Meta analysis

Consumption of the Dietary Flavonoids Quercetin, Luteolin and Kaempferol and Overall Risk of Cancer - A Review and Meta-Analysis of the Epidemiological Data

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Abstract

Numerous epidemiological and preclinical studies suggest that flavonoids may play an important role in the decreased risk of cancer associated with a diet rich in plant-derived foods. In this article, we have reviewed the epidemiological studies assessing the relationship between the consumption of three of the most common flavonoids, i.e. quercetin, luteolin and kaempferol, and the risk of developing cancer. We have also performed a meta-analysis on the consumption of these three flavonoids (alone and combined) and overall risk of cancer. The analysis of data from 18 case-control studies (8585 cases with cancer and 9975 control subjects) revealed that a high consumption of these three flavonoids (combined) was associated with a statistically significant reduction of overall cancer risk (OR: 0.73; 95% CI: 0.63, 0.84; p<0.01). A reduction of overall cancer risk was also observed for quercetin (OR: 0.73; 95% CI: 0.62, 0.86; p<0.01), kaempferol (OR: 0.86; 95% CI: 0.73, 1.11; p>0.05) and luteolin (OR: 0.90; 95% CI: 0.69, 1.18; p>0.05), which was statistically significant for quercetin. A high intake of these three flavonoids (combined) was also associated with a statistically significant reduction of lung cancer risk (OR: 0.67; 95% CI: 0.49, 0.91; p<0.05) and colon cancer risk (OR: 0.75; 95% CI: 0.57, 0.98; p<0.05). The analysis of data from 14 cohort studies (385033 individuals and 10809 cancer cases) showed a statistically significant reduction of overall cancer risk for the three flavonoids combined (RR: 0.89; 95% CI: 0.80, 1.00; p<0.05), for quercetin (RR: 0.82; 95% CI: 0.71, 0.96; p<0.05) and for kaempferol (RR: 0.88; 95% CI: 0.78, 0.99; p<0.05), and a non-statistically significant reduction for luteolin (RR: 0.95; 95% CI: 0.67, 1.34; p>0.05). These results suggest that consumption of foods rich in the flavonoids quercetin, kaempferol and luteolin may reduce the risk of developing cancer.

Introduction

Epidemiological studies have shown that a diet rich in plant-derived foods is consistently associated with a reduced risk of developing chronic diseases. A common guideline from the American Cancer Society, the American Heart Association and the American Diabetes Association to prevent these diseases is to increase the consumption of plant-derived foods and to eat at least five servings of a variety of vegetables and fruits daily (Eyre et al. 2004). Although it is not clear which compounds in plant foods are responsible for their preventive effect, evidence suggests that flavonoids may participate in this activity.

Flavonoids comprise a large group of plant secondary metabolites characterized by a diphenylpropane structure. They are widely distributed in the plant kingdom and are commonly found in fruits, vegetables and certain beverages. Numerous preclinical and some clinical studies suggest that flavonoids have potential for the prevention and treatment of several diseases. Several epidemiological studies support a protective role of diets rich in foods with flavonoids and a reduced risk of developing cancer and cardiovascular diseases (Hertog et al. 1993a; Hertog et al. 1993b; Le Marchand, 2002; Maron, 2004; Mojzisova and Kuchta, 2001; Neuhouser, 2004). Preclinical in vitro and in vivo investigations have shown possible mechanisms by which flavonoids may confer cancer and cardiovascular protection (Middleton E Jr et al. 2000; Xiao et al. 2011). In addition to their preventive potential, certain flavonoids may be useful for the treatment of several diseases including cancer (Calderon-Montano et al. 2011; Clere et al. 2011; Li et al. 2007; Liu et al. 2010; Lopez-Lazaro, 2002; Lopez-Lazaro, 2009; Middleton E Jr et al. 2000; Ren et al. 2003; Wang, 2000).

