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Quercetin in Foods, Cardiovascular Disease, and Cancer

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INTRODUCTION

The history of flavonoids has been characterized by controversies regarding their relevance to human health. In 1936 Szent-Györgi showed that two flavonoids derived from citrus fruit decreased capillary fragility and permeability in humans (1). Flavonoids were thus called vitamin P (for permeability) and also vitamin C₂, because it was found that some flavonoids had vitamin C-sparing activities (2). However, the claim that flavonoids were vitamins could later not be substantiated, and both terms were dropped around 1950. Following the discovery of the mutagenicity of quercetin, a major food flavonol, in the late 1970s, much attention was paid to its potential carcinogenicity, which was subsequently disproved (reviewed in Refs. 3,4). Later much attention was paid to their antimutagenic and anticarcinogenic activities. Finally, in recent years the antioxidant capacities of flavonoids and their potential role in inhibition of LDL oxidation were reported, as was an inhibitory effect on platelet aggregation.

These findings have resulted in an increased interest in the health aspects of these so-called nonnutritive bioactive compounds. However, until recently the experimental findings had not been confirmed in studies involving humans. With the determination of the content quercetin and related flavonols and flavones in foods (5,6), it became possible to investi-

gate in epidemiological studies the association between intake of these flavonoids, some of their major food sources, such as tea and red wine, and disease occurrence in humans. In the present overview, the results of these investigations will be summarized. Particular attention will be paid to flavonols and flavones, and particularly to the flavonol quercetin because of its postulated role in carcinogenesis, atherosclerosis, and thrombosis. Other effects of flavonoids have also been reported, such as immune-stimulating effects, antiallergic effects, antiviral effects, estrogenic activity, and anti-diarrhetic effects (7-10). However, these aspects will not be discussed here.

FLAVONOIDS IN FOODS

Flavonoids share the common skeleton of diphenylpyrans (C₆-C₃-C₆), e.g., two benzene rings (A and B) linked through a heterocyclic pyran or pyrone ring (C) in the middle. The carbon atoms in the C and A rings are numbered from 2 to 8, and those in the B ring from 2' to 6' (Fig. 1) (11). This basic structure allows a multitude of substitution patterns and variations in the C ring, giving rise to flavonols, flavones, catechins, flavanones, anthocyanid-

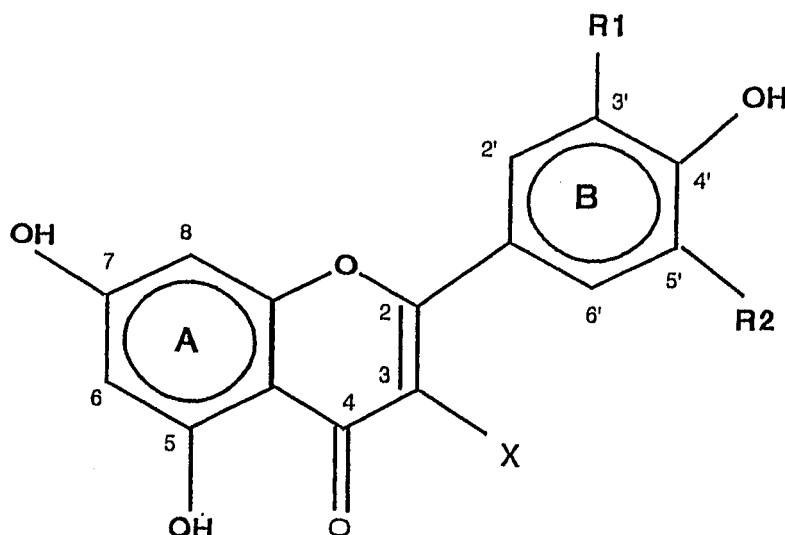


Figure 1 Structure of flavonoids: Flavonols: X = OH; quercetin: R₁ = OH, R₂ = H; kaempferol: R₁ = H, R₂ = H; myricetin: R₁ = OH, R₂ = OH. Flavones: X = H; apigenin: R₁ = H, R₂ = H; luteolin: R₁ = OH, R₂ = H.

ins, and isoflavonoids (Table 1). Flavonoids comprise one of the large groups of secondary plant metabolites occurring widely throughout the plant kingdom, including food plants. Over 4000 different types of flavonoids have been described, and the number is still increasing (12). Total daily flavonoid intake in the United States was estimated to be around 1 g (11). However, this is probably an overestimation. No recent estimation of total flavonoid intake in humans has been done.

