Polyphenols and disease risk in epidemiologic studies[1–4]

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ABSTRACT

Plant polyphenols, a large group of natural antioxidants, are serious candidates in explanations of the protective effects of vegetables and fruits against cancer and cardiovascular diseases. Epidemiologic studies are useful for evaluation of the human health effects of long-term exposure to physiologic concentrations of polyphenols, but reliable data on polyphenol contents of foods are still scarce. The aim of this review is to summarize available epidemiologic data on the health effects of polyphenols, focusing on the flavonoid subclasses of flavonols, flavones, and catechins and on lignans. Data obtained to date suggest beneficial effects of both flavonoids and lignans on cardiovascular diseases but not on cancer, with the possible exception of lung cancer. There is a need for more research on stroke and lung diseases such as asthma and chronic obstructive pulmonary disease. Most studies to date have included only flavonols and flavones. With data becoming available for other polyphenols, these compounds should be included in future studies. Careful design of prospective studies is important to offset some of the major drawbacks of epidemiologic studies, including residual confounding (by smoking and other dietary factors) and exposure assessment. *Am J Clin Nutr* 2005;81(suppl):317S–25S.

KEY WORDS Review, epidemiology, polyphenols, flavonoids, flavonols, catechins, lignans, antioxidants, phytoestrogens, cancer, cardiovascular diseases, stroke

INTRODUCTION

Epidemiologic studies suggest a protective effect of vegetables and fruits against cancer and cardiovascular diseases (CVDs) (1, 2). Various hypotheses have been suggested to explain these beneficial effects of increased consumption of vegetables and fruits. An attractive hypothesis is that vegetables and fruits contain compounds that have protective effects, independent of those of known nutrients and micronutrients. Plant polyphenols, a large group of natural antioxidants ubiquitous in a diet high in vegetables and fruits, certainly are serious candidates. All plant phenols are derived from the common intermediate phenylalanine, or its close precursor shikimic acid, through the shikimic acid pathway in plants. They can be divided into at least 10 different classes on the basis of their general chemical structures, with the common characteristic being at least one aromatic ring structure with one or more hydroxyl groups. A large variety of plant (poly)phenols exist, including cinnamic acids, benzoic acids, flavonoids including proanthocyanidins, stilbenes, coumarins, lignans, and lignins. Within each family of plant phenols, many compounds may be present. For example, > 6000 different flavonoids occurring in plants have been described.

In addition to their antioxidant properties, polyphenols show several interesting effects in animal models and in vitro systems; they trap and scavenge free radicals, regulate nitric oxide, decrease leukocyte immobilization, induce apoptosis, inhibit cell proliferation and angiogenesis, and exhibit phytoestrogenic activity (3–6). These effects may contribute to their potentially protective role in cancer and CVDs. The question remains of whether these data are relevant for human disease outcomes, where exposure to polyphenols is chronic and at relatively low concentrations, depending on bioavailability and metabolism. An important phenomenon is that, after absorption, polyphenols are subject to phase II metabolism, yielding methoxylated, glucuronidated, and sulfated compounds (7). This may greatly influence their bioactivity, but only a few studies have examined this to date. In addition, bacteria present in the human colon metabolize polyphenols. The major polyphenol metabolites are a variety of phenolic acids such as homovanillic acid (8). As a consequence, body tissues are exposed to high concentrations of these phenolic acids.

Although no information on causality can be obtained, epidemiologic studies are useful for evaluation of the human health effects of long-term exposure to physiologic concentrations of polyphenols. Reliable data on polyphenol contents of foods are needed for studies of the potential role of dietary polyphenols in cancer and CVD prevention. Comprehensive data are available only for the flavonoid subclasses of flavonols, flavones, and catechins, but data on other polyphenols, such as lignans, are forthcoming. In this article, we provide an overview of epidemiologic studies on the health effects of flavonols, flavones, catechins, and lignans conducted to date.

FLAVONOIDS

Studies

Of the 6 major classes of flavonoids, comprehensive data on their contents in foods are available only for the flavonols (quercetin,

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TABLE 1
Prospective studies of flavonoid intake and risk of CVDs[1]