Quercetin, luteolin and kaempferol are flavonoids widely distributed in plant-derived foods (Calderon-Montano et al. 2011; Kelly, 2011; Lopez-Lazaro, 2009). Numerous epidemiological reports (case-control and cohort studies) have evaluated the possible association between the consumption of foods containing these flavonoids and the risk of developing specific cancers. In this work, we have reviewed the data from these epidemiological reports. We have also performed a meta-analysis to assess the association between the consumption of these three flavonoids (alone and combined) and the overall risk of cancer. There is consistent evidence from this analysis that intake of these flavonoids, alone and combined, may reduce the overall risk of cancer.

Consumption of Quercetin, Luteolin and Kaempferol and Cancer Risk: A Review of the Epidemiological Data

Case-control studies

The relationship between consumption of quercetin, kaempferol and luteolin and lung cancer risk has been evaluated in four case-control studies. Lam et al. (2010) conducted a case-control study with 1822 lung cancer cases and 1991 hospital controls, observing an association between the consumption of quercetin-rich foods (apples, grapes, onions, artichoke, fennel, celery, beans, apricots, plums, turnips, peppers, strawberries, tomatoes and broccoli) and a significant 53% decrease in lung cancer risk (OR: 0.47; 95% CI: 0.35, 0.64: p for trend <0.001). Another case-control study of 558 lung cancer cases and a group of 837 controls revealed that the consumption of food rich in quercetin (OR: 0.65; 95% CI: 0.44–0.95; p for trend: 0.025) and kaempferol (OR: 0.68; 95% CI: 0.51, 0.90; p for trend: 0.0079) was inversely associated with lung cancer risk among tobacco smokers. The lung cancer global risk (smokers and nonsmokers) was also decreased for kaempferol (OR: 0.72; 95% CI: 0.56, 0.91; p for trend: 0.0069) and for quercetin, but the association was not statistically significant (OR: 0.77; 95% CI: 0.56, 1.10; p for trend: 0.11) (Cui et al. 2008). A case-control study conducted by Le Marchand et al. (2000) with 582 lung cancer cases and 582 controls found an inverse association between consumption of quercetin-rich foods (onions and apples) and lung cancer risk; this association was statistically significant, with a 40%–50% decreased risk in the highest compared with the lowest category of intake (OR: 0.50; 95% CI: 0.3, 0.9; p for trend: 0.001 for onions and OR: 0.60, 95% CI: 0.40, 1.00; p for trend: 0.03 for apples). The authors also reported a non-statistically significant inverse association between intake of the individual flavonoid quercetin and lung cancer risk (OR: 0.70; 95% CI: 0.40, 1.10; p for trend: 0.07), and between intake of kaempferol and a reduced risk of this cancer (OR: 0.90; 95% CI: 0.50, 1.40; p for trend: 0.41) (Le Marchand et al. 2000). A case-control study carried out in Spain with 103 cases of lung cancer and 206 hospital controls found a nonsignificant association for the highest vs. lowest tertile intake of kaempferol (OR: 0.51; 95% CI: 0.22, 1.17; p for trend: 0.10), but no protective effect was observed for quercetin or luteolin (Garcia-Closas et al. 1998).

Several case-control studies have assessed the relationship between intake of flavonoids and risk of developing cancers of the gastrointestinal tract. Theodoratou et al. (2007) conducted a case-control study with 1456 cases of colorectal cancer and 1456 controls and found that a high intake of