As with other flavonoids, the most frequently found flavonols and flavones are those with B-ring hydroxylation in the 3'- and 4'-positions (13). Flavones lack the hydroxyl group at C3 in the middle ring that characterizes the flavonols. Quercetin and kaempferol are typical flavonols, the corresponding flavones being luteolin and apigenin, respectively (Fig. 1). Flavonols and flavones occur in foods usually as *O*-glycosides, with D-glucose as the most frequent sugar residue. Other sugar residues are D-galactose, L-rhamnose, L-arabinose, D-xylose, as well as D-glucuronic acid. In general, D-series sugars occur as β -glycosides, whereas the L-series sugars occur in the α -configuration. The preferred binding site for the sugar residues is C3 and, less frequently, in the A-ring, at the C7-position (13,14). The sugar-free part of the flavonoid molecule is called the aglycone. Quercetin (3,5,7,3',4'-pentahydroxyflavone), occurs in nature with mono-, di-, tri-, and tetrasaccharides attached at C3, and less commonly at the C7-position. More than 179 different quercetin glycosides have been described (15).

Flavonols and flavones are located mainly in the leaves and the outer parts of plants, while only trace amounts are found in plant parts below the soil surface. An exception is onion tubers, which contain a large amount of quercetin 4'-D-glucosides. In vegetables, quercetin glycosides predominate, but glycosides of kaempferol, luteolin, and apigenin are also present. Fruits almost exclusively contain quercetin glycosides (6,13). Flavonol and flavone

Table 1 Classes of Flavonoids and Their Dietary Sources

Class	Typical sources	Representative (aglycon)
Flavonols	Tea, onions, red wine, fruit	Quercetin
Flavones	Vegetables, citrus fruits	Apigenin
Flavanones	Citrus fruit	Hesperitin
Anthocyanidins	Berries, colored fruit	Cyanidin
Catechins	Tea, wines	Epigallocatechin
Isoflavonoids	Legumes	Genistein

Source: Adapted from Ref. 11.

contents of selected foods are shown in Table 2. These data were obtained after acid hydrolysis of the parent glycosides and are expressed as aglycones (5,6).

FLAVONOL AND FLAVONE INTAKE

We calculated that the combined average intake of the five flavonols and flavones analyzed by us is approximately 23 mg/day, using our analytical data in combination with data on food consumption in The Netherlands provided by the National Food Consumption Survey 1987-88 (16). Quercetin is predominant at 16 mg/day. The main food sources of flavonols and flavones in The Netherlands were black tea (48% of total intake), onions (29%), and apples (7%). Flavonols and flavones in herbs and spices may contribute to flavonol and flavone intake in humans. Black pepper contains about 2 g/kg of kaempferol, and 4 g/kg of quercetin and kaempferol combined was found in clove (17,18), but no quantitative data on herbs have been published. The estimated intake of herbs and spices in The Netherlands is probably less than 2 g/day, and assuming that spices and herbs contain an average of 1 g/kg, herbs and spices would contribute approximately 2 mg to total flavonol and flavone intake. This figure, which is obviously only a very rough estimate, probably overestimates the contribution of herbs and spices to flavonol and flavone intake in The Netherlands. However, in other countries, such as some Asian countries in which the

Table 2 Content of Some Flavonols and Flavones (mg/100 g fresh weight) in Vegetables, Fruit, and Beverages

Food	Quercetin	Kaempferol	Myricetin	Luteolin
Lettuce	0.7-3.0	<0.2	<0.1	<0.1
Onion	28-49	<0.2	<0.1	<0.1
Endive	<0.1	1.5-9.5	<0.1	<0.1
Red pepper	<0.1	<0.2	<0.05	0.7-1.4
Broad beans	2.0	<0.2	2.6	<0.1
Apples	2.1-7.2	<0.2	<0.1	<0.1
Strawberry	0.8-1.0	12	<0.1	<0.1
Black tea (bags)*	1.7-2.5	1.3-1.7	0.3-0.5	<0.1
Red wine*	0.4-1.6	<0.1	0.7-0.9	<0.1
Apple juice*	0.3	<0.1	<0.05	<0.1

Source: Refs. 5, 6.