Reference	Country	Population	Flavonoid[2]	Comparison (high vs low intake)[3]	Follow-up time	Outcome[4]	No. of cases	Adjusted RR (high vs low)[5]	*P* for trend
				mg/d	*y*				
CAD									
Sesso et al, 2003 (15)	US	38 484 F	Flavonols, flavones	47.4 vs 8.9	6.9	Total CVD	519	0.80 (0.59, 1.09)	0.80
Geleijnse et al, 2002 (16)	Netherlands	4807 MF	Flavonols	40.0 vs 16.8	5.6	Nonfatal MI	116	0.93 (0.57, 1.52)	—
						MI	30	0.35 (0.13, 0.98)	—
Knekt et al, 2002 (13)	Finland	9131 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	28	CAD	681	0.93 (0.74, 1.17)	0.30
Arts et al, 2001 (17)	US	32 857 F	Catechins	74.8 vs 3.6	13	CAD	767	0.85 (0.67, 1.07)	—
Arts et al, 2001 (18)	Netherlands	806 M	Catechins	124.0 vs 25.3	10	CAD	90	0.49 (0.27, 0.88)	0.02
Hirvonen et al, 2001 (19)	Finland	25 372 M	Flavonols, flavones	17.8 vs 3.9	6.1	Nonfatal MI	1122	0.77 (0.64, 0.93)	—
						CAD	815	0.89 (0.71, 1.11)	—
Yochum et al, 1999 (20)	US	34 492 F	Flavonols, flavones	28.6 vs 4.0	10	CAD	438	0.62 (0.44, 0.87)	0.11
Hertog et al, 1997 (21)	Netherlands	804 M	Flavonols, flavones	41.6 vs 12.0	10	CAD	90	0.47 (0.27, 0.82)	0.01
Hertog et al, 1997 (14)	UK	1900 M	Flavonols, flavones	42.8 vs 13.5	14	CAD	131	1.60 (0.90, 2.90)	0.12
Knekt et al, 1996 (22)	Finland	2745 M	Flavonols, flavones	>4.8 vs <2.1	26	CAD	324	0.67 (0.44, 1.00)	0.12
		2380 F	Flavonols, flavones	> 5.5 vs < 2.4	26	CAD	149	0.73 (0.41, 1.32)	0.73
Rimm et al, 1996 (23)	US	34 789 M	Flavonols, flavones	40.0 vs 7.1	6	Nonfatal MI	486	1.08 (0.81, 1.43)	—
		38 036 M	Flavonols, flavones	40.0 vs 7.1	6	CAD	140	0.77 (0.45, 1.35)	—
Hertog et al, 1993 (24)	Netherlands	805 M	Flavonols, flavones	41.6 vs 12.0	5	CAD	43	0.32 (0.15, 0.71)	0.003
Stroke									
Knekt et al, 2002 (13)	Finland	9131 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	28	Incident stroke	806	0.79 (0.64, 0.98)	0.01
Arts et al, 2001 (18)	Netherlands	806 M	Catechins	124.0 vs 25.3	10	Incident stroke	88	0.92 (0.51, 1.68)	0.75
Hirvonen et al, 2000 (25)	Finland	26 497 M	Flavonols, flavones	16.4 vs 4.2	6.1	Incident stroke	736	0.98 (0.80, 1.21)	0.81
Yochum et al, 1999 (20)	US	34 492 F	Flavonols, flavones	28.6 vs 4.0	10	Stroke	131	1.18 (0.70, 2.00)	0.83
Keli et al, 1996 (26)	Netherlands	552 M	Flavonols, flavones	33.3 vs 14.2	15	Incident stroke	42	0.27 (0.11, 0.70)	0.004

[1] MI, myocardial infarction; —, no data provided.
[2] Flavonols: quercetin, kaempferol, myricetin; flavones: apigenin, luteolin; flavanones: hesperetin, naringenin, eriodictyol; catechins: (+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate, (−)-epigallocatechin gallate.
[3] Mean, median, or category cutoff value.
[4] Death, unless indicated otherwise.
[5] 95% CI in parentheses.
[6] Quartiles were constructed for men and women separately, but RR is provided for sexes combined only.

kaempferol, and myricetin), flavones (apigenin and luteolin), and catechins [(+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-epigallocatechin gallate]. The flavonoid data used in most epidemiologic studies were based on analyses conducted in the Netherlands (9–12) but were supplemented in some studies with data for additional food items. Recently, data became available for flavanones in Finnish foods (hesperetin, naringenin, and eriodictyol) (13). Except for one study from the United Kingdom (14), all epidemiologic studies of flavonoids are from the Netherlands, Finland, or the United States.