quercetin was associated with a significant decrease of colon cancer risk (OR: 0.76; 95% CI: 0.56, 1.02; p for trend: 0.046). They also found a positive but non-significant association with rectal cancer (OR: 0.68, 95% CI: 0.48, 0.98; p for trend: 0.071). This association was stronger among nonsmokers than smokers (OR: 0.52; 95% CI: 0.30, 0.90; p for trend: 0.03 for nonsmokers and OR: 0.78; 95% CI: 0.54, 1.13; p for trend: 0.374 for smokers). A case-control study with 261 cases and 404 control subjects evaluated the association between the intake of four different flavonoid subclasses and colorectal cancer risk (Kyle et al. 2010). This study found a reduced risk of developing colon cancer and quercetin intake (OR: 0.40; 95% CI 0.20, 0.80; p for trend: 0.01) but not effect was observed for rectal cancers (OR: 0.90; 95% CI: 0.40, 1.90; p for trend: 0.38). Consumption of kaempferol was not associated with colon (OR: 1.20; 95% CI: 0.70, 1.10; p for trend: 0.98) or rectal (OR: 1.00; 95% CI: 0.40, 2.30; p for trend: 0.98) cancer risk (Kyle et al. 2010). A case-control study conducted in Spain with 354 gastric cancer cases and 354 controls (Garcia-Closas et al. 1999) reported a protective effect of quercetin and kaempferol against gastric cancer. People consuming the highest amount of kaempferol or quercetin had a significant lower incidence of this cancer (OR: 0.62; 95% CI: 0.35, 1.10; p for trend: 0.02 for quercetin and OR: 0.48; 95% CI: 0.26, 0.88; p for trend: 0.04 for kaempferol) (Garcia-Closas et al. 1999). This protective effect of quercetin in gastric cancer was also found in a case-control study carried out by Ekström et al. (2011) in Sweden. They found a strong association between consumption of quercetin and a reduced risk of noncardia gastric adenocarcinoma, with a statistical significance for the highest daily quercetin intake relative to the lowest intake (OR: 0.57; 95% CI: 0.40, 0.83; p for lineal trend: <0.001). This protective effect was stronger between smokers (OR: 0.61; 95% CI: 0.40, 1.01). Nevertheless, a high intake of quercetin did not show a clear positive association in cardia gastric cancer (RR: 0.76; 95% CI: 0.40, 1.44; p for trend: 0.35).

A case-control study carried out in Uruguay with 351 breast cancer cases and 356 hospitalized controls found that a high intake of quercetin together with a high intake of fiber had a positive effect in breast cancer risk (OR: 0.36; 95% CI: 0.24, 0.55). No association between consumption of quercetin and the breast cancer risk, however, was observed (De Stefani et al. 1997). Another case-control study with 353 breast cancer cases and 701 controls evaluated the association between urinary levels of flavanols and risk of breast cancer, not observing an association between levels of quercetin or kaempferol in urine and breast cancer risk (OR: 1.00; 95% CI: 0.70, 1.41; p for trend: 0.694 for quercetin and OR: 1.10; 95% CI: 0.76, 1.58; p for trend: 0.491 for kaempferol) (Luo et al. 2010).

Two case-control studies have evaluated the possible association between flavonoids intake and risk of prostate cancer. McCann et al. (2005) conducted a case-control study with 433 prostate cancer cases and 538 controls and found that consumption of an high amount of quercetin was not significantly associated with prostate cancer risk (OR: 0.73; 95% CI: 0.49, 1.09; p for trend: 0.37). Similar results were observed for kaempferol (OR: 0.85; 95% CI: 0.59, 1.22; p for trend: 0.67). Strom et al. (1999) conducted another case-control study of 83 prostate cancer cases and 107 controls and did not observe significant associations between intake of the flavonoids quercetin, kaempferol and luteolin and a lower prostate cancer risk (OR: 0.96; 95% CI: 0.53, 1.76; p for trend: 0.90 for quercetin; OR: 0.77; 95% CI: 0.42, 1.43; p for trend: 0.41 for kaempferol and OR: 0.83; 95% CI: 0.45, 1.51; p for trend: 0.54 for luteolin).

Three case-control studies have evaluated the possible relationship between a high intake of the flavonoids quercetin, kaempferol and luteolin and the risk of developing ovarian, endometrial or bladder cancers. Gates et al. (2009) conducted a study of 1141 cases of epithelial ovarian cancer and 1183 controls and did not observe an association between consumption of quercetin (OR: 1.09; 95% CI: 0.67, 1.75; p for trend: 0.80) or luteolin (OR: 1.04; 95% CI: 0.59, 1.81; p for trend: 0.99) and ovarian cancer risk. In the case of kaempferol the association was weak (OR: 0.79; 95% CI: 0.51, 1.22; p for trend: 0.29). An inverse association between consumption of cauliflower, which contains both kaempferol and quercetin, and a reduced risk of this cancer was observed (RR: 0.68; 95% CI: 0.45, 1.02; p for trend 0.05) (Gates et al. 2009). A case-control study, conducted by Bandera et al. (2009) with 424 endometrial cancer cases and 398 controls evaluated the association between quercetin intake and endometrial cancer risk. The study revealed that a diet rich in quercetin was significantly associated with a decreased risk of endometrial cancer (OR: 0.65; 95% CI: 0.41, 1.01; p for trend 0.02) (Bandera et al. 2009). A case-control study conducted in Spain with 497 bladder cancer cases and 1113 controls (547 neighborhood controls and 566 hospitals controls) found no association between intake of the flavonoids quercetin (OR: 1.21; 95% CI: 0.80, 1.90; p for trend: 0.94), luteolin (R: 0.95; 95% CI: 0.60, 1.40; p for trend: 0.40) or kaempferol (OR: 1.35; 95% CI: 0.90, 2.10; p for trend: 0.11) and bladder cancer risk (Garcia et al. 1999).