*mg/100 mL.

use of spices is much more common, herbs and spices could contribute significantly to flavonol and flavone intake.

We determined intake of quercetin and related flavonols in Japan, The Netherlands, the former Yugoslavia, the United States, Finland, Italy, and Greece by chemical analyses of equivalent food composites representing their average diet around 1960 (19) (Table 3). The main sources of quercetin were tea in Japan and The Netherlands, red wine in Italy, and onions in the United States, the former Yugoslavia, and Greece. In Finland, consumption of berries such as lingonberries is an important source of quercetin and myricetin. Flavonol and flavone intake was highest in Japan at 64 mg/day and lowest in Finland at 6 mg/day (Table 3). Average intake of flavonols and flavones in a small number of epidemiological prospective cohort studies published so far are 20 mg/day in middle-aged to older American males (20), 26 mg/day in elderly Dutch men (21), about 4 mg/day in Finnish middle-aged men and women (22), and 26 mg/day in Welsh middle-aged men. Flavonol and flavone intake thus exceeds that of other dietary antioxidants such as β -carotene (2–3 mg/day) and vitamin E (7–10 mg/day), and equals approximately one-third that of vitamin C (70–100 mg/day) (23). Flavonols and flavones thus make a major contribution to the antioxidant potential of the human diet.

QUERCETIN AND CANCER RISK

Animal Studies

Flavonoids, including quercetin, inhibited chemically induced tumors in a number of experimental animal studies. Topical application of quercetin inhibited rat skin tumor promotion induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) (24,25), possibly by inhibition of epidermal ornithine decarboxylase activity. Quercetin and other flavonoids also inhibited 7,12-dimethylbenz(a)anthracene-, benzo(a)pyrene-, 3-methylcholanthrene-, and *N*-methyl-*N*-nitrosourea-induced skin tumorigenesis in mice (26). Of particular interest are two studies in which the effect of dietary administered flavonols were investigated. Verma and coworkers reported that dietary quercetin (2% and 5% by weight of the diet) inhibited mammary tumor initiation by DMBA and tumor promotion with TPA (27). Using an experimental mouse model of colon cancer, Deschner and coworkers showed that under low fat intake, dietary quercetin (2%) and rutin (4%) suppressed hyperproliferation of colonic epithelial cells and ultimately colon tumor incidence induced by azoxymethanol, presumably by inhibiting the promotion phase (28). The same investigators recently confirmed their findings when a high-fat diet was present (29). Elangovan and coworkers showed

Table 3 Flavone and Flavonol Content of Duplicates of the Diets of Middle-Aged Men Around 1960 in Various Countries and Estimated Contribution of Foods to Total Intake

Countries	Quercetin intake (mg/day)	Total flavonol and flavone intake ^a (mg/day)	Vegetables and fruit (%)	Red wine (%)	Tea (%)
Finland	6	6	100	0	0
USA	11	13	80	0	20
Serbia	10	12	98	2	0
Greece	15	16	97	3	0
Italy	21	27	54	46	0
The Netherlands	13	33	36	0	64
Croatia	30	49	82	18	0
Japan	31	64	10	0	90

^aSum of quercetin, kaempferol, myricetin, apigenin, and luteolin.

Source: Ref. 19.

that a diet supplemented with 1% quercetin reduced 20-methylcholanthrene-induced fibrosarcomas in mice by 48% (30). The effect of quercetin on human cancer cells was also investigated *in vitro*. Quercetin inhibited *in vitro* the development of squamous cell carcinoma (31) and of acute leukemias (32). Quercetin also inhibited growth *in vitro* of cells from various human cancers such as stomach (33), colon (34), and ovarian (35). Yoshida and coworkers (1992) suggested that these antiproliferative effects of quercetin were due to the specific arrest of the G₁ phase of the cell cycle (36). In summary, the following mechanisms of action of quercetin and other hydroxylated flavonoids have been suggested by *in vitro* and *in vivo* research: inhibition of the metabolic activation of carcinogens by modulation of the activity of detoxifying enzymes; forming of inactive complexes with ultimate carcinogens; scavenging of reactive oxygen species; and inhibition of the arachidonic acid metabolism (37). However, these are speculations based on addition of large amounts of quercetin to cells or to animals with artificially induced cancers. The track record of this type of study in predicting human cancer is generally poor.