CVDs

To date, 12 cohort studies on flavonoid intake and the risk of coronary artery disease (CAD) and 5 cohort studies on the risk of stroke have been published (**Table 1**). Seven of these prospective studies found protective effects of flavonols and flavones or of catechins with respect to fatal or nonfatal CAD, and reductions of mortality risk were up to 65%. These studies were as follows: the Zutphen Elderly Study, with a small cohort of 805 men in the Netherlands after 5 and 10 y of follow-up monitoring (21, 24), the Finnish Mobile Clinic Health Examination Survey (significant among men only) (22), the Iowa Women's Health Study, a cohort study of 34 500 women in the United States (20), the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study among 25 000 male smokers (19), the Dutch Zutphen Elderly Study for catechins (18), and the Rotterdam Study in the Netherlands, a cohort study of 4800 men and women (16). In a large cohort study of 35 000 male US health professionals, a suggestion of a reduction in coronary mortality rates with high flavonol intake was found only among men with a previous history of CAD [relative risk (RR): 0.63; 95% CI: 0.33, 1.20] (23). In contrast, a trend for increased CAD mortality rates (*P* for trend = 0.12) was found in the Caerphilly Study, a cohort study of 1900 Welsh men (14). It was suggested that the English habit of adding milk to tea (the major source of flavonols for this cohort) could inhibit the absorption of flavonols, thus explaining the lack of protection of tea flavonols against CAD. Proteins bind phenols efficiently and therefore might inhibit absorption from the gastrointestinal tract when consumed together with flavonoids. However, it was shown that the absorption of flavonols was not impaired with the addition of milk (27). Residual confounding by lifestyle factors

might have affected evaluation of the results of this study among Welsh men.

Two of 5 studies of flavonoid intake and stroke risk found an inverse association, ie, the Zutphen Elderly Study and the Finnish Mobile Clinic Health Examination Survey (Table 1). In the Zutphen Elderly Study, a protective effect was observed for flavonols and flavones (26) but not for catechins (18).

Cancer

Associations between the intake of flavonoids and the incidences of a variety of cancers have been studied in 7 prospective cohort studies (**Table 2**) and 4 case-control studies. Significant associations were observed only for lung cancer and colorectal cancer. Two Finnish studies with relatively low intakes of flavonols and flavones, ie, the Finnish Mobile Clinic Health Examination Survey (30) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (32), found inverse associations with lung cancer risk (RR: 0.53; 95% CI: 0.29, 0.97; and RR: 0.56; 95% CI: 0.45, 0.69, respectively). In contrast, a borderline positive association was found for colorectal cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (RR: 1.70; 95% CI: 1.00, 2.70; P for trend = 0.10). For catechins, an inverse association was reported for rectal cancer (RR: 0.55; 95% CI: 0.32, 0.95; P for trend = 0.02), but not for colon cancer, among postmenopausal women in the United States. No evidence for an effect of flavonoid intake was found for the incidence of any epithelial cancer or cancer of the stomach, urinary tract, prostate, or breast. None of the case-control studies of prostate (34), lung (35), testicular (36), and ovarian (37) cancer found significant associations.

Other chronic diseases

Because of their antioxidant and antiinflammatory properties, flavonoids may also beneficially influence other chronic diseases involving oxidative stress or inflammation, such as rheumatoid arthritis and chronic obstructive pulmonary disease (COPD). Knekt et al (13) studied the associations between the intake of flavonols, flavones, and flavanones and the incidences of rheumatoid arthritis, type 2 diabetes mellitus, cataracts, and asthma among a cohort of ~10 000 male and female participants in the Finnish Mobile Clinic Health Examination Survey (Table 2). A significant inverse association was observed only for asthma (RR: 0.65; 95% CI: 0.47, 0.90; P for trend = 0.04). This finding supported an earlier cross-sectional study, in which intake of flavonoids was beneficially associated with pulmonary function and symptoms of COPD. Pulmonary function (measured as forced expiratory volume in 1 s) was better among subjects in the highest quintile, compared with the lowest quintile, of intake of flavonols, flavones, and catechins (44 mL; 95% CI: 18, 69 mL). Catechin intake alone was most strongly associated with the forced expiratory volume in 1 s (130 mL; 95% CI: 101, 159 mL) and with all 3 symptoms of COPD [cough odds ratio (OR): 0.72; 95% CI: 0.58, 0.90; phlegm OR: 0.60; 95% CI: 0.47, 0.75; breathlessness OR: 0.69; 95% CI: 0.52, 0.90] (38).

LIGNANS

Studies

Plant lignans can be converted by human intestinal bacteria into the so-called enterolignans, ie, enterolactone and enterodiol. Enterolignans are found in biological fluids of humans and animals (6, 39). It was shown, that in addition to the well-known enterolignan precursors secoisolariciresinol and matairesinol, several other plant lignans were converted into enterolactone and enterodiol, although with varying degrees of efficiency (40). The health effects of lignans were evaluated in epidemiologic studies that used both the intake of secoisolariciresinol and matairesinol and plasma or urinary concentrations of enterolactone and enterodiol as exposure estimates. The calculated intake of secoisolariciresinol and matairesinol was based on published food composition tables (41–43), of which that provided by De Kleijn et al (41) is the most comprehensive. Of 8 published studies on enterolignan concentrations and the risk of CVD or cancer, only 2 measured enterodiol in addition to enterolactone. Enterolactone is usually measured with a time-resolved fluoroimmunoassay, which is not available for enterodiol (44).