Cohort studies

Cohort studies have evaluated the relationship between dietary intake of the flavonoids quercetin, kaempferol and luteolin and the risk of developing several types of cancer, including lung, colorectal, gastric, breast, ovarian, endometrial, renal and pancreatic cancers. In a cohort study with 10054 participants the association between intake of flavonoid-containing foods and risk of several chronic diseases was assessed (Knekt et al. 2002). Quercetin was mainly provided by apples and onions, and kaempferol by white cabbage. The study revealed that a high quercetin intake was significantly associated with a lower lung cancer risk (RR: 0.42; 95% CI: 0.25, 0.72; p for trend: 0.001). Consumption of apples, which are an important source of quercetin, was also strongly associated with a reduced risk of lung cancer (RR: 0.40; 95% CI: 0.22, 0.74; p for trend: 0.001). The study did not find an clear association between lung cancer risk and kaempferol consumption (RR: 0.81; 95% CI: 0.51, 1.28; p for trend: 0.26) (Knekt et al. 2002). No positive correlation was found in another prospective study conducted in 38408 women between consumption of foods containing quercetin, kaempferol or luteolin and a reduced risk of developing lung cancer (Wang et al. 2009).

Three cohort studies did not find statistically significant inverse associations between intake of quercetin and kaempferol-rich foods and risk of colorectal cancer. One of them found that risk of colorectal cancer tended to be lower with a high quercetin intake, although this association was not statistically significant (RR: 0.62; 95% CI: 0.33, 1.17; p for trend: 0.22) (Knekt et al. 2002). Similar results were obtained in another study which included 71,976 women from the Nurses' Health Study and 35,425 men from the Health Professionals (RR: 1.06; 95% CI: 0.84, 1.34; p for trend: 0.23) (Lin et al. 2006a). Neither of these studies found a significant association between kaempferol intake and risk of colorectal cancer (RR: 1.13; 95% CI: 0.60, 2.12; p for trend: 0.96; RR: 1.12; 95% CI: 0.90, 1.39; p for trend: 0.25) (Knekt et al. 2002; Lin et al. 2006). The third prospective study, conducted with 38408 women, did not find a positive correlation between consumption of foods containing quercetin, kaempferol or luteolin and colorectal cancer risk (Wang et al. 200). In a nutritional intervention trial, the association between consumption in the diet of individual flavonoids and risk of advanced colorectal adenoma recurrence was assessed (Bobe et al. 2008b). After a follow-up period of 4 years the study revealed an association between kaempferol intake and a significant decrease in risk for advanced colorectal adenoma recurrence (RR: 0.44; 95% CI: 0.22, 0.89; p for trend: 0.03). This protective effect was also observed for quercetin (RR: 0.59; 95% CI: 0.29, 2.20; p for trend: 0.04) (Bobe et al. 2008a).