Epidemiological Studies

Studies on Quercetin

Epidemiological studies consistently show an inverse association between the consumption of fruit and vegetables and cancer risk at various sites (38,39). On the average, participants with the highest consumption of fruit and vegetables experienced a 50% reduced risk of cancers of the alimentary and respiratory tract compared to participants with the lowest intakes. Fruit and vegetable consumption could be a marker for other aspects of lifestyle which are responsible for the lower cancer rates, but it is also possible that fruits and vegetables contain substances that prevent cancer. Flavonoids such as quercetin could be such substances. We therefore investigated, in the Seven Countries Study, whether intake of quercetin and related flavonols at baseline measurements around 1960 (see above) was associated with cancer mortality rates in 16 cohorts after 25 years of follow-up (19). About 13,000 men were followed up for 25 years, and the lowest cancer mortality rates were observed in Belgrade, Serbia (8.4% of men), whereas in Zutphen, The Netherlands, 17.8% of the men had died from some form of cancer. The average intake of quercetin and related flavonols was not independently related to colorectal cancer, lung cancer, and all-cause cancer mortality rates across the cohorts. Flavonol intake was positively related to mortality from stomach cancer, but this effect was not independent of vitamin C intake and percentage of smokers in the cohorts. The positive

association between flavonol intake and stomach cancer could have been confounded by infections with *Helicobacter pylori*, as these infections are more common in countries with a high flavonoid intake and less common in countries with a low flavonoid intake. Differences in flavonol and flavone intake between countries seems therefore not to contribute to differences in cancer mortality rates in various countries. However, comparisons between other countries might yield different results, especially since the countries of the Seven Countries Study were selected on the basis of differences in CHD mortality rates and CHD risk factors rather than cancer mortality rates.

Three prospective epidemiological cohort studies have investigated the association between cancer incidence and flavonol and flavone intake. We investigated in the Zutphen Elderly Study whether intake of flavonols was related to all-cause cancer mortality and incidence in a cohort of approximately 700 elderly men (4). During the 5 years of follow-up, 59 men initially free of the disease developed cancer of the alimentary or respiratory tract and 34 men died from cancer. Flavonol intake was not associated with incidence of these cancers, nor with cancer mortality. After adjustment for age, diet, and other risk factors (e.g., smoking), the relative risk of the highest tertile versus the lowest tertile of flavonol intake was 1.02 (95% CI 0.51–2.04) (Fig. 2). Similar results were obtained when the association between quercetin intake and cancer risk were investigated. The number of cancer cases at specific sites was too small to allow further investigation. The association between flavonol and flavone intake and cancer incidence has also been studied in The Netherlands Cohort Study on diet and cancer (41). This is a study of 120,852 Dutch men and women aged 55–69 years, followed up since 1986. At baseline participants filled in a food frequency questionnaire, which was used to calculate individual flavonol and flavone intake. During 4.3 years of follow-up 200 cases of stomach cancer, 650 of colon cancer, 764 of lung cancer, and 650 of breast cancer were registered. Mean intake of flavonol and flavones was 28 mg/day, half provided by the consumption of tea. Relative risks of flavonol and flavone intake and cancer risk at various sites was calculated in quintiles of flavonol and flavone intake. An initial inverse association between flavonol and flavone intake and lung and stomach cancer risk disappeared after adjustment for other dietary antioxidants. Flavonol and flavone intake was also not associated with breast and colon cancer risk; the relative risks in all categories were close to unity. Hertog and coworkers investigated in the Caerphilly Cohort Study among 1900 Welsh men the association between flavonol intake around 1980 and all-cause cancer mortality during 14 years of follow-up. Again, flavonol intake at baseline, mainly provided by the consumption of

