake (range) mg/day	0.0 (0, 0.02)	0.05 (0.03, 0.2)	2.1 (0.2, 3.7)	12.5 (4.2, 22.9)	29.2 (22.9, 176.5)
CHD deaths	174	155	134	148	156
Person-years	76,119	93,027	81,502	88,512	83,487
CHD death rate/1000 person-years	2.29	1.67	1.64	1.67	1.87
RR (95% CI)	1.00	0.72 (0.58, 0.90)	0.71 (0.57, 0.90)	0.75 (0.59, 0.94)	0.93 (0.73, 1.20)
RR (95% CI) multivariate	1.00	0.78 (0.62, 0.98)	0.78 (0.62, 0.99)	0.85 (0.67, 1.09)	1.00 (0.77, 1.29)

* RR, risk ratio; CI, confidence interval; adjusted for age and total energy intake (N = 34,492).
† Adjusted for age, total energy intake, marital status, educational attainment, high blood pressure, diabetes mellitus, body mass index, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy, use of vitamin supplements, alcohol intake, intake of whole grains, intake of saturated fatty acids, intake of polyunsaturated fatty acids, intake of cholesterol, and intake of dietary vitamin C, vitamin E, folate, and carotene (N = 32,857).
‡ Risk ratios also adjusted for other catechins listed in table.
§ Sum of (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate.

the intake of (+)-catechin plus (−)-epicatechin and CHD death, whereas "gallate" intake was not associated with CHD death. Adjusting for lifestyle and dietary potential confounders attenuated the observed associations, but for (+)-catechin plus (−)-epicatechin an inverse trend remained (RRs from lowest to highest quintile of intake: 1.00, 0.95, 0.97, 0.77, 0.76). The latter is graphically depicted in Figure 1, using cubic spline regression modeling.

The major sources of catechins were tea (59% of total catechin intake), apples and pears (26%), chocolate (6%), and fruits other than apples or pears (5%). The total intake of catechins among women drinking tea was 36.9 mg/day compared with 10.0 mg/day for women not drinking tea (Table 3). Tea drinkers obtained on average 55% of their catechin intake from tea; their intake of catechins from sources other than tea was only slightly higher than that of women not drinking tea (Table 3). The intake of (−)-epigallocatechin gallate and (−)-epigallocatechin was zero in non-tea drinkers because the occurrence of these catechins is limited to tea. Tea drinking was associated with a healthful lifestyle and a diet that was relatively high in vitamins and whole grains, and low in saturated fat and alcohol (Table 3).

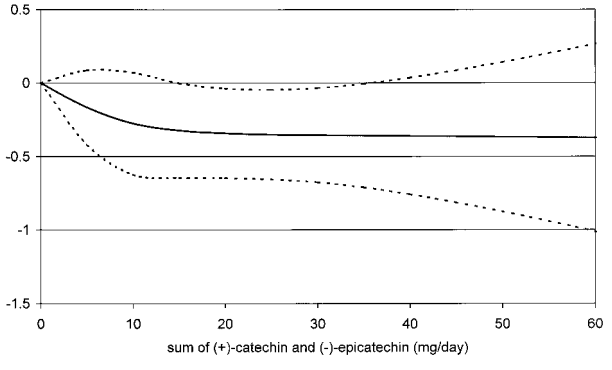

FIGURE 1. Mulivariate adjusted cubic spline regression model (knots at 2.2, 5.8, 17.3, and 30.1), depicting the association (solid line) and 95% confidence interval (dotted line) beween the intake of (+)-catechin plus (−)-epicatechin and coronary heart disease mortality for 32,857 cardiovascular disease-free, postmenopausal women, 1986–1998. Iowa Women's Health Study

In Table 4 RRs of CHD death are presented for tertiles of catechins from various sources, adjusted for the other sources listed in the table. In the age and energy-adjusted model, catechins from apples, chocolate and wine were, independent of each other, inversely associated with CHD death. After multivariate adjustment, only apples (RRs from lowest to highest tertile of intake: 1.00, 0.95, and 0.78), and wine (RRs from lowest to highest tertile of intake: 1.00, 0.73, and 0.77) remained inversely associated with CHD death. Similar results were obtained when we entered the numbers of servings of the foods themselves into the models, rather than the levels of catechins (data not shown).

