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## REVIEW

# Dietary Flavonoids and Cancer Risk: Evidence From Human Population Studies

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***Abstract:*** *High dietary intake of fruits and vegetables is consistently associated with a reduced risk of common human cancers, including cancers of the lung, breast, prostate, and colon. It is unknown which bioactive compound or compounds in plant foods provide the chemoprotective effects. One class of compounds currently under investigation is flavonoids, a large group of compounds with similar structure, consisting of two phenolic benzene rings linked to a heterocyclic pyran or pyrone. Although there are numerous in vitro and animal model data suggesting that flavonoids influence important cellular and molecular mechanisms related to carcinogenesis, such as cell cycle control and apoptosis, there are limited data from human population studies. This article reviews data from four cohort studies and six case-control studies, which have examined associations of flavonoid intake with cancer risk. There is consistent evidence from these studies that flavonoids, especially quercetin, may reduce the risk of lung cancer. Further research using new dietary databases for food flavonoid content is needed to confirm these findings before specific public health recommendations about flavonoids can be formulated.*

## Introduction

Fruit and vegetable intake is consistently associated with a reduced risk of cancer (1–4). In 1997, the World Cancer Research Fund, in association with the American Institute for Cancer Research, published a comprehensive report, which examined over 30 yr of epidemiological research of diet and cancer risk (5). The panel concluded that there was convincing evidence for an inverse association of fruit and vegetable intake for cancers of the lung, stomach, mouth, pharynx, esophagus, colon, and rectum (5). Since publication of the report, interest continues in investigating whether specific fruits and vegetables, or bioactive compounds found in fruits and vegetables, may have unique protective properties. These kinds of data are important for formulating focused published health recommendations both for the general population and for those who are at increased risk of specific cancers due to family history or lifestyle behaviors (for example, smoking).

Plant foods contain thousands of bioactive compounds, which may reduce the risk of common human cancers. For many years, β-carotene was presumed to be the primary phytochemical responsible for the consistent inverse associations of fruit and vegetable intake with cancer risk (4,6,7). More recently, there has been an increasing amount of research on other phytochemicals (8), such as isoflavones (9,10), glucosinolates (11,12), and allium compounds (13). Of particular interest among the plant compounds under investigation for their putative chemoprotective properties are flavonoids, a large group of compounds with similar structure, which consists of two phenolic benzene rings linked to a heterocyclic pyre or pyrone (14). Over 5,000 flavonoids exist and can generally be grouped into one of the following subclasses: flavonols, flavonones, isoflavones, flavins, and anthocyanidins (15,16). Within these subclasses are the specific compounds examined in the studies reviewed in this article (for example, catechins and quercetin). Flavonoids have a wide variety of biological effects, and those of particular interest in relation to cancer prevention include their antimutagneic and antiproliferative capability, strong antioxidant capacity, and involvement in cell signaling, cell cycle regulation, and angiogenesis (17).

The objective of this article is to review the epidemiological literature that reports associations of dietary flavonoid intake with cancer risk. The review is restricted to manuscripts published in the English language, to those cited in the MEDLINE® database of the National Library of Medicine, and to studies with at least 50 cases or disease endpoints (although it is important to note that no published studies with

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fewer than 50 cancer cases were found in the literature search). We also focused this report on flavonoids found in fruits and vegetables because two reviews of tea polyphenols in relation to cancer risk have recently been published (18,19).

## Food Sources of Flavonoids

Flavonoids are ubiquitous in the plant food supply, but the subclasses do not seem to be uniformly distributed (15). For many plants, the skins of the fruit or the outer edge of the vegetable as well as the leaves contain the most concentrated sources of flavonoids. In addition, flavonoid content is influenced by factors such as season, sunlight, climate, and food preparation and processing (14).