Three cohort studies have analyzed the possible association between flavonoid intake and risk of developing breast cancer. One of these studies (Knekt et al. 2002) revealed that risk of breast cancer tended to be lower with a high quercetin intake (RR: 0.62; 95% CI: 0.37, 1.03; p for trend: 0.25) and kaempferol intake (RR: 0.87; 95% CI: 0.53, 1.41; p for trend: 0.70) Another prospective study evaluated the association between intake of flavonol-rich foods and breast cancer risk in 90630 women and found no correlation between quercetin or kaempferol intake and breast cancer risk (RR: 1.05; 95% CI: 0.83, 1.33; p for trend: 0.81 for quercetin and RR: 1.01; 95% CI: 0.80, 1.27; p for trend: 0.91) (Adebamowo et al. 2005). The third prospective study, conducted in 38408 women, did not find a positive correlation between consumption of foods containing quercetin, kaempferol or luteolin and breast cancer risk (Wang et al. 2009).

Two cohort studies have evaluated the possible association between consumption of diets rich in flavonoids and the risk of developing pancreatic cancer. Nöthlings et al. (2007) conducted a cohort study to evaluate the possible association between consumption of kaempferol-containing foods (i.e. onions, tea, apples, cruciferous and other vegetables) and pancreatic cancer risk in 183518 participants. After a follow-up period of 8 years, the authors found that kaempferol consumption was inversely associated with pancreatic cancer risk (RR: 0.78; 95% CI: 0.58, 1.05; p for trend: 0.017). This association was greater among smokers (RR: 0.27; 95% CI: 0.14, 0.55; p for trend: <0.0001). Quercetin consumption was also associated with a non-significant reduction of pancreatic cancer risk (RR: 0.80; 95% CI: 0.60, 1.06; p for trend: 0.087) and a significant reduction of pancreatic cancer risk in smokers (RR: 0.55; 95% CI: 0.30, 0.99; p for trend: 0.008) (Nothlings et al. 2007). Similar results were obtained in a cohort study conducted in Finland with 27111 healthy male smokers aged 50-69 years (Bobe et al. 2008). The study showed a significant association between kaempferol intake and pancreatic cancer risk (RR: 0.37; 95% CI: 0.17, 0.79; p for trend: 0.009). This study also found a decreased pancreatic cancer risk with quercetin intake, but this association was not significant (RR: 0.59; 95% CI: 0.29, 1.23; p for trend: 0.06). No association was observed, however, for luteolin (RR: 1.35; 95% CI: 0.70, 2.61; p for trend: 0.67) (Bobe et al. 2008).

The correlation between intake of foods rich in quercetin, kaempferol or luteolin and incidence of epithelial ovarian cancer was evaluated in a cohort study in 66940 women (Gates et al. 2007). The study found a significant decrease in epithelial ovarian cancer incidence associated with kaempferol intake (RR: 0.57; 95% CI: 0.34, 0.96; p for trend: 0.02) and with luteolin intake (RR: 0.59; 95% CI: 0.42, 0.81; p for trend: 0.001). It also found an inverse association between epithelial ovarian cancer risk and consumption of tea (RR: 0.63; 95% CI: 0.40, 0.99; p for trend 0.03) and broccoli (RR: 0.67; 95% CI: 0.45, 1.01, p for trend 0.06); tea and broccoli are rich in kaempferol. No protective effect was observed with quercetin intake (RR: 1.05; 95% CI: 0.68, 1.62; p for trend 0.52). Another prospective study conducted in 38408 women did not find a positive correlation between consumption of foods containing kaempferol, quercetin or luteolin and the risk of ovarian or endometrial cancers (Wang et al. 2009).

Wilson et al. (2009) evaluated the correlation between consumption of foods containing quercetin, kaempferol or luteolin and renal cell cancer risk in a cohort study with 27111 men. The authors found a significant 40% decreased risk of renal cell cancer in people consuming quercetin-containing foods (RR: 0.60; 95% CI: 0.40, 0.90; p for trend: 0.015). No significant associations between kaempferol or luteolin intake and a reduced renal cell cancer risk were observed (RR: 0.80; 95% CI: 0.60, 1.10; p for trend: 0.351 for kaempferol and RR: 1.10; 95% CI: 0.80, 1.70; p for trend: 0.926 for luteolin) (Wilson et al. 2009). A cohort study found that risk of cancers of urinary organs tended to be lower in people with diets rich in kaempferol (RR: 0.67; 95% CI:

0.34, 1.31; p for trend: 0.11) and quercetin (RR: 0.87; 95% CI: 0.44, 1.72; p for trend: 0.49) (Knekt et al. 2002). A cohort study conducted by Knekt et al (2002) did not find association between risk of gastric cancer and quercetin intake (RR: 1.03; 95% CI: 0.52, 2.07; p for trend: 0.82), or kaempferol intake (RR: 1.14; 95% CI: 0.59, 2.22; p for trend: 0.98).