Table 5 shows RRs of CHD death for women at high risk and for women at low risk by quintiles of intake of (+)-catechin plus (−)-epicatechin (top panel), and "gallates" (bottom panel). Contrary to our hypothesis, we observed an inverse trend between the intake of (+)-catechin and (−)-epicatechin and CHD death in

TABLE 3. Baseline Characteristics by Tea Drinking Status for 34,492, Cardiovascular Disease-Free, Postmenopausal Women

	Non-Drinkers of Tea (N = 14,768)	Tea Drinkers (N = 19,724)
Flavonoid intake		
Total catechins (mg/d)*	10.0 (8.5)†	36.9 (37.8)
(+)-catechin	3.0 (2.3)	4.1 (2.5)
(−)-epicatechin	6.9 (6.6)	10.7 (7.8)
(+)-gallocatechin	0.01 (0.02)	1.5 (2.1)
(−)-epigallocatechin	0 (0)	2.4 (3.3)
(−)-epicatechin gallate	0.04 (0.1)	10.5 (14.6)
(−)-epigallocatechin gallate	0 (0)	7.8 (10.9)
Catechins from tea (mg/d)	0 (0)	26.3 (36.8)
Catechins not from tea (mg/d)	10.0 (8.5)	10.7 (8.0)
Flavonols + flavones (mg/d)	8.3 (6.5)	18.1 (13.8)
Demographics		
Age (y)	61.5 (4.2)	61.6 (4.2)
Education (% > high school)	36.1	43.0
Anthropometry		
Body mass index (kg/m^2)	26.8 (5.1)	27.0 (5.0)
Waist-to-hip ratio	0.837 (0.088)	0.836 (0.083)
Self-reported illness		
Diabetes mellitus (%)	5.8	5.8
Hypertension (%)	34.3	34.5
Cardiovascular diseases (%)‡	10.1	9.4
Lifestyle behaviors		
Current smoker (%)	18.3	12.9
Pack-years of smoking	11.0 (19.0)	8.1 (16.4)
Vitamin supplement use (%)	32.4	33.2
Alcohol (% never drinkers)	55.5	53.3
Physical activity (% engaging in moderate to high activity)	50.5	54.2
Hormone replacement therapy (% ever)	36.7	39.2
Diet§		
Energy intake (kcal/d)	1,736 (604.3)	1,850 (604.4)
Alcohol intake (g/d)	4.3	3.5
Saturated fat intake (g/d)	24.4	23.9
Polyunsaturated fat intake (g/d)	12.0	12.1
Cholesterol intake (mg/d)	275	274
Whole grain intake (servings/wk)	11.0	11.6
Dietary vitamin C intake (mg/d)	150	158
Dietary vitamin E intake (mg/d)	8.2	8.4
Dietary folate intake (μg/d)	300	321
Dietary carotenoid intake (IU/d)	8,650	9,411

* Sum of: (+)-catechin, (−)-epicatechin, (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate.
† Values are means (standard deviation) or percentages where indicated.
‡ Includes women with self-reported cardiovascular diseases at baseline, N = 38,205.
§ All diet means, except energy intake, were adjusted for total energy intake.

the women at low risk only. The association showed an inconsistent dose response. Among the women at high risk, (+)-catechin and (−)-epicatechin intake was not clearly associated with CHD death. "Gallate" intake was not associated with the risk of CHD death in the low risk group, nor in the high risk group.

Discussion

In this population-based prospective study of postmenopausal women who where reportedly free of cardiovascular diseases at baseline, the intake of (+)-catechin and (−)-epicatechin was inversely associated with CHD mortality, whereas the intake of "gallates," catechins characteristic of tea, was not. Consequently, we observed no more than an inverse trend between the total intake of catechins and CHD mortality. Adjustment for lifestyle and dietary potential confounders attenuated the observed associations, but the inverse trend with (+)-catechin plus (−)-epicatechin remained. These data do not support the reported strong inverse association between total catechin intake and CHD mortality among elderly men in the Netherlands.[9,22] In the Dutch study, 87% of the catechins were derived from tea, and both tea and catechins not from tea were independently associated with a reduced risk of CHD death. The average intake of catechins in the Iowa women was 25.4 mg/day (range: 0–278 mg/day), compared with 72 mg/day (range: 0–355.4 mg/day) in the Dutch men. The lower catechin intake in our study may partially explain the lack of an association; however, the range of intake among the women is wide, the intake in the highest quintile is comparable to the level at which an effect was observed in the Dutch study, and the women's intake of (+)-catechin and (−)-epicatechin was similar to the Dutch men's intake of non-tea catechins.