Until recently, investigations of dietary flavonoid intake with cancer risk have been limited by the lack of reliable data on the flavonoid content of foods. The USDA Database for the Flavonoid Content of Selected Foods was published in early 2003. This database lists the flavonoid values for 19 compounds from 255 foods. All values in the database were generated by high-performance liquid chromatography (HPLC), which yields good separation of the myriad flavonoid compounds. Table 1 lists the subclasses of compounds included in the database, and details can be found at the Nutrient Data Laboratory website: http://www.nal.usda.gov/fnic/foodcomp. This resource greatly facilitates future quantitative studies of flavonoids and risk of cancer in humans. It is important to note, though, that the investigations reviewed here were all published prior to the release of the 2003 flavonoid database.

## Cohort Studies of Dietary Flavonoids and Cancer Risk

Table 2 gives results from five publications, conducted in four cohorts, which examined associations of dietary flavonoids with cancer risk in humans (20–24). The Zutphen Elderly Study has been collecting data on risk factors for chronic disease among elderly men in The Netherlands for nearly 20 yr. In 1994, an analysis showed a nearly statistically significant 43% reduced risk of all cancers associated with high vs. low consumption of flavonoids and a halving in risk for gastrointestinal and respiratory cancers ($P = 0.06$) (20). A later study from this cohort focusing on catechin reported no association of this particular compound with risk for any epithelial cancer or with risk for lung cancer (data not shown) (22). Men in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) were followed from enrollment in 1985–1988 to the end of the intervention trial in 1993. Hirvonen et al. reported that, among men whose dietary flavonoid intake was in the highest compared with the lowest quartile at baseline, there was a 44% reduced risk of lung cancer after a median follow-up time of 6 yr. There was a near statistically significant decreased risk of renal cell carcinoma and increased risk of colorectal cancer for the highest compared with the lowest quartiles of flavonoid consumption but no association with other cancers (21). Among postmenopausal women in Iowa, the highest vs. lowest quintile of baseline catechin intake was associated with an approximate halving in risk of rectal cancer after 13 yr of follow-up (23).

One of the largest and most comprehensive cohort studies was the Finnish Mobile Health Examination Survey, which evaluated five flavonoids and cancer risk at six organ sites after a maximum of 30 yr of follow-up (24). There was a statistically significant 58% and 36% reduction in lung cancer risk for men in the highest quartile of baseline quercetin and naringenin consumption, respectively, compared with men in the lowest quartile (24). Hesperetin consumption was associated with a statistically significant 42% reduction in lung cancer risk for the third compared with the first quartile of consumption, but there was no further protection at higher levels of consumption. Prostate cancer was the only other solid tumor for which there was a protective association from flavonoid consumption in this large cohort. Compared with men in the lowest quartile of myricetin intake, the risk of prostate cancer for those in the top quartile of consumption was reduced by 57%. None of the other flavonoids was sig-

**Table 1.** Bioactive Compounds and Their Food Sources in the 2003 USDA Database for the Flavonoid Content of Selected Foods[a]

| Subclass of Flavonoid | Specific Compounds | Principal Food Sources |
|---|---|---|
| Flavonols | Quercetin, kaempferol, myricetin, isohamnetin | Apples, black tea, blueberries, broccoli, buckwheat, cocoa, cranberries, green beans, green tea, kale, onions, red wine |
| Flavones | Luteolin, apigenin | Celery, parsley, peppermint |
| Flavonones | Hesperetin, naringenin, eriodictyol | Chili peppers, citrus fruits |
| Flavon-3-ols | (+)-Catechin, (+)-gallocatechin, (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin 3-gallate, (-)epigallocatechin 3-gallate, theaflavin, theaflavin 3-gallate, theflavin 3′-gallate, theaflavin 3,3′-digallate, thearubigins | Apricots, blackberries, black tea, broadbeans, chocolate, grapes, green tea, red wine |
| Anthocyanidins | Cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin | Blueberries, cherries, elderberries, raspberries, red wine |