CVDs

Two publications (45, 46) from one Finnish cohort study in which plasma enterolactone concentrations were studied in relation to CVD risk reported significant inverse associations (**Table 3**). In the Finnish Kuopio Heart Disease Risk Factor Study, a 65% lower risk of incident CAD was observed (46). With 2 additional years of follow-up monitoring, the risk of CAD death was of the same order of magnitude (RR: 0.44) and similar, although results were only borderline significant for total CVD deaths (RR: 0.55) (45). The association between serum enterolactone concentrations and plasma F_2-isoprostane concentrations (a biomarker of in vivo lipid peroxidation) was studied cross-sectionally in a subset of 100 male participants in the Antioxidant Supplementation in Atherosclerosis Prevention Study (47). With higher enterolactone concentrations, F_2-isoprostane concentrations were significantly lower ($P = 0.02$).

No studies on lignan intake and CVD risk have been published to date, but 2 cross-sectional studies related lignan intake to CVD risk factors. Of several risk factors studied among postmenopausal US women, only the waist-hip ratio (difference between extreme quartiles: −0.017; 95% CI: −0.030, −0.002; P for trend = 0.03) and the metabolic syndrome score, a summary score of several risk factors (difference between extreme quartiles: −0.55; 95% CI: −0.82, −0.28; P for trend = 0.0001), were associated with intake of secoisolariciresinol and matairesinol (48). Aortic stiffness, assessed with pulse-wave velocity measurements of the aorta, was borderline significantly inversely associated with lignan intake among postmenopausal Dutch women (49). The regression coefficient for those with a high intake of lignans was −0.41 (95% CI: −0.93, 0.11; P for trend = 0.06), compared with those with a low intake. The protective effect was most pronounced and significant among women with a postmenopausal time of > 20 y.

Cancer

To date, 3 prospective, nested, case-control studies and 3 case-control studies have studied plasma or urinary lignan concentrations and cancer risk (**Table 4**); all except one investigated breast cancer incidence. The 2 prospective, nested, case-control studies on breast cancer risk, among Dutch postmenopausal women (54) and among female participants in 3 cohorts in northern Sweden (53), found no relationship with plasma or urinary enterolactone concentrations. In contrast, all 3 case-control studies found an

TABLE 2
Prospective studies of flavonoid intake and risk of incident cancer and other chronic diseases[1]