Potential explanations for the distinct associations of (+)-catechin and (−)-epicatechin versus "gallates" with CHD mortality include differences in bioavailability, metabolism, or bioactivity. Studies reporting on pharmacokinetic parameters of catechins were reviewed recently.[23] Plasma levels of (−)-epigallocatechin gallate and (−)-epicatechin are generally comparable. *In vitro* antioxidant activities of the different catechins do not suggest that "gallates" have lower bioactivity,[5] but the relevance of these tests to the *in vivo* situation remains to be established.

Tea is not only the major source of "gallates," but it is also a good source of (−)-epicatechin: tea-drinkers obtained on average 29% (standard deviation: 25.5) of their (−)-epicatechin from tea. The correlation between the sum of (+)-catechin and (−)-epicatechin and the "gallates" was 0.53. If (+)-catechin and (−)-epicatechin were the only bioactive catechins, then tea would still be expected to be inversely associated with CHD mortality because of its high (−)-epicatechin content. The data from Table 4 show that this is not the case: catechins from tea were not associated with CHD mortality in the present study. Several studies support our findings: three American cohort studies reported that consumption of approximately 1 cup of tea daily compared with no tea

TABLE 4. Risk Ratios of Coronary Heart Disease (CHD) Death According to Intake of Catechins from Selected Foods for 34,492, Cardiovascular Disease-Free, Postmenopausal Women

Catechin Source	Catechin Intake Category 1	2	3
Tea			
Median catechin intake (range) mg/day	0	2.5 (2.5, 5.0)	34.6 (14.9, 207.9)
CHD deaths	351	177	239
Person-years	180,264	111,563	130,821
CHD death rate/1000 person-years	1.95	1.59	1.83
RR (95% CI)*	1.00	0.86 (0.71, 1.03)	0.94 (0.80, 1.12)
RR (95% CI) multivariate†	1.00	0.89 (0.73, 1.08)	0.99 (0.83, 1.18)
Apples and pears			
Median catechin intake (range) mg/day	1.1 (0, 1.7)	6.6 (2.2, 6.6)	15.5 (6.7, 93.2)
CHD deaths	228	374	165
Person-years	104,464	212,400	105,785
CHD death rate/1000 person-years	2.18	1.76	1.56
RR (95% CI)	1.00	0.82 (0.70, 0.98)	0.67 (0.54, 0.83)
RR (95% CI) multivariate	1.00	0.95 (0.79, 1.14)	0.78 (0.62, 0.98)
Chocolate			
Median catechin intake (range) mg/day	0.2 (0, 0.5)	0.9 (0.6, 1.2)	2.3 (1.3, 49.7)
CHD deaths	301	238	228
Person-years	140,414	141,385	140,849
CHD death rate/1000 person-years	2.14	1.68	1.62
RR (95% CI)	1.00	0.76 (0.64, 0.90)	0.68 (0.56, 0.81)
RR (95% CI) multivariate	1.00	0.94 (0.78, 1.13)	0.88 (0.71, 1.08)
Wine			
Median catechin intake (range) mg/day	0	0.2 (0.04, 0.5)	0.7 (0.6, 36.5)
CHD deaths	606	79	82
Person-years	293,169	61,964	67,515
CHD death rate/1000 person-years	2.07	1.28	1.22
RR (95% CI)	1.00	0.65 (0.51, 0.82)	0.63 (0.50, 0.79)
RR (95% CI) multivariate	1.00	0.73 (0.57, 0.94)	0.77 (0.59, 0.98)
Legumes			
Median catechin intake (range) mg/day	0	0.2	0.4 (0.4, 16.7)
CHD deaths	290	328	149
Person-years	162,482	172,388	87,778
CHD death rate/1000 person-years	1.79	1.90	1.70
RR (95% CI)	1.00	1.11 (0.94, 1.30)	0.95 (0.77, 1.16)
RR (95% CI) multivariate	1.00	1.14 (0.97, 1.35)	0.97 (0.78, 1.21)
Other fruits			
Median catechin intake (range) mg/day	0.4 (0, 0.5)	0.8 (0.6, 1.1)	2.0 (1.2, 39.2)
CHD deaths	258	237	272
Person-years	133,910	150,405	138,334
CHD death rate/1000 person-years	1.93	1.58	1.97
RR (95% CI)	1.00	0.86 (0.72, 1.04)	0.98 (0.82, 1.18)
RR (95% CI) multivariate	1.00	0.92 (0.76, 1.11)	1.07 (0.88, 1.31)