*a:* http://www.nal.usda.gov/fnic/foodcomp

**Table 2.** Cohort Studies of Dietary Flavonoids and Cancer Risk

| Ref. (yr) | Location | Subjects | Cancer | Exposure | Odds Ratio (95% CI)[a] | *P* Trend | Comments |
|---|---|---|---|---|---|---|---|
| 20 (1994) | The Netherlands | 738 elderly men | | | | | |
| | | 75 cases | Any cancer | Total flavonoids[b] | 0.57 (0.31, 1.08)[c] | 0.08 | |
| 21 (2001) | Finland | 27,110 male smokers | | | | | |
| | | 791 cases | Lung | Total flavonoids[b] | 0.56 (0.45, 0.69)[d] | <0.001 | Participants were enrolled in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study |
| | | 156 cases | Urothelial | | 1.2 (0.73, 1.8)[d] | 0.77 | |
| | | 59 cases | Renal | | 0.63 (0.36, 1.1)[d] | 0.10 | |
| | | 226 cases | Prostate | | 1.3 (0.87. 1.8)[d] | 0.24 | |
| | | 133 cases | Colorectal | | 1.7 (1.0, 2.7)[d] | 0.10 | |
| | | 111 cases | Stomach | | 1.2 (0.71, 1.9)[d] | 0.51 | |
| 22 (2001) | The Netherlands | 728 elderly men | | | | | |
| | | 96 cases | Epithelial cancer[e] | Catechin | 0.94 (0.56, 1.59)[f] | 0.82 | Cohorts for Refs. 20 and 22 are identical |
| 23 (2002) | Iowa | 34,651 postmenopausal women | | | | | |
| | | 137 cases | Upper digestive | Catechin | 0.71 (0.46, 1.11)[g] | 0.31 | |
| | | 635 cases | Colon | | 1.10 (0.85, 1.44)[g] | 0.63 | |
| | | 132 cases | Rectum | | 0.55 (0.32, 0.95)[g] | 0.02 | |
| | | 549 cases | Lung | | 0.94 (0.72, 1.23)[g] | 0.94 | |
| | | 1,069 cases | Breast | | 1.04 (0.84, 1.28)[g,h] | 1.0 | |
| | | 276 cases | Uterus | | 1.00 (0.73, 1.36)[g,h] | 0.54 | |
| | | 151 cases | Ovary | | 0.73 (0.44, 1.24)[g,h] | 0.21 | |
| | | 130 cases | Pancreas | | 0.74 (0.46, 1.20)[g] | 0.77 | |
| | | 114 cases | Kidney | | 0.73 (0.40, 1.32)[g] | 0.12 | |
| | | 103 cases | Bladder | | 1.12 (0.65, 1.93)[g] | 0.93 | |