Consumption of Quercetin, Luteolin and Kaempferol and Cancer Risk: A Meta-Analysis of the Epidemiological Data

Methods

We performed a search of MEDLINE and the Cochrane Library for articles published before January 2012. English-language, original observational cohort studies and case-control studies were included. Relevant reports were identified using a combination of the following medical subject heading terms: “flavonoid” or “flavonoids” or “quercetin” or “luteolin” or “kaempferol”, and “cancer”, and “case-control” or “cohort” or “prospective” or “retrospective” or “epidemiological”. The reference lists of pertinent articles were also inspected. After data extraction, we estimated the summary association between flavonoid intake and cancer risk in case-control and cohort studies separately. We also studied separately the effects of the flavonoids luteolin, quercetin and kaempferol on overall cancer risk. The association between flavonoid consumption and cancer risk was assessed by comparing cancer incidence in the group of participants with the lowest intake of the flavonoid with that of the group with the highest intake (i.e., lowest vs. highest quantiles of intake).

We performed all the statistical analysis in R with the metafor Package (Viechtbauer, 2010). We used a random effect model for our meta-analysis (res command in the metaphor Package) to account for within-study and between-study variances which are potentially explained by explanatory variables such as country, type of cancer, year of publication and number of individual observations in each study. Using the command leave1out from the metafor package, we performed a sensitivity analysis of the influence of individual studies on the summary estimate and we repeated the meta-analysis by excluding one study at a time. We evaluated the heterogeneity among studies with a Cochrane Q test (significant at P<0.05) finding no evidence that results are significantly affected by a single study neither for case-control or cohort studies (Viechtbauer, 2010; Viechtbauer and Cheung, 2010). Due to the fact that this test has limited sensibility that varies with the type of study, we also quantified heterogeneity with the estimation of the variance of the true effects because of between studies heterogeneity. We used the command rma in R to analyze potential sources of heterogeneity across studies (significant at P<0.05). The meta-regression analysis variables included as controls year of publication, number of observations in each study and categorical variables such as country or type of cancer. Publication bias was also tested by using Egger and Begg analysis (Egger et al. 1997; Begg and Mazumdar, 1994) and visual inspection of the funnel plots.

Case-control studies

The analysis of data from 18 case-control studies (8585 cases with cancer and 9975 control subjects) revealed that a high consumption of these three flavonoids (combined) was associated with a statistically significant reduction of the cancer risk (pooled OR: 0.73; 95% CI: 0.63, 0.84; p<0.01; Illustration 1) when lowest versus highest quantiles of intake were compared. Consumption of quercetin (pooled OR: 0.73; 95% CI: 0.62, 0.86; p<0.01; Illustration 2) was associated with a significant reduction of cancer risk, whereas the evidence was not compelling for kaempferol (pooled OR: 0.86; 95% CI: 0.73, 1.11; p>0.05; Illustration 3) and luteolin (pooled OR: 0.90; 95% CI: 0.69, 1.18; p>0.05; Illustration 4). Pooled ORs from the sensitivity analysis for total consumption of flavonoids ranged from 0.71 (95% CI: 0.61, 0.82) after excluding Garcia et al. (1999) to 0.76 (95% CI: 0.66, 0.87) after excluding De Stefani et al. (1997). Indeed, the removal of any of the 18 studies did not have any material impact on the level of significance of the estimated pooled OR. Besides, we found a significant heterogeneity among the studies at the conventional significant levels in the case of quercetin and for the average effect. According to this result, we run a meta-regression analysis to apprise whether the type of cancer were significantly related to the strength of the association between flavonoids intake and cancer risk; however, the test of moderators with P=0.97 and the test for residual heterogeneity with P=0.002 for the average provide a clear indication that the type of cancer does not explain the heterogeneity in the data. Similar conclusions are obtained when the two tests are run only for quercetin with tests for moderators P=0.97 and residual heterogeneity P=0.0003. The Begg (P=0.88) and Egger (P=0.68) tests, as well as visual inspection of the funnel plot (not shown), did not suggest publication bias.