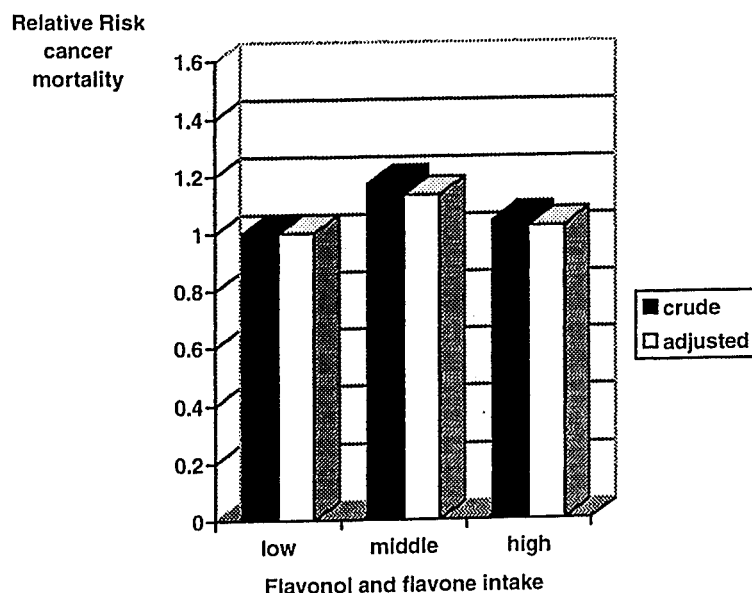


Figure 2 Flavonol and flavone intake and incidence of cancers of the alimentary and respiratory tract after 5 years of follow-up in 738 men participating in the Zutphen Elderly Study. (From Ref. 40.)

tea, was not associated with cancer risk; all relative risks were close to unity.

Studies on Tea

Information on cancer-protective effects of flavonoids can also be derived from epidemiological studies on tea consumption and cancer. These associations have been investigated in a number of mainly case-control studies. Yang and Wang reviewed recently the epidemiology of tea (42), showing that positive, none, and inverse associations between tea consumption and cancer risk at various sites had been reported. Tea consumption was not associated with cancer risk in the Zutphen Elderly Study (40) nor with risk of cancer at various sites in The Netherlands Cohort Study (43). A positive association between tea consumption and cancer (mainly esophageal tumors) has been observed and has been attributed to the drinking temperature of tea, rather than to its chemical constituents (42). A small number of studies performed in Asian countries have supported a protective effect of green tea drinking on stomach cancer (44). However, these findings have not been reproduced consistently (45).

In summary, the results of epidemiological studies reported so far do not show a clear protective effect of tea drinking on cancer risk, but a protective effect of tea consumption on selected cancers in specific populations cannot be ruled out.

Studies on Wine and Onions

Intake of alcoholic beverages, including wine, is elevated in people who later develop cancers of the mouth, throat, and esophagus (46). In a meta-analysis involving 27 epidemiological studies, wine consumption was not associated with risk of colorectal cancer (47). It seems therefore less likely that wine consumption has a major protective effect against various types of cancers.

Onions are an important source of quercetin in populations in which tea and wine consumption is low. A large number of case-control studies have consistently shown an inverse association between consumption of onions and other *Allium* vegetables and cancer risk, particularly cancer of the stomach, colon, and rectum (48). So far, The Netherlands Cohort Study is the only prospective cohort study in which specifically the relation between onion consumption and cancer risk at several sites was investigated. In most other prospective cohort studies, consumption of onions was categorized into the vegetable group or was not taken into account at all. In The Netherlands Cohort Study, onion consumption was inversely with stomach cancer risk, but not with lung or colon carcinoma risk (48). During 3.3 years of follow-up 139 cases of stomach cancer occurred and those consuming more than half an onion a day had a 50% reduced risk of stomach cancer in comparison with 3123 randomly chosen healthy cohort members. The authors suggest that this inverse association is probably not due to the quercetin content of onions, because tea was not associated with stomach cancer. However, it is still possible that the higher absorption of quercetin from onions than from tea explains the discrepancy. Thus, there is still a possibility that the quercetin-glucose compounds from onions offer some protection against malignancies of the digestive tract.

QUERCETIN AND CARDIOVASCULAR DISEASES

Experimental Studies

Damage by reactive oxygen species is believed to play an important role in atherogenesis through the generation of oxidized low-density lipoproteins (LDL) (49). Oxidized LDL are thought to be absorbed by macrophages, leading to foam cell formation and ultimately to growth of atherosclerotic