*(continued)*

**Table 2.** *(Continued)*

| Ref. (yr) | Location | Subjects | Cancer | Exposure | Odds Ratio (95% CI)[a] | *P* Trend | Comments |
|---|---|---|---|---|---|---|---|
| 24 (2002) | Finland | 9,865 adult males and females | | | | | |
| | | 74 cases | Stomach | Quercetin | 1.03 (0.52, 2.07)[i] | 0.82 | |
| | | | | Kaempferol | 1.14 (0.59, 2.22)[i] | 0.98 | |
| | | | | Myricetin | 1.16 (0.59, 2.26)[i] | 0.29 | |
| | | | | Hesperetin | 0.88 (0.43, 1.80)[i] | 0.67 | |
| | | | | Naringenin | 0.94 (0.47, 1.88)[i] | 0.67 | |
| | | 90 cases | Colorectal | Quercetin | 0.62 (0.33, 1.17)[i] | 0.22 | |
| | | | | Kaempferol | 1.13 (0.60, 2.12)[i] | 0.96 | |
| | | | | Myricetin | 1.31 (0.71, 2.43)[i] | 0.39 | |
| | | | | Hesperetin | 0.97 (0.50, 1.90)[i] | 0.84 | |
| | | | | Naringenin | 0.93 (0.48, 1.82)[i] | 0.95 | |
| | | 81 cases | Urinary organs | Quercetin | 0.87 (0.44, 1.72)[i] | 0.49 | |
| | | | | Kaempferol | 0.67 (0.34, 1.31)[i] | 0.11 | |
| | | | | Myricetin | 0.78 (0.41, 1.49)[i] | 0.23 | |
| | | | | Hesperetin | 0.83 (0.40, 1.70)[i] | 0.94 | |
| | | | | Naringenin | 0.81 (0.39, 1.66)[i] | 0.90 | |
| | | 169 cases | Lung | Quercetin | 0.42 (0.25, 0.72)[i] | 0.001 | Men only, 5,128 males in cohort |
| | | | | Kaempferol | 0.81 (0.51, 1.28)[i] | 0.26 | |
| | | | | Myricetin | 1.20 (0.78, 1.83)[i] | 0.98 | |
| | | | | Hesperetin | 0.74 (0.46, 1.18)[i] | 0.07 | |
| | | | | Naringenin | 0.64 (0.39, 1.04)[i] | 0.02 | |
| | | 95 cases | Prostate | Quercetin | 0.76 (0.40, 1.42)[i] | 0.35 | |
| | | | | Kaempferol | 1.03 (0.53, 2.02)[i] | 0.54 | |
| | | | | Myricetin | 0.43 (0.22, 0.86)[i] | 0.002 | |
| | | | | Hesperetin | 1.47 (0.80, 2.71)[i] | 0.26 | |
| | | | | Naringenin | 1.48 (0.80, 2.73)[i] | 0.27 | |
| | | 125 cases | Breast | Quercetin | 0.62 (0.37, 1.03)[i] | 0.25 | 4,647 females in cohort |
| | | | | Kaempferol | 0.87 (0.53, 1.41)[i] | 0.70 | |
| | | | | Myricetin | 0.95 (0.57, 1.60)[i] | 0.63 | |
| | | | | Hesperetin | 1.08 (0.63, 1.86)[i] | 0.93 | |
| | | | | Naringenin | 1.14 (0.67, 1.94)[i] | 0.82 | |

*a:* Relative risks are for highest relative to lowest quantile of intake.
*b:* Sum of quercetin, kaempherol, myricetin, luteolin, and apignin.
*c:* Adjusted for age, smoking, body mass index, physical activity, and intake of energy, alcohol, vitamin C, β-carotene, vitamin E, and fiber.
*d:* Relative risks for lung cancer are adjusted for age, trial arm (study vitamins vs. placebo), and smoking. Relative risks for prostate, colorectal, and stomach cancer are adjusted for age and trial arm only.
*e:* Includes cancers of the oropharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, kidney, bladder, and lung.
*f:* Adjusted for age, physical activity, total energy, alcohol, smoking, body mass index, and intake of coffee, fiber, vitamin C, vitamin E, and β-carotene.
*g:* Adjusted for age, body mass index, waist-hip ratio, physical activity, smoking, and intake of energy, alcohol, and fruits and vegetables.
*h:* Relative risks for breast, ovary, and uterus cancer exclude women with baseline mastectomy, hysterectomy, or oophorectomy, leaving 21,502 for analysis. Additional adjustments for use of estrogen replacement therapy, age at menarche, age at menopause, and age at first pregnancy.
*i:* Adjusted for age, sex, geographic area, occupation, smoking, and body mass index.