Ref	Country	Population	Flavonoid[2]	Comparison (high vs low intake)[3]	Follow-up time[4]	Outcome	No. of cases	Adjusted RR (high vs low)[5]	*P* for trend
Cancer				*mg/d*	*y*				
Total									
Knekt et al, 2002 (13)	Finland	9865 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	30	Any cancer	1093	0.89 (0.74, 1.06)	0.33
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13	Any cancer	5038	0.97 (0.88, 1.06)	0.65
Arts et al, 2001 (29)	Netherlands	728 M	Catechins	123.7 vs 25.2	10	Epithelial cancer	96	0.94 (0.56, 1.59)	0.82
Knekt et al, 1997 (30)	Finland	9959 MF	Flavonols, flavones	M > 4.8 vs < 2.1,[6] F > 5.5 vs < 2.4	24	Any cancer	997	0.87 (0.70, 1.09)	—
Hertog et al, 1994 (31)	Netherlands	738 M	Flavonols, flavones	> 29.9 vs < 19	5	Any cancer	75	1.21 (0.66, 2.21)	0.54
						Alimentary and respiratory tract	57	1.02 (0.51, 2.04)	0.96
Lung									
Knekt et al, 2002 (13)	Finland	5218 M	Flavonols, flavones, flavanones	> 26.9 vs < 4.3	30		169	0.64 (0.39, 1.04)	0.02
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13		549	0.94 (0.72, 1.23)	0.94
Arts et al, 2001 (29)	Netherlands	728 M	Catechins	123.7 vs 25.2	10		42	0.92 (0.41, 2.07)	0.80
Hirvonen et al, 2001 (32)	Finland	27 110 M	Flavonols, flavones	16.3 vs 4.2	6.1		791	0.56 (0.45, 0.69)	0.0001
Goldbohm et al, 1998 (33)	Netherlands	3799 MF	Flavonols, luteolin	43.5 vs 12.7	4.3 (case-cohort)		676	0.99 (0.69, 1.42)	0.68
Knekt et al, 1997 (30)	Finland	9959 MF	Flavonols, flavones	M > 4.8 vs < 2.1,[6] F > 5.5 vs < 2.4	24		151	0.53 (0.29, 0.97)	—
Stomach									
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13	Upper digestive tract	176	0.71 (0.46, 1.11)	0.31
Knekt et al, 2002 (13)	Finland	9865 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	30		74	0.87 (0.44, 1.75)	0.73
Hirvonen et al, 2001 (32)	Finland	27 110 M	Flavonols, flavones	16.3 vs 4.2	6.1		111	1.20 (0.71, 1.90)	0.51
Goldbohm et al, 1998 (33)	Netherlands	3306 MF	Flavonols, luteolin	43.5 vs 12.7	4.3 (case-cohort)		183	0.86 (0.47, 1.57)	0.54
Knekt et al, 1997 (30)	Finland	9959 MF	Flavonols, flavones	M > 4.8 vs < 2.1,[6] F > 5.5 vs < 2.4	24		64	1.15 (0.48, 2.78)	—
Colorectum									
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13	Colon	635	1.10 (0.85, 1.44)	0.63
						Rectum	132	0.55 (0.32, 0.95)	0.02
Knekt et al, 2002 (13)	Finland	9865 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	30		90	0.84 (0.43, 1.64)	0.95
Hirvonen et al, 2001 (32)	Finland	27 110 M	Flavonols, flavones	16.3 vs 4.2	6.1		133	1.70 (1.00, 2.70)	0.10
Goldbohm et al, 1998 (33)	Netherlands	3726 MF	Flavonols, luteolin	43.5 vs 12.7	4.3 (case-cohort)		603	0.97 (0.71, 1.32)	0.95
Knekt et al, 1997 (30)	Finland	9959 MF	Flavonols, flavones	M > 4.8 vs < 2.1,[6] F > 5.5 vs < 2.4	24		72	0.74 (0.32, 1.68)	—
Urinary tract									
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13	Kidney	114	0.73 (0.40, 1.32)	0.12
						bladder	103	1.12 (0.65, 1.93)	0.93
Knekt et al, 2002 (13)	Finland	9865 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	30		81	0.69 (0.34, 1.41)	0.57
Hirvonen et al, 2001 (32)	Finland	27 110 M	Flavonols, flavones	16.3 vs 4.2	6.1	Urothelial renal cell	156	1.20 (0.73, 1.80)	0.77
							92	0.63 (0.36, 1.10)	0.10
Knekt et al, 1997 (30)	Finland	9959 MF	Flavonols, flavones	M > 4.8 vs < 2.1,[6] F > 5.5 vs < 2.4	24		54	0.84 (0.29, 2.45)	—
Prostate									
Knekt et al, 2002 (13)	Finland	5218 M	Flavonols, flavones, flavanones	> 26.9 vs < 4.3	30		95	1.11 (0.61, 2.01)	0.57
Hirvonen et al, 2001 (32)	Finland	27 110 M	Flavonols, flavones	16.3 vs 4.2	6.1		226	1.30 (0.87, 1.80)	0.24
Knekt et al, 1997 (30)	Finland	5260 M	Flavonols, flavones	> 4.8 vs < 2.1	24		62	1.39 (0.56, 3.46)	—
Breast									
Arts et al, 2002 (28)	US	34 651 F	Catechins	75.1 vs 3.6	13		1069	1.04 (0.84, 1.28)	1.00
Knekt et al, 2002 (13)	Finland	4647 F	Flavonols, flavones, flavanones	> 39.5 vs < 8.5	30		125	1.23 (0.72, 2.10)	0.53
Goldbohm et al, 1998 (33)	Netherlands	2203 F	Flavonols, luteolin	44.6 vs 13.5	4.3 (case-cohort)		605	1.02 (0.72, 1.44)	0.74
Knekt et al, 1997 (30)	Finland	4699 F	Flavonols, flavones	> 5.5 vs < 2.4	24		87	0.72 (0.36, 1.48)	—

Continues

TABLE 2
Continued

Ref	Country	Population	Flavonoid[2]	Comparison (high vs low intake)[3]	Follow-up time[4]	Outcome	No. of cases	Adjusted RR (high vs low)[5]	*P* for trend
Other									
Rheumatoid arthritis									
Knekt et al, 2002 (13)	Finland	9283 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3[6] F > 39.5 vs < 8.5	28		90	1.18 (0.62, 2.26)	0.83
Type 2 diabetes mellitus									
Knekt et al, 2002 (13)	Finland	9878 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	28		526	0.98 (0.77, 1.24)	0.75
Cataracts									
Knekt et al, 2002 (13)	Finland	10 022 MF	Flavonols, flavones, flavanones	M > 26.9 vs < 4.3,[6] F > 39.5 vs < 8.5	28		132	1.36 (0.84, 2.21)	0.28
Asthma									
Knekt et al, 2002 (13)	Finland	10 039 MF	Flavonols, flavones, flavanones	M >26.9 vs <4.3,[6] F >39.5 vs <8.5	28		382	0.65 (0.47, 0.90)	0.04