Cohort studies

The analysis of data from 14 cohort studies (385033 individuals and 10809 cancer cases) showed a statistically significant reduction of overall cancer risk for the three flavonoids combined (RR: 0.89; 95% CI: 0.80, 1.00; p<0.05; Illustration 5), for quercetin (RR: 0.82; 95% CI: 0.71, 0.96; p<0.05; Illustration 6) and for kaempferol (RR: 0.88; 95% CI: 0.78, 0.99; p<0.05; Illustration 7), and a non-statistically significant reduction for luteolin (RR: 0.95; 95% CI: 0.67, 1.34; p>0.05; Illustration 8). Pooled ORs from the sensitivity analysis for total consumption of flavonoids ranged from 0.89 (95% CI: 0.70, 1.12) after excluding Lin et al. (2006) to 0.93 (95% CI: 0.74, 1.16) after excluding Bobe et al. (2008a). Again, we did not find a significant heterogeneity among the studies at the conventional significant levels. According to this result, in the meta-regression analysis none of the 4 variables assessed were significantly related to the strength of the association between flavonoids intake and cancer risk (P=0.91). Neither the Begg (P=0.12) nor the Egger (P=0.42) suggest evidence of publication bias. Moreover, visual inspection of the funnel plot (not shown) did not suggest a publication bias.

Discussion

Numerous epidemiological studies have evaluated the possible relationship between the consumption of foods containing flavonoids and the risk of developing specific cancers. In this article, we have reviewed and performed a meta-analysis of the epidemiological studies (case-control and prospective studies) assessing the relationship between the consumption of three of the most common flavonoids, i.e. quercetin, luteolin and kaempferol, and the risk of developing cancer (Illustration 9).

The analysis of data from 18 case-control studies (8585 cases with cancer and 9975 control subjects) revealed that a high consumption of these three flavonoids (combined) was associated with a statistically significant reduction of overall cancer risk (OR: 0.73; 95% CI: 0.63, 0.84; p<0.01), when compared lowest vs. highest quantiles of intake (Illustration 1). These data indicate that people with a diet rich in foods containing these flavonoids may reduce the risk of developing cancer by 27 % in relation to people with diets deficient in these foods. Similar results were obtained when the meta-analysis was performed with the individual flavonoid quercetin (OR: 0.73; 95% CI: 0.62, 0.86; p<0.01; Illustration 2). A non-statistically significant 14 % and 10% reduction of overall cancer risk were respectively observed for kaempferol (OR: 0.86; 95% CI: 0.73, 1.11; p>0.05; Illustration 3) and luteolin (OR: 0.90; 95% CI: 0.69, 1.18; p>0.05; Illustration 4).

Although the aim of our study was to assess the relationship between flavonoid consumption and overall cancer risk, we also performed a meta-analysis to evaluate the association between consumption of the three flavonoids (combined) and the risk of developing specifics cancers when two or more case-control studies were available. Results showed that a high intake of quercetin, kaempferol and luteolin (combined) was associated with a statistically significant reduction of lung cancer risk (OR: 0.67; 95% CI: 0.49, 0.91; p<0.05) and colon cancer risk (OR: 0.75; 95% CI: 0.57, 0.98; p<0.05).

The meta-analysis of data from 14 cohort studies (385033 individuals and 10809 cancer cases) showed a statistically significant reduction of overall cancer risk for the three flavonoids combined (RR: 0.89; 95% CI: 0.80, 1.00; p<0.05), for quercetin (RR: 0.82; 95% CI: 0.71, 0.96; p<0.05) and for kaempferol (RR: 0.88; 95% CI: 0.78, 0.99; p<0.05), and a non-statistically significant reduction for luteolin (RR: 0.95; 95% CI: 0.67, 1.34; p>0.05) (Illustrations 5-8). These data suggest that people with diets rich in foods containing these flavonoids may reduce the risk of developing cancer by 5-18 % in relation to people with diets deficient in these foods.