**Table 3.** Case-Control Studies of Dietary Flavonoids and Cancer Risk

| Ref. (yr) | Location | Subjects | Cancer | Exposure | Odds Ratio (95% CI)[a] | *P* Trend | Comments |
|---|---|---|---|---|---|---|---|
| 25 (1998) | Spain | 103 cases and 206 hospital controls | Lung | Quercetin | 1.89 (0.72, 4.92)[b] | 0.19 | Females only; cases and controls matched on age, area of residence, and hospital |
| | | | | Kaempferol | 0.51 (0.22, 1.17)[b] | 0.10 | |
| | | | | Luteolin | 0.59 (0.24, 1.43)[b] | 0.40 | |
| 26 (1999) | Uruguay | 541 cases and 540 hospital controls | Lung | Total flavonoids | 0.59 (0.40, 0.87)[c] | 0.01 | Males only; cases and controls matched on age (10 yr), residence, and urban/rural status |
| | | | | Quercetin | 0.58 (0.39, 0.85)[c] | 0.0007 | |
| | | | | Kaempferol | 0.79 (0.55, 1.17)[c] | 0.16 | |
| 27 (1999) | Spain | 497 cases and 547 neighborhood controls + 566 hospital controls | Bladder | Quercetin | 1.21 (0.8, 1.9) | 0.94 | Cases and controls matched by sex, age, area of residence, and hospital |
| | | | | Kaempferol | 1.35 (0.9, 2.1) | 0.11 | |
| | | | | Luteolin | 0.95 (0.6, 1.4) | 0.40 | |
| | | | | Myricetin | 0.82 (0.6,1.2) | 0.20 | |
| 28 (1999) | Spain | 354 cases and 354 hospital controls | Stomach | Quercetin | 0.62 (0.35, 1.10)[d] | 0.02 | Cases and controls matched by age, sex, area of residence, and hospital |
| | | | | Kaempferol | 0.48 (0.26, 0.88)[d] | 0.04 | |
| | | | | Myricetin | 1.12 (0.67, 1.85)[d] | 0.45 | |
| 29 (2000) | Hawaii | 582 cases selected from the Hawaii SEER[e] Cancer Registry and 582 population controls | Lung | Quercetin | 0.7 (0.4, 1.1)[f] | 0.07 | Cases and controls matched on sex, ethnicity, and age |
| | | | | Kaempferol | 0.9 (0.5, 1.4)[f] | 0.41 | |
| | | | | Myricetin | 1.0 (0.6, 1.6)[f] | 0.42 | |
| | | | | Hesperetin | 1.2 (0.7, 2.0)[f] | 0.54 | |
| | | | | Naringenin | 0.7 (0.5, 1.1)[f] | 0.17 | |
| 30 (2003) | Greece | 820 cases and 1,548 hospital controls | Breast | Flavonones | 0.96 (0.87, 1.07)[g] | | Hospital controls were either visitors or orthopedic patients |
| | | | | Flavan-3-ols | 0.93 (0.78, 1.11)[g] | | |
| | | | | Flavonols | 0.91 (0.78, 1.06)[g] | | |

*a:* Odds Ratios are for the highest compared with the lowest quantile of intake.
*b:* Adjusted for intake of vitamin E, vitamin C, total carotenoids, and each of the other flavonoids.
*c:* Adjusted for age, education, family history of lung cancer, body mass index, smoking, total energy, and total fat intake.
*d:* Adjusted for intake of total energy, nitrites, nitrosamines, vitamin C, total carotenoids, and each of the other flavonoids.
*e:* Surveillance, Epidemiology and End Results is a cancer registry program of the National Cancer Institute.
*f:* Adjusted for smoking and intake of β-carotene and saturated fat.
*g:* Odds ratios are per 1 SD increase in intake of the compound per day. Adjusted for age, place of birth, age at first pregnancy, age at menarche, menopausal status, body mass index, fruit and vegetable consumption, and other flavonoids. Authors did not break down the classes into specific flavonoid compounds. Readers are referred to Table 1.

nificantly associated with cancer risk at any site in the Finnish Mobile Health Survey (24).

## Case-Control Studies of Flavonoids and Cancer Risk

Table 3 gives results from six case-control studies of dietary flavonoid intake and cancer risk (25–30). Total flavonoids and quercetin were associated with a reduced risk of lung cancer in two studies but a nonsignificant increased risk in a third study (25,26,29). The magnitude of protection ranged from 30% to 42% reduction in risk for persons in the top vs. bottom quantiles of intake. High vs. low quercetin and kaempferol intakes were associated with 40% and 50% reduction in risk, respectively, for stomach cancer. There was no statistically significant association of any flavonoids with either bladder cancer or breast cancer risk (27,30).

