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Associations of Flavonoids Consumption with Cancer Risks among Populations: A Global Study

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ABSTRACT

Dietary flavonoids may have protective effects against cancerous development. Research to date established some relationships between flavonoids and cancer risks. However, no global approach has been used to explore these relationships. The main objective of the present study was to establish relationships between consumptions of flavonoids subclasses and relative risks of different cancers at global level. The cancer incidence data for 162 populations was obtained from WHO. The flavonoid intakes were derived from food consumption data FAO with USDA flavonoid databases. Multiple linear regression models were performed for flavonoid subclasses. A negative association existed between the consumption of total flavonoids and cancer incidence rates of liver and cervix uteri. Incidence rates of most cancers were positively correlated with the consumption of flavonols and flavan-3-ols. However, incidence rates of most cancers were negatively correlated with the consumption of flavones and theaflavin. A similar negative correlation existed between cervix uteri cancer and the consumption of anthocyanidin. Flavanones were positively correlated to prostate and lip with oral cavity cancers, whereas flavones were positively related to lip with oral cavity and pharynx cancers. At a global level, our findings suggested that low flavonol and flavan-3-ol, high theaflavin and flavone diets are desirable for prevention of most cancers. However, cancers of lip with oral cavity and pharynx *vs.* flavone and liver *vs.* flavan-3-ol are exceptions to this rule.

INTRODUCTION

Many factors, known and unknown, contribute to risks for cancers. Cancers are now the second leading cause of death throughout the world with potential increasing. Estimation of 10 million incidences of cancers around the world and 7 million deaths occurred in 2000[1-3]. Cancer deaths in the world are predicted to continue to increase to over 11 million in 2030[4].

Flavonoids have possible connections with human health, especially they may play a role in cancer development. There are more than 6,000 types of flavonoids that discovered[5]. They can be grouped into one of the following subclasses: (a) flavonols, (b) flavones, (c) flavanones, (d) flavan-3-ols, (e) anthocyanidins and (f) isoflavones[6,7]. Flavonoids may reduce the risk of different cancers[8]. Laboratory and epidemiological studies found that flavonoids involving in cancer prevention[9]. Flavonoids function as one of cancer prevention components because they have many mechanisms of action including antioxidant capacity, antimutagenic and antiproliferative capability, involvement in cell signaling, cell cycle regulation, and angiogenesis[10,11]. *In vitro* and animal model studies suggest that flavonoids influence signal transduction pathway[12,13], inhibit inflammation[14] and inhibit proliferation in human cancer cell lines[15]. For example, researchers in the Seven Countries Study found a relation between flavonoid intake and mortality from stomach cancer. It has been found that consumption of fruits and vegetables associated with a 50% reduction in respiratory tract cancer risk and flavonoids may play a major role in this[9]. Moreover, meta-analysis data suggested that 20 mg/day of flavonoids intake is associated with a 10% reduction in the risk of developing lung cancer. However, this is not true for all populations[16]. Research to date established some relationships between flavonoids and cancer risks. However, no global approach has been used to explore these relationships. Therefore, the objective of study is to establish relationships between flavonoid consumption and relative risks of different cancers.

METHODS

Data sources

Incidence data obtained from WHO, age-adjusted incidence rates of 26 types of cancers for a specific country per 100,000 people per year for 2008, which were estimated as the annual average for the most recent 5-year[17]. Two databases were used for calculating average flavonoid consumption for each country. First, the Food Balance Sheets Database-Food

Consumption Food Items is from FAO[18]. FAO estimated two-year average of per person available food items for human consumption for each country. However, the actual food consumption may be lower because of the magnitude of waste of food in the household. The amounts and types of consumed foods are estimated by the Government agencies of each country. The food consumption data was from 2006-2008. This database provides the food items with quantity for an average individual from each country expressed as grams per person per day (g/person/d). Flavonoid-containing foods include cereals, roots and tubers, honey, beans, nuts, oilcrops oils, vegetables, fruits, coffee, tea, coca, wine, beer and spices. Second, the United States Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods-Release 3 was published in September of 2011[19]. This database contains 500 foods with specific flavonoid values for 28 compounds from five classes: flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins. All values in the database were generated by HPLC, capillary zone electrophoresis, and micellar electrokinetic capillary chromatography. Values are reported as mg/ 100 g of fresh weight of edible portion of food, and values of beverages were reported as served. Then, food items in FAO were converted to USDA Standard Reference codes. Secondly, food items data were linked with the flavonoid database. However, some categories were not specified in the FAO database, the average flavonoid content from these categories were used in the calculation. Thirdly, the average flavonoid intakes for each country were calculated by multiplying the concentration of the individual flavonoid (mg/100g food) with the daily consumption (g/d) of the selected food item. Finally, estimated total intake of individual flavonoids is the sum of individual flavonoid intakes from all food sources.