Our meta-analysis of case-control studies revealed a strong and statistically significant reduction of overall cancer risk in populations with a high intake of flavonoids (OR: 0.73; 95% CI: 0.63, 0.84; p<0.01; Illustration 1). This reduction, however, was lower when cohort studies were analyzed (RR: 0.89; 95% CI: 0.80, 1.00; p<0.05; Illustration 5). The different nature of these two types of epidemiological observational studies might account for this variation. In case-control studies, history of exposure to flavonoids is estimated in people with cancer (cases) and without cancer (controls). In cohort studies, exposure to flavonoids is assessed for several years in a group of healthy people until a part of it develops the disease. Then, in both types of study, the percentage of people with cancer in the group with the lowest intake of the flavonoid is generally compared with that of the group with the highest intake. Although the difficulty of obtaining reliable information about flavonoid exposure is higher in case-control studies than in cohort studies, case-control studies usually consider much longer periods of exposure than cohort studies. The duration of the study is important because a short study with a short follow-up period may be inadequate to reveal the possible cancer preventive activity of a dietary constituent. For intance, a cohort study assessed the influence of multivitamin use in colon cancer risk and found that women who used multivitamins had no benefit with respect to colon cancer after 4 years of use (RR, 1.02) and had only non-significant risk reductions after 5-9 (RR, 0.83) or 10-14 (RR, 0.80) years of use. After 15 years of use, however, the risk was clearly lower (RR: 0.25; CI: 0.13, 0.51]) (Giovannucci et al. 1998). These data agree with the fact that cancer may take even

several decades to develop completely. For example, it is estimated that 5–20 years are necessary for normal colon cells to form adenomas and that these adenomas require 5–15 additional years to become an invasive colon cancer (O'Shaughnessy et al. 2002). Evidence suggests that the possible cancer preventive activity of diverse groups of dietary constituents, including flavonoids, may occur at the initial stages of carcinogenesis through their known antioxidant and antimutagenic activities (Calderon-Montano et al. 2011; Lopez-Lazaro, 2002; Lopez-Lazaro, 2009; Pietta, 2000). When an antimutagenic compound is taken by people with precancerous lesions, it may be unable to induce cancer preventive effects, as the precancerous cells of these people already have mutated genomes. This means that people from cohort studies who developed cancer a few years after the beginning of the study probably had mutations before flavonoid exposure started to be assessed. Therefore, assuming that the antimutagenic properties of flavonoids play an important role in their cancer preventive properties, some cohort studies may have overlooked, to some extent, the possible cancer preventive activity of flavonoids. This would not occur in case-control studies, which usually consider much longer period of exposure (history of exposure). In brief, unlike case-control studies, cohort studies generally consider relatively short periods of exposure to flavonoids and may have missed to some extent the possible cancer preventive activity of these dietary constituents. This may explain why our meta-analysis of case-control studies revealed a stronger relationship between exposure to the flavonoids quercetin, luteolin and kaempferol and reduced overall cancer risk than our meta-analysis of cohort studies.

Preclinical in vitro and in vivo studies support the association between a high consumption of the flavonoids quercetin, luteolin and kaempferol and a reduced overall cancer risk found in our meta-analysis of epidemiological studies. Numerous in vitro studies have shown that these three flavonoids have a variety of pharmacological activities involved in cancer prevention (e.g. antimutagenic, antioxidant and anti-inflammatory activities), some of which have been observed at submicromolar concentrations. In vivo experiments have also shown that these three flavonoids can prevent cancer in animal models of carcinogenesis (reviewed in Calderon-Montano et al. 2011; Kelly, 2011; Lopez-Lazaro, 2009). Limitations of the observational epidemiological studies analyzed in this article must be noted, however. The main limitation is the possible presence of other bioactive constituents (e.g. vitamins, minerals and other phytochemicals) in the flavonoid-rich foods used in the analyzed studies, which may participate in (or even mediate) the cancer preventive activity detected in our meta-analysis.

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Competing Interests

None

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