[1] —, no data provided.
[2] Flavonols: quercetin, kaempferol, myricetin; flavones: apigenin, luteolin; flavanones: hesperetin, naringenin, eriodictyol; catechins: (+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin gallate, (−)-epigallocatechin gallate.
[3] Mean, median, or category cutoff value.
[4] Design in parentheses if other than prospective cohort.
[5] 95% CI in parentheses.
[6] Quartiles were constructed for men and women separately, but RR is provided for sexes combined only.

inverse association between lignan concentrations and breast cancer risk (52, 55, 56). When a subset of postmenopausal women only was included in the analysis of the Shanghai Breast Cancer Study, the inverse association was no longer significant and the RR increased from 0.40 (95% CI: 0.24, 0.64) to 0.50 (95% CI: 0.23, 1.10) (51). In all of these case-control studies, plasma or urine was collected after diagnosis and sometimes even after initiation of treatment of the disease, which might have influenced lignan concentrations through changes in the diet as a result of disease or through other mechanisms. The only study on prostate cancer risk conducted to date found no association with plasma enterolactone concentrations among a large cohort of male residents of Finland, Norway, and Sweden (50).

Intake of the lignans secoisolariciresinol and matairesinol was studied in relation to the risk of several cancers in 1 prospective cohort and 3 case-control studies, all from the United Stated (Table 4). A significant inverse association was observed for breast cancer among premenopausal women (RR: 0.49) but not postmenopausal women (RR: 0.72) in western New York State (58). In contrast, breast cancer risk was borderline significantly elevated with a high intake of secoisolariciresinol and matairesinol among a large group of women participating in the multiethnic Bay Area Breast Cancer Study (RR: 1.3) (59) and of secoisolariciresinol only in the prospective California Teachers Study (RR: 1.4) (57). In the latter study, the association was substantially attenuated to a RR of 1.2 (95% CI: 0.9, 1.6) after adjustment for wine consumption. This led the authors to conclude that the increased risk with secoisolariciresinol was attributable to confounding by alcohol consumption.

Significant or borderline significant protective associations were also reported for endometrial cancer (60), ovarian cancer (37), and thyroid cancer (61) among female participants. No associations between lignan intake and incident prostate (34) or testicular (36) cancer were found.

TABLE 3
Prospective studies of serum lignans and risk of CVDs[1]

Reference	Country	Population	Lignan	Comparison (high vs low plasma concentration)	Follow-up time[2]	Outcome[3]	No. of cases	Adjusted RR (high vs low)[4]	*P* for trend
				nmol/L	*y*				
Vanharanta et al, 2003 (45)	Finland	1889 M	ENL	> 23.9 vs < 6.9	12.2	CVD	103	0.55 (0.29, 1.01)	0.04
						CAD	70	0.44(0.20, 0.96)	0.03
Vanharanta et al, 1999 (46)	Finland	2005 M	ENL	> 30.1 vs < 7.2	10 (nested case-control)	Incident CAD	167	0.35 (0.14, 0.88)	0.01

[1] ENL, enterolactone.
[2] Design in parentheses if other than prospective cohort.
[3] Death, unless indicated otherwise.
[4] 95% CI interval in parentheses.

TABLE 4
Prospective and case-control studies on plasma or urinary lignan concentrations or dietary lignan intake and incident cancer[1]