plaques (50). This hypothesis still awaits confirmation in humans. Flavonoids are potent radical scavengers and metal chelators due to their polyphenolic structure. Their antioxidant and radical-scavenging activities are reviewed in other chapters of this book. In general, optimal antioxidant activity of flavonoids is associated with the presence of multiple phenolic groups (especially 3' and 4' hydroxyl groups), a carbonyl group at C-4, and free C3 and C5 hydroxyl groups (51). Optimal radical-scavenging activities have been found for an *o*-dihydroxy structure in the B ring, 2,3 double bond, and a 4-oxo function in the C ring, and finally 3 and 5-OH groups in the A and C rings (52). Flavonols such as quercetin, which combines these features, scavenged superoxide anions (53), hydroxyl radicals (54), lipid peroxyl radicals (55), and formed ligands with metal ions (56). However, quercetin and myricetin also showed pro-oxidant action in vitro in the presence of Fe^{3+} (57). Flavonoids inhibited LDL oxidation by macrophages in vitro, probably by protecting α -tocopherol in LDL from being oxidized by free radicals, by reducing the formation of free radicals in the macrophages, or by regenerating oxidized α -tocopherol (58). Quercetin also reduced the cytotoxicity of oxidized LDL, whereas flavones such as apigenin were ineffective (59). There are also claims for effects of quercetin on the hemostatic component of atherosclerosis. Quercetin and rutin were modest inhibitors of platelet aggregation in platelet-rich plasma in vitro (60). However, a trial of quercetin-rich foods in humans produced no evidence for effects on platelet aggregation.

Epidemiological Studies

Studies on Quercetin

The association between flavonoids (mainly quercetin) and cardiovascular disease has been investigated in two prospective cohort studies conducted in The Netherlands, one in Finland, one study among U.S. male health professionals, and one study among Welsh men. It was also investigated in one cross-cultural ecological study. In the Zutphen Elderly Study (see above), the intake of quercetin and four other flavonols and flavones of approximately 800 elderly men was determined in 1985, and the men were followed for 5 years. Forty-three men died from coronary heart disease during this period. Flavonol and flavone intake, expressed as tertiles, was inversely associated with mortality from coronary heart disease (Fig. 3) and to a lesser extent with incidence of first myocardial infarction. These effects were independent of known risk factors for coronary heart disease such as serum cholesterol, body mass index, blood pressure, smoking, and intake of antioxidant vitamins, alcohol, and fat (61). We also investigated the

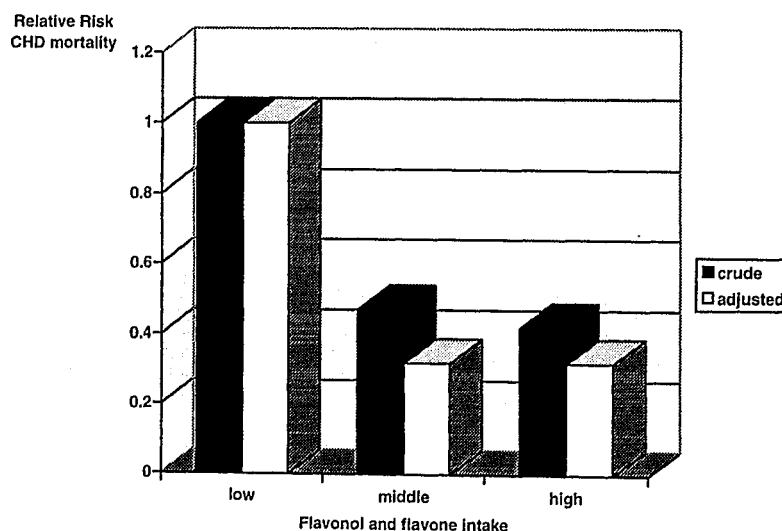


Figure 3 Flavonol and flavone intake of 805 men aged 65–84 years participating in the Zutphen Elderly Study and mortality from coronary heart disease (43 cases) after 5 years of follow-up. (From Ref. 61.)

association between long-term flavonol and flavone intake and risk of stroke in a cohort of 552 middle-aged Dutch men free from a history of stroke at baseline (the Zutphen Study). The men were divided into quartiles of flavonol and flavone intake and followed for 15 years. During this period 42 men had a first stroke (mainly thrombotic) event. Flavonol and flavone intake was inversely associated with stroke risk. Again, this association was not affected by adjustment for confounding risk factors (62). In both studies, the men in the highest category of flavonol and flavone intake (> 30 mg/day) had about one-third the risk of getting the disease compared with men in the lowest category. Quercetin was the major flavonoid in both studies, and analysis of the association between quercetin intake yielded essentially the same results as total flavonols and flavones. Knekt and co-workers examined the association between flavonol intake and coronary mortality in a cohort of 5133 Finnish men and women. They observed an inverse association between flavonol intake, mainly provided by onions and apples, and coronary mortality after 24 years of follow-up in both men and women. After adjustment for antioxidant vitamins and fatty acids, the relative risk in the highest vs. the lowest quartiles of flavonoid intake was 0.73 (95% CI 0.41–1.32) for women and 0.67 (95% CI 0.44–1.00) in men (22). However, Rimm and coworkers found no association between flavo-