Statistical analysis

Multiple linear regression analyses were performed by using SPSS software (IBM version 20) to assess the relationship between flavonoids intake and cancers incidence. In a multiple linear regression analysis, incidence rates were used as dependent variable and five flavonoid subclasses as independent variables with energy adjusted intake to address the quantity as well as quality of diet to test which subclasses of flavonoids significantly contribute to cancer risks. The level of significance was put at $p < 0.05$. Log-transformed variables, which are particularly appropriate for normalizing rates, were used for incidence data analyses [20].

RESULTS

The average intake of flavonoid in the world from 2006-2008 was 809.4 mg/person/day. Figure 1 and 2 show the global consumption patterns of total flavonoid, flavan-3-ols, anthocyanidins, flavanones, flavonols, flavones and theaflavin. African countries consumed much lower total flavonoids than the rest of the world. The highest total flavonoids consumption occurs mostly in South American and Europe (Figure 2). Flavonoid intake was highest in Paraguay at 4448.8 mg/d and lowest in Togo at 89.6 mg/d. Figure 2 shows that the higher flavan-3-ols consumption was among South American and European countries, flavone among Asian and Middle Eastern countries, theaflavin among South American countries, flavanone among Central American countries, anthocyanidin among Asian, European and Middle Eastern countries and flavonol among South American, Asian, European and Middle Eastern countries. Tea and cocoa beans were the major sources for flavan-3-ols. The high tea consumption in Paraguay, Uruguay and Argentina and the high cocoa bean consumption in Estonia placed these countries on the top of the chart for consumption of flavn-3-ols as vegetables and fruits did for anthocyanidins in China, Bosnia and Herzegovina and Greece; tea for theaflavins in Paraguay, Uruguay and Argentina; vegetables for flavonols in Paraguay, China and Uruguay; citrus fruits for flavanones in Belize and Bahamas; and spices for flavones in Nepal, Brunei Darussalam and Kuwait.

Table 1 shows the multiple regression coefficients between the log of different cancer incidence rates and consumption of flavonoids subclasses, energy adjusted. Flavonol consumption was found positively correlated with the cancer incidence rates of 17 following cancers: nasopharynx, colorectum, gallbladder, pancreas, larynx, lung, melanoma of skin, breast, corpus uteri, testis, kidney, bladder, brain with nervous system, thyroid, hodgkin lymphoma, multiple myeloma and leukaemia. Similarly, flavan-3-ol consumption showed positive correlation with the cancer incidence rates of 19 following cancers: lip with oral cavity, oesophagus, colorectum, pancreas, lung, melanoma of skin, breast, corpus uteri, ovary, prostate, testis, kidney, bladder, brain with nervous system, thyroid, hodgkin lymphoma, non-hodgkin lymphoma, multiple myeloma and leukaemia. However, flavan-3-ol consumption was found negatively correlated with the liver cancer incidence rates (*B*= -0.0003). Theaflavin consumption similarly was found negatively correlated with the cancer incidence rates of 18 following cancers: nasopharynx, colorectum, pancreas, lung, melanoma of skin, breast, corpus uteri, ovary, prostate, testis, kidney, bladder, brain with nervous system, thyroid, hodgkin lymphoma, non-hodgkin lymphoma, multiple myeloma and

leukaemia. Anthocyanidin consumption also showed only negative correlation (*B*= -0.001) with the cancer incidence rates of cervix uteri, prostate, non-hodgkin lymphoma and multiple myeloma. Flavones were also negatively correlated with following cancers: prostate, melanoma of skin, nasopharynx, testis, corpus uteri, liver, pancreas, bladder, kidney, brain with nervous system and hodgkin lymphoma. However, flavone consumption was found positively correlated with the lip with oral cavity and other pharynx cancer incidence rates. Flavanone consumption was also shown a positive correlation with the cancer incidence rates of prostate (*B*= 0.004) and lip with oral cavity, but negative correlation with the cancer incidence rates of other pharynx and stomach. It clearly demonstrated that consumption of flavan-3-ol is positively correlated with the largest number of cancers, followed by flavonol, flavones and flavanone. The most significant positive correlations were between the consumption of flavonol and cancers of colorectum and nasopharynx. On the other hand, the most significant negative correlations were between the consumption of flavone and prostate cancer, followed by nasopharynx and melanoma of skin cancers.

Table 1. Multiple regression coefficients between the log of different cancer incidence rates and consumption of flavonoid subclasses.