Ref	Country	Population	Lignan	Comparison (high vs low)[2]	Design[3]	No. of cases	Adjusted RR (high vs low)[4]	*P* for trend
Plasma or urinary levels								
Prostate								
Stattin et al, 2002 (50)	Scandinavia	3344 M	ENL	> 15.6 vs < 4.3	Nested case-control (3–24 y)	794	1.08 (0.83, 1.39)	—
Breast								
Dai et al, 2003 (51)	China	234 F	ENL, END	— (urine)	Case-control	117	0.50 (0.23, 1.10)	0.09
Dai et al, 2002 (52)	China	500 F	ENL, END	— (urine)	Case-control	250	0.40 (0.24, 0.64)	<0.01
Hulten et al, 2002 (53)	Sweden	740 F	ENL	39.8 vs 5.3	Nested case-control (5–15 y)	248	1.1 (0.7, 1.7)	—
den Tonkelaar et al, 2001 (54)	Netherlands	356 F	ENL	969.9 vs 235.6 (urine, μmol/mol creatinine)	Nested case-control (9 y)	88	1.43 (0.79, 2.59)	0.25
Pietinen et al, 2001 (55)	Finland	402 F	ENL	>34.8 vs <6.2	Case-control	194	0.38 (0.18, 0.77)	0.03
Ingram et al, 1997 (56)	Australia	288 F	ENL	>5250 vs <1450 (urine, nmol/24 h)	Case-control	144	0.36 (0.15, 0.86)	0.01
			END	> 480 vs <170 (urine, nmol/24 h)	Case-control	144	0.73 (0.33, 1.64)	0.29
Dietary intake								
Prostate								
Strom et al, 1999 (34)	US	190 M	SECO	>0.48 vs <0.48	Case-control	83	1.20 (0.65, 2.21)	0.55
			MAT	>0.05 vs <0.05	Case-control	83	0.89 (0.47, 1.66)	0.71
Breast								
Horn-Ross et al, 2002 (57)	US	111 526 F	SECO	>0.12 vs <0.05	Cohort (2 y)	711	1.40 (1.00, 1.80)	0.02
			MAT	>0.03 vs <0.01	Cohort (2 y)	711	1.10 (0.80, 1.40	0.2
McCann et al, 2002 (58)	US	617 F premenopausal	ENL, END[5]	>0.67 vs <0.46	Case-control	301	0.49 (0.32, 0.75)	—
		933 F postmenopausal	ENL, END[5]	>0.67 vs <0.46	Case-control	439	0.72 (0.51, 1.02)	—
Horn-Ross et al, 2001 (59)	US	2983 F	SECO, MAT	>0.22 vs <0.10	Case-control	1272	1.30 (1.00, 1.60)	—
Endometrial								
Horn-Ross et al, 2003 (60)	US	942 F	SECO, MAT	>0.24 vs <0.12	Case-control	482	0.68 (0.44, 1.10)	0.03
Ovarian								
McCann et al, 2003 (37)	US	820 F	SECO, MAT	>0.71 vs <0.30	Case-control	124	0.43 (0.21, 0.85)	<0.05
Thyroid								
Horn-Ross et al, 2002 (61)	US	1134 F	SECO, MAT	>0.16 vs <0.06	Case-control	590	0.68 (0.43, 1.10)	0.07
Testicular								
Walcott et al, 2002 (36)	US	295 M	SECO, MAT	>1.42 vs <0.28 μg/1000 kcal	Case-control	159	0.96 (0.11, 8.09)	0.27

[1] ENL, enterolactone; END, enterodiol; SECO, secoisolariciresinol; MAT, matairesinol; —, no data provided.
[2] Mean, median, or category cutoff value; plasma values in nmol/L, urine values as indicated, intake levels in mg/d.
[3] Follow-up time in parentheses.
[4] 95% CI in parentheses.
[5] ENL and END production from foods determined by in vitro fermentation with human fecal microflora.

DISCUSSION

In the past decade, several well-designed, prospective, cohort studies in which the health effects of flavonoids were studied have been published. The data regarding CVD suggest protective effects of high intakes of flavonols and flavones and possibly of catechins. However, only a few studies are available for catechins and for stroke; given the results obtained to date, these deserve more study. A meta-analysis of tea consumption in relation to CAD and stroke, including all studies published up to October 2000, was conducted by Peters et al (62). Most studies included in the current review were also included in that meta-analysis, because they provided data not only for tea, which is a major flavonoid source, but also for flavonoids. Peters et al (62) found evidence for publication bias, particularly with respect to stroke, and therefore urged caution in interpreting the results for this endpoint. Publication bias might have occurred for flavonoid epidemiologic studies as well. Another striking finding is that studies of CAD or myocardial infarction conducted in continental Europe reported strong inverse associations, whereas studies conducted elsewhere did not. Summarized RRs for drinking 3 cups per day compared with no tea were 1.62 (95% CI: 1.15, 2.30) for 2 studies from the United Kingdom, 0.27 (95% CI: 0.16, 0.44) for 3 studies from continental Europe, and 0.95 (95% CI: 0.84, 1.08) for 8 studies from the United States. Explanations for this phenomenon, which also seems to occur for flavonoids, include differing associations with a healthy lifestyle and publication bias. However, no satisfactory explanation has been provided, and research into these differences seems worthwhile.