nol and flavone intake and nonfatal myocardial infarction in 34,789 U.S. males after 6 years of follow-up, whereas a modest nonsignificant inverse association between flavonol and flavone intake and coronary mortality was found in 4814 men with a previous history of coronary heart disease (20). In 1900 Welsh men we did not find an association between flavonol intake and incidence and mortality from coronary heart disease after 14 years of follow-up. Tea with milk was the major source of flavonols in this population.

We also investigated the contribution of flavonols and flavones (mainly quercetin) in explaining the variance in coronary heart disease mortality rates across 16 cohorts from seven countries. As described above under cancer, flavonol and flavone intake at baseline was determined by chemical analyses of food composites collected in 1987 representing the average diet in each of the cohorts. Flavonol and flavone intake around 1960 was inversely correlated with mortality rates from coronary heart disease in the 16 cohorts, explaining about 25% of the variance. About 90% of the total variance in CHD mortality rates across the cohorts could be explained by the combined effects of intake of saturated fat (explaining 73%), percentage of smokers (9%), and flavonol and flavone intake (8%). These results were independent from the intake of alcohol and antioxidant vitamins (19).

Studies on Tea

Tea was the major source of flavonols in the Dutch and Welsh studies, and tea consumption was inversely associated with both CHD mortality and stroke incidence in the Zutphen (Elderly) Study. On the other hand, tea consumed with milk was positively associated with CHD mortality and all-cause mortality in Welsh men participating in the Caerphilly Cohort Study. A number of cross-sectional studies suggested an inverse association between black or green tea consumption and serum cholesterol (63–66) but a causal effect was ruled out by controlled experiments (67). Only a small number of studies investigated the association between tea consumption and cardiovascular disease risk. Most were directed at measuring the possible risk-enhancing effects of caffeine holding drinks, i.e., coffee and tea, and therefore did not specifically investigate a protective effect of tea. Brown and coworkers reported no association between tea consumption and prevalence of CHD in Scottish men and women (68). In the Health Professionals Follow-Up Study comprising 45,589 U.S. men, there was no association between tea consumption and cardiovascular disease risk (69). However, mean tea consumption was very low in this cohort. Stensvold et al. reported an inverse association in a Norwegian population study be-

tween tea drinking, serum cholesterol, and mortality from CHD, although the latter was not statistically significant (64). Serafini and colleagues reported that the antioxidant capacity of plasma increased in human volunteers after consumption of 300 ml of black and green tea, thus suggesting that physiological amounts of tea could result in potential healthy effects in humans (70). On the other hand, Maxwell and Thorpe reported in a letter to the editor that tea consumption did not affect plasma antioxidant activity measured by chemiluminescence in a similar intervention trial (71). Addition of milk to tea completely abolished the plasma antioxidant-raising effect of tea consumption in the trial performed by Serafini et al., suggesting that the absorption of antioxidants such as the flavonols present in tea is inhibited by the addition of milk. It is known that flavonoids bind proteins (reviewed in Ref. 72), and it is conceivable that flavonoids in tea bind to milk proteins and are therefore not absorbed from the gastrointestinal tract. Vorster et al. examined the effect of tea consumption on hemostatic factors in a placebo-controlled intervention trial lasting 4 weeks. No effect of tea consumption on plasma fibrinogen, tissue-type plasminogen activator, or plasminogen activator inhibitor-1 was found (73).