* RR, risk ratio; CI, confidence interval; adjusted for other foods listed in table, age, and total energy intake (N = 34,492).
† Adjusted for other foods listed in table, age, total energy intake, marital status, educational attainment, high blood pressure, diabetes mellitus, body mass index, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy, use of vitamin supplements, alcohol intake, intake of whole grains, intake of saturated fatty acids, intake of polyunsaturated fatty acids, intake of cholesterol, and intake of dietary vitamin C, vitamin E, folate, and carotene (N = 32,857).

was not associated with myocardial infarction incidence,[24] myocardial infarction death,[25] or CHD death.[15] Two studies from the United Kingdom reported that tea consumption was not associated with CHD,[13] or that CHD mortality actually increased with increasing tea consumption.[26] Tea consumption in these studies was high: at least 5 cups daily in the highest consumption category. Contrary to this, two Dutch,[10,11] and one American study[12] reported strong inverse associations between tea consumption and coronary disease, and one study from Norway[27] showed that the consumption of 1 cup of tea daily was inversely associated with CHD mortality. A possible explanation offered previously for the observed discrepancies between studies was inadequate adjustment for confounders. Whereas tea consumption is generally associated with a healthful lifestyle, the opposite is the case in the two studies from United Kingdom, the only studies where there was a suggestion of an increased risk with high tea consumption. In our study, tea consumption was associated with a healthy lifestyle, but not with CHD mortality. Another potential explanation for the lack of an association of a high tea consumption with CHD mortality could be that women with subclinical disease had changed their lifestyle and dietary habits. Nevertheless, exclusion of the deaths that occurred during the first two years of follow-up did not modify the reported results.

Two of the five other sources of catechins, apples and wine, were inversely associated with CHD death. A high intake of apples has been associated with a reduced risk of cardiovascular diseases in two European studies,[11,28] but not in one American study.[15] The strong inverse association with apple consumption in our study raises the question whether (+)-catechin and (−)-epicatechin are merely indicators of a diet high in fruits and vegetables. Adjustment for folate, vitamin C, vitamin E,

TABLE 5. Risk Ratios of Coronary Heart Disease (CHD) Death among High and Low Risk Groups by Quintiles of Catechin Intake for 38,205 Postmenopausal Women, Including Women with Prevalent Cardiovascular Disease at Baseline

	Quintile of Intake				
	1	2	3	4	5
Sum of (+)-catechin and (−)-epicatechin					
Low risk group*					
CHD deaths	79	85	93	61	96
Person-years	58,749	66,392	72,564	71,638	72,373
CHD death rate/1000 person-years	1.35	1.28	1.28	0.85	1.33
RR (95% CI)†	1.00	0.87 (0.64, 1.20)	0.83 (0.60, 1.14)	0.54 (0.37, 0.77)	0.74 (0.52, 1.07)
RR (95% CI) multivariate‡	1.00	0.90 (0.65, 1.25)	0.88 (0.63, 1.23)	0.54 (0.37, 0.80)	0.76 (0.52, 1.12)
High risk group*					
CHD deaths	196	149	109	129	110
Person-years	33,014	26,252	20,773	21,749	21,060
CHD death rate/1000 person-years	5.94	5.68	5.25	5.93	5.22
RR (95% CI)	1.00	0.95 (0.77, 1.19)	0.88 (0.69, 1.13)	0.94 (0.74, 1.20)	0.83 (0.62, 1.10)
RR (95% CI) multivariate	1.00	0.94 (0.74, 1.18)	0.96 (0.73, 1.24)	1.00 (0.77, 1.29)	0.85 (0.63, 1.15)
"Gallates"§					
Low risk group					
CHD deaths	70	74	85	93	92
Person-years	55,888	75,542	66,722	72,299	71,265
CHD death rate/1000 person-years	1.25	0.98	1.27	1.29	1.29
RR (95% CI)	1.00	0.74 (0.53, 1.03)	0.96 (0.69, 1.33)	0.98 (0.71, 1.36)	1.07 (0.75, 1.53)
RR (95% CI) multivariate	1.00	0.71 (0.50, 1.01)	0.99 (0.70, 1.38)	1.03 (0.74, 1.44)	1.10 (0.76, 1.59)
High risk group					
CHD deaths	174	161	107	115	136
Person-years	28,112	27,166	22,544	22,372	22,655
CHD death rate/1000 person-years	6.19	5.93	4.75	5.14	6.00
RR (95% CI)	1.00	0.96 (0.77, 1.19)	0.77 (0.60, 0.99)	0.86 (0.67, 1.10)	1.03 (1.79, 1.34)
RR (95% CI) multivariate	1.00	0.96 (0.77, 1.21)	0.78 (0.60, 1.01)	0.87 (0.67, 1.12)	1.05 (0.80, 1.37)