Attempts to distinguish the effects of flavonols and flavones from those of catechins were undertaken with data from the Zutphen Elderly Study (18, 29) and demonstrate one of the major limitations of component-based epidemiologic studies. Each food contains a large number of different compounds, some known and quantified, some less well characterized, and some unknown or unmeasurable. Many compounds tend to be present in the same foods or families of foods. The intake of catechins, for example, was positively correlated with the intake of fruits and vegetables and their constituents, eg, vitamin C, vitamin E, carotenoids, folate, and fiber. For the intake of vitamin C, β-carotene, and fiber, correlations in several European populations on the order of 0.40-0.70 were reported (63). When the correlation is too high, it is impossible to ascertain independent effects of dietary components, because of multicollinearity. This was the case for flavonols and catechins in the Zutphen Elderly Study. Tea

supplied 87% of this population's intake of catechins and 61% of the intake of flavonols and flavones (24). To circumvent multicollinearity problems but still distinguish the effects of catechins from those of flavonols, subgroups were defined, ie, tea, catechins from sources other than tea, and flavonols from sources other than tea. Independent effects on CAD mortality rates were borderline significant for tea ($P = 0.06$) and catechins from other sources than tea ($P = 0.11$). For correct interpretation of results of dietary component-based epidemiologic studies, adjustment for other dietary factors (both nutrient and nonnutrient) is of major importance.

Data are less convincing for cancer. Of several cancers studied, protective effects have been reported only for lung cancer in relation to flavonol and flavone intake. Together with data from one cohort study and one cross-sectional study suggesting beneficial effects on asthma and lung function, these data suggest a role for flavonoids in lung health that merits additional investigation. For colorectal cancer, data are inconsistent, with 1 positive, 1 inverse, and 4 null associations. Residual confounding by smoking is the most serious drawback of the flavonoid studies published to date. Unhealthy (or healthy) behaviors tend to cluster. Smoking, which is the single most important risk factor for many cancers and an important determinant of CVDs, is associated with higher intakes of energy, alcohol, and fat, lower intakes of fruits and vegetables, lower socioeconomic status, and physical inactivity (64–66). Previous studies showed that consumption of important sources of flavonoids, such as tea in the Netherlands (67) and in Japan (68) and wine in Denmark (69), is associated with healthy dietary patterns. Residual confounding occurs if confounders such as smoking are insufficiently accounted for in statistical analyses. Insufficient control for confounders can occur as a result of misclassification of the confounding factors, and control thus depends on the quality and amount of detail with which the confounders are measured. In particular, if the confounding is strong, as is usually the case for smoking, then misclassification of the confounder can yield spurious associations (70). Studying associations among lifelong nonsmokers is an effective way of ruling out residual confounding by smoking, and this should be done in future studies.

The strong inverse associations found for plasma enterolactone concentrations and the risk of CAD in a prospective study in Finland and supportive data from several cross-sectional studies make this an exciting new area of research that requires more investigation. Lignans are phytoestrogens, and their effect on breast cancer is a more traditional area of research in which several studies have been conducted to date. Inverse associations were reported only for case-control studies, whereas no associations between lignans and breast or prostate cancer were found in 3 prospective studies. Case-control studies may suffer from several drawbacks that make them less suitable for studying the effects of diet on the risk of disease. Recall bias, with misclassification of subjects because case subjects remember their diet differently, compared with control subjects, if this is assessed with questionnaires after diagnosis of the disease, is one hazard. If biomarkers of exposure are used instead of questionnaires, then the possibility exists that the biomarker levels are influenced by the disease state if the samples are collected after onset of the disease. Because significant associations were reported only for the case-control studies, these biases might have influenced the lignan data reported to date. Therefore, more prospective studies should be conducted on the lignan-cancer association before any conclusions are drawn.

The quality of dietary intake assessment and of food composition tables is crucial in the component-based epidemiologic approach. Imprecision of exposure measurement is an important limitation of these studies. If valid biomarkers are available, then these may replace questionnaire-based assessment of exposure; for most compounds, however, no biomarkers that reflect long-term exposure are available. No studies using biomarkers of flavonoid intake have been conducted to date. In contrast, several studies have used plasma or urinary enterolactone concentrations as biomarkers of lignan exposure. A major drawback of most of those studies was that enterodiol, the other enterolignan produced by the colonic microflora, was not measured. It was recently shown that not only secoisolariciresinol and matairesinol but also several other plant lignans, including pinoresinol and lariciresinol, are converted into enterolignans (71). We determined the concentrations of these 2 additional lignans in plant foods and found that their intake is severalfold higher than that of secoisolariciresinol and matairesinol (IEJ Milder, ICW Arts, and PCH Hollman, unpublished results, 2004). These compounds should be included in future evaluations of the health effects of dietary lignans.

Epidemiologic studies can be useful tools to study the health effects of polyphenols. Data obtained to date suggest of a beneficial effect on CVD but not on cancer, with the possible exception of lung cancer. There is a need for more research on stroke and lung diseases such as asthma and COPD. Most studies have included flavonols and flavones only. With data becoming available for other polyphenols, these should be included in future studies. Careful design of prospective studies is important to offset some of the major drawbacks of epidemiologic studies, including residual confounding (by smoking and other dietary factors) and exposure assessment.

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