## Commentary

The cohort and case-control studies reviewed in this article provide modest evidence that flavonoid intake may reduce cancer risk. The evidence is particularly intriguing for inverse associations of total flavonoids, foods rich in flavonoids and quercetin against lung cancer (21,24,26,29). Only one study examined rectal cancer, but there was evidence of a halving of risk associated with high vs. low catechin intake (23). Because only a very limited number of epidemiological studies have been conducted to examine the associations of dietary intake of flavonoids with cancer risk, it is premature to make public health recommendations at this time. However, the data to date are promising and emphasize the need for further investigations of these important bioactive plant compounds.

Flavonoids influence several important biological functions, which may explain the observed inverse associations of flavonoids with cancer risk. The free radical scavenging ability of flavonoids has been fairly well characterized in experimental systems. More recently, in vitro and animal model systems suggest that flavonoids influence signal transduction pathway (31,32), stimulate apoptosis (33), inhibit inflammation (34), and inhibit proliferation in human cancer cell lines (35). Selected flavonoids may also increase transcription of phase II detoxifying enzymes, which supports a cancer protective effect via the clearance of procarcinogenic substances that are detoxified and eliminated by phase II enzyme

products (36). A study conducted with azoxymethane (AOM)-treated mice who were fed with either a standard diet, a standard diet plus rutin, or a standard diet plus quercetin showed that the flavonoids substantially decreased the number of focal areas of dysplasia that were induced by the AOM exposure (37). This type of evidence is intriguing because it suggests that flavonoids may be related to events early in the carcinogenesis pathway. With this in mind, future studies in human populations may benefit most from cohort designs, which can assess diet over a prolonged period of time and capture dietary exposures that influence early carcinogenic events. One important caveat, however, is that these in vitro and animal model studies tested isolated flavonoids, which may not accurately represent the action of the compound in the context of the food matrix in a mixed diet.

Limitations of the observational studies reviewed in this article must be noted. All studies in nutritional epidemiology are limited by the fact that bioactive compounds in foods are highly correlated. The influence of any one nutrient or compound is not completely independent of other nutrients (38). The possibility cannot be ruled out that the protective associations observed for flavonoids are simply either markers of unmeasured constituents of plants or a marker of a generally healthy lifestyle. Moreover, the variability in findings across the studies reviewed in this article may be due to differences in study design and analysis. For example, food-frequency questionnaires were used in some studies (29), whereas diet histories (21,24) or household food disappearance data (22) were used in other studies. Estimates of dietary intake using different assessment methods are not necessarily comparable. The studies also used different nutrient databases to obtain flavonoid values, which could contribute to the inconsistencies in result. It is also important to note that databases are not able to capture all of the variability in plant flavonoid content that may be attributable to factors such as sunlight and heat. Another potential limitation is that, whereas the Zutphen Elderly Study, ATBC, and the Iowa Women's Health Study assessed total flavonoids or one class of flavonoids (catechin), the other cohorts and most of the case-control studies assessed exposure to very specific flavonoids. These differences in the exposure may have contributed to inconsistencies in study findings. Finally, studies did not uniformly adjust relative risks or odds ratios for potential confounding factors. As with all observational investigations, residual confounding can still occur in spite of statistical adjustments, which can bias estimates of risk. For these reasons, caution should be exercised in the interpretation of the results presented in this article.

## Conclusion

In conclusion, there is modest evidence that flavonoids, particularly quercetin, are inversely associated with cancer risk. Additional studies using updated dietary databases with HPLC values for flavonoid estimates from food will provide evidence regarding the strength of association of these plant compounds with cancer risk. Moreover, feeding studies that are able to characterize the absorption, metabolism, and disposition of plant flavonoids and their interaction with key enzyme systems will be critical to understanding the biological basis for an inverse association of flavonoid intake with cancer risk. In the meantime, the public is urged to follow dietary guidance for cancer prevention, which includes consumption of five or more servings of fruits and vegetables per day.

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