* Low risk: free of baseline cardiovascular diseases and diabetes mellitus, and not smoking at baseline (N = 27,573). High risk: prevalent cardiovascular diseases or diabetes mellitus at baseline, current smokers (N = 10,632).
† RR, risk ratio; CI, confidence interval; adjusted for other catechins listed, age, and total energy intake.
‡ Adjusted for other catechins listed, age, total energy intake, marital status, educational attainment, high blood pressure, body mass index, waist-to-hip ratio, physical activity, pack-years of smoking, use of estrogen replacement therapy, use of vitamin supplements, alcohol intake, intake of whole grains, intake of saturated fatty acids, intake of polyunsaturated fatty acids, intake of cholesterol, and intake of dietary vitamin C, vitamin E, folate, and carotene.
§ Sum of (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate.

and carotenoids did not essentially alter the observed associations, nor did additional adjustment for total fruit and vegetable intake (data not shown). Apples are a good source of flavonols as well, and flavonol intake has previously been shown to be inversely associated with CHD death in this study[29] and in other studies.[11,28] We were unable to adjust for flavonol intake because of the high correlation between catechins and flavonols in our study (0.87), which was partly attributable to the fact that the intake of onions, a major source of flavonols in the US,[15] was not ascertained. There is an ongoing debate whether the often observed inverse association between wine consumption and cardiovascular diseases is stronger than could be explained solely by its alcohol content.[30–33] In our study, the inverse association of CHD with wine consumption remained after adjustment for alcohol intake. Wine intake, however, was generally low, and it is questionable whether the relatively small contribution of wine to the total catechin intake would have any physiological significance.

There is evidence suggesting that dietary antioxidants may be particularly beneficial in subjects with an otherwise less healthful lifestyle.[14] Epidemiologic studies that appear to support this hypothesis include the study by Rimm and coworkers[15] who reported that a suggestion of an inverse trend between flavonols and CHD death was limited to men with prevalent cardiovascular diseases, and the study by Geleijnse and coworkers[10] that showed that tea drinking was inversely associated with severe aortic atherosclerosis only. In our study, however, tea catechins were unrelated to CHD death among both high and low risk subjects, whereas the intake of (+)-catechin and (−)-epicatechin was inversely associated with CHD death in low risk subjects only. The CHD death rate was more than four times greater in our high than low risk group, which validates our definition of high risk. The high risk group was composed of women with very diverse profiles: smokers, diabetics, and women with prevalent cardiovascular diseases. Analyses by each of these groups individually gave similar but less clear results owing to smaller numbers (data not shown).

Several limitations of our study should be pointed out. Misclassification of dietary exposure could have occurred at both the dietary assessment level, and in the assignment of catechin levels to the foods reported. The ability of the questionnaire to determine intakes of various foods[17] and nutrients[34] was validated previously and found to be satisfactory. Moreover, of all the catechin containing foods, tea was estimated most accurately.[17] Data on the catechin contents of foods were primarily limited to analyses conducted in the Netherlands,[19,20] but catechin levels determined in foods purchased in Minnesota were within the same range. Catechin contents, however, are known to vary greatly by variety,[19,23] thus individual preferences for particular varieties of foods would lead to misclassification. Also, the catechin

content of tea infusions depends, among other things, on the brewing time.[20] The generally used standard time of five minutes may be too long for US habits, and we therefore may have overestimated the catechin content of US tea. These limitations all most likely would have attenuated true effects, but there is no reason to assume they attenuated more severely the relation between CHD death and tea intake than that with other catechin containing foods.

Thus, the results from this study suggest that possible preventive effects of catechins might be limited to certain types of catechins, that is, (+)-catechin and (−)-epicatechin, or that these are indicators for a healthy lifestyle in general or for certain components of the diet that are as yet unknown or unavailable for epidemiologic evaluation.

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