Studies on Red Wine

Moderate wine consumption is associated with a lower risk of CHD than is abstinence. Renaud and de Lorgeril reported that wine consumption was inversely associated with CHD mortality in a comparison of 17 selected countries (74). Similarly, Criqui et al. showed that wine ethanol had the strongest and most consistent correlation with CHD mortality in a comparison of 21 developed countries (75). Klatsky and Armstrong reported that among 81,825 U.S. citizens, red wine drinkers had a lower risk of coronary artery disease than participants with no alcoholic beverage preference (76). In a prospective 12-year cohort study conducted in Denmark (77), persons who drank three to five glasses of wine per day had an approximately 50% lower risk of dying from cardiovascular diseases and, to a lesser extent, from all causes. This effect was independent of age or education. Klurfeld and Kritchewsky (78) showed that specifically red wine and not white wine reduced coronary atherosclerosis in rabbits. In human experimental studies, red wine consumption in contrast to white wine led to increase in antioxidant capacity of serum (79,80) and reduced the susceptibility of LDL cholesterol to oxidation (81). However, these findings could not be reproduced by de Rijke and coworkers in a carefully controlled trial (82). It is therefore uncertain whether wine constituents other than alcohol add to the cardioprotective effects of red wine. Rimm et al. reviewed the epidemiological

literature and concluded that there is no hard evidence for a specific effect of red wine; all alcoholic beverages are about equally effective and elevation of HDL cholesterol is the most likely mechanism (83).

Inhibition of platelet aggregation has also been invoked. Seigneur and colleagues (84) showed that administration of 0.5 liter of red wine to volunteers during 2 weeks led to reduced platelet aggregation, whereas white wine did not have this effect. Intravenous administration of red wine and grape juice also inhibited *in vivo* platelet activity in canine coronary arteries (85). Ruf and colleagues reported that dietary administration of red wine, in contrast to other alcoholic beverages, reduced platelet aggregation in rats and did not result in a rebound effect on platelets after alcohol withdrawal (86). This platelet rebound effect has been associated with sudden death and myocardial infarction in humans. The authors argue that the reduction in the rebound effect was primarily due to tannins in red wine, which counteracted the lipid peroxidation associated with alcohol drinking. On the other hand, consumption of 30 g/day of alcohol for 4 weeks either from red wine or from pure alcohol resulted in similar decreases of collagen-induced platelet aggregation and fibrinogen in humans, whereas ADP-induced platelet aggregation and t-PA antigen were not affected by the treatment (87). The authors suggest that the known positive effect of red wine on hemostasis is due to alcohol and not to nonalcoholic fractions in red wine. It is uncertain to what extent various platelet aggregation tests predict risk of CHD in humans, and mechanisms involving platelet inhibition should be considered speculative for now.

CONCLUSION

Cancer

Quercetin reduces the number and sites of tumors in certain animal models, but until now intake of quercetin and related flavonols and quercetin-rich foods has not been associated with a lower incidence of or mortality from cancer in humans. It is possible that tumors in humans are not caused by the type and dose of carcinogens used in animal studies, or that the anticarcinogenic effects of flavonols and flavones are only achieved at very high doses not reached through a normal diet. On the other hand, the follow-up period in cohort studies may have been too short to see an effect. Consumption of vegetables and fruit is associated with a reduced risk of cancer, especially with tumors of the alimentary and respiratory tracts, but the foods associated with lower cancer rates, such as green-yellow vegetables, are not important sources of quercetin. Therefore, quercetin probably does not play a major role in the explanation of the cancer-protective effect

of vegetables and fruit. However, a role for quercetin from onions in explaining the lower risk of stomach cancer in frequent onion users cannot be ruled out.

Cardiovascular Disease

Two prospective cohort studies showed an inverse association of quercetin intake with coronary mortality, one showed an inverse association with stroke incidence, and two studies showed no association with coronary heart disease incidence. In one of the latter studies, a modest nonsignificant inverse association with a second coronary attack was found. A cross-cultural study showed that populations with a high amount of flavonols and flavones in their diet are characterized by a low average mortality from coronary heart disease. The epidemiological evidence is therefore compatible with a protective effect, but the evidence is not conclusive. Flavonoids lowered oxidation and cytotoxicity of LDL, and affected hemostasis in vitro, but human studies of wine and tea yielded inconclusive or contradictory results. A limitation of diet trials in humans is that little is known about the absorption of flavonoids. For instance, the lack of an association between flavonol intake and coronary heart disease in the Welsh study could be due to the addition of milk to tea, lowering the absorption of flavonoids. In conclusion, the possibility that dietary quercetin lowers cardiovascular disease risk remains open, while a major benefit in preventing cancer is less likely.

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