Variable	Flavonol	Flavone	Flavanone	Flavan-3-ol	Theaflavin	Anthocyanidin
Lip, oral cavity	-0.001	0.005*	0.001*	0.0002*	-0.0003	-0.0003
Nasopharynx	0.008*	-0.009*	-0.0005	0.0001	-0.001*	0.0001
Other pharynx	0.001	0.004*	-0.001*	-0.00004	-0.0001	-0.0002
Oesophagus	0.0003	-0.0003	-0.0005	0.0002*	-0.0003	0.0001
Stomach	0.001	-0.001	-0.002*	-0.00004	0.0003	0.0002
Colorectum	0.008*	-0.003	-0.001	0.001*	-0.001*	-0.0004
Liver	-0.002	-0.005*	-0.001	-0.0003*	0.0002	0.0003
Gallbladder	0.003*	0.001	-0.0003	0.00004	-0.0002	-0.0003
Pancreas	0.006*	-0.005*	-0.001	0.0003*	-0.001*	-0.0001
Larynx	0.003*	-0.002	-0.001	0.00005	-0.0002	0.0002
Lung	0.007*	-0.002	0.0001	0.0004*	-0.001*	0.0004
Melanoma of skin	0.005*	-0.009*	-0.0004	0.001*	-0.001*	-0.001
Breast	0.003*	-0.001	0.001	0.0003*	-0.001*	-0.0003
Cervix uteri	-0.003	-0.002	-0.00003	-0.0001	0.0003	-0.001*
Corpus uteri	0.007*	-0.006*	0.001	0.0005*	-0.001*	-0.0002
Ovary	0.002	0.001	0.0001	0.0003*	-0.0005*	-0.0002
Prostate	0.004	-0.012*	0.004*	0.001*	-0.001*	-0.001*
Testis	0.003*	-0.007*	0.0002	0.0004*	-0.001*	-0.0002
Kidney	0.005*	-0.005*	-0.001	0.0004*	-0.001*	0.00002
Bladder	0.006*	-0.005*	-0.001	0.0003*	-0.001*	-0.0001
Brain, nervous system	0.007*	-0.004*	-0.0004	0.0003*	-0.001*	-0.0001
Thyroid	0.004*	-0.002	0.0001	0.0002*	-0.001*	-0.0004
Hodgkin lymphoma	0.004*	-0.003*	-0.0005	0.0001*	-0.0005*	-0.0001
Non-Hodgkin lymphoma	0.002	-0.0004	-0.0004	0.0003*	-0.001*	-0.001*
Multiple myeloma	0.003*	-0.001	0.0004	0.0003*	-0.001*	-0.001*
Leukaemia	0.004*	-0.002	-0.0001	0.0002*	-0.001*	-0.0001

* indicates statistical significance at 0.05 level ($p < 0.05$).

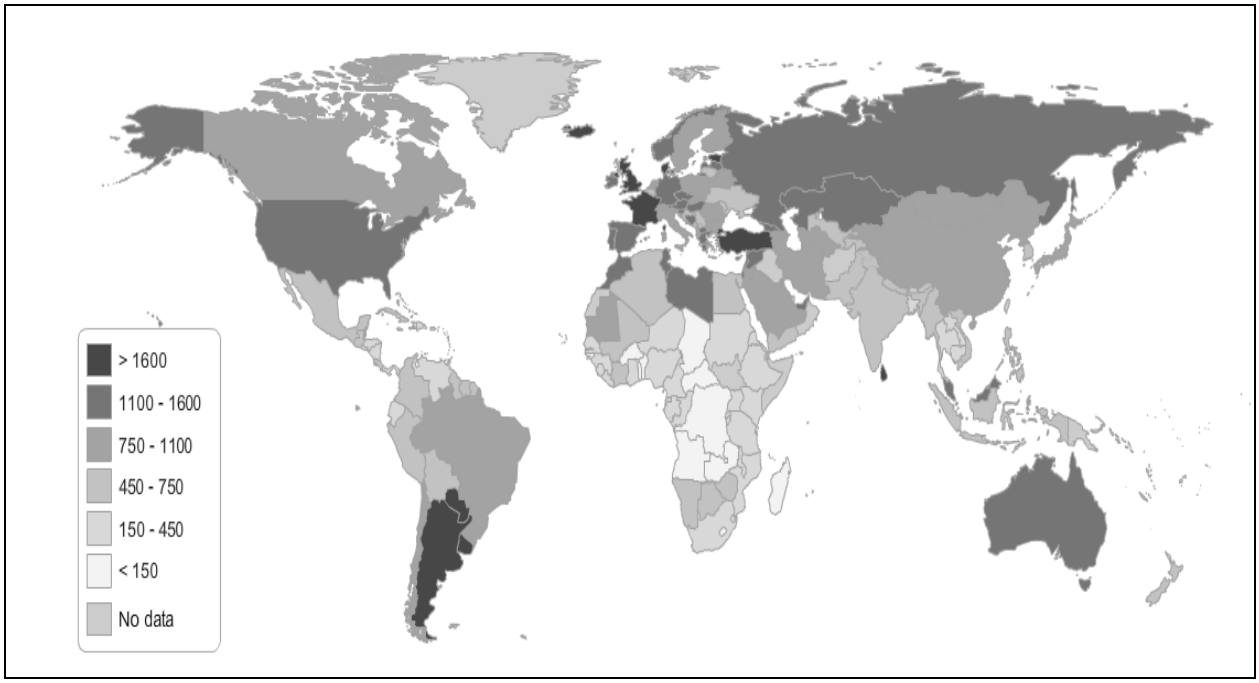

Figure1. Global dietary flavonoids consumption pattern (mg per person per day) from 2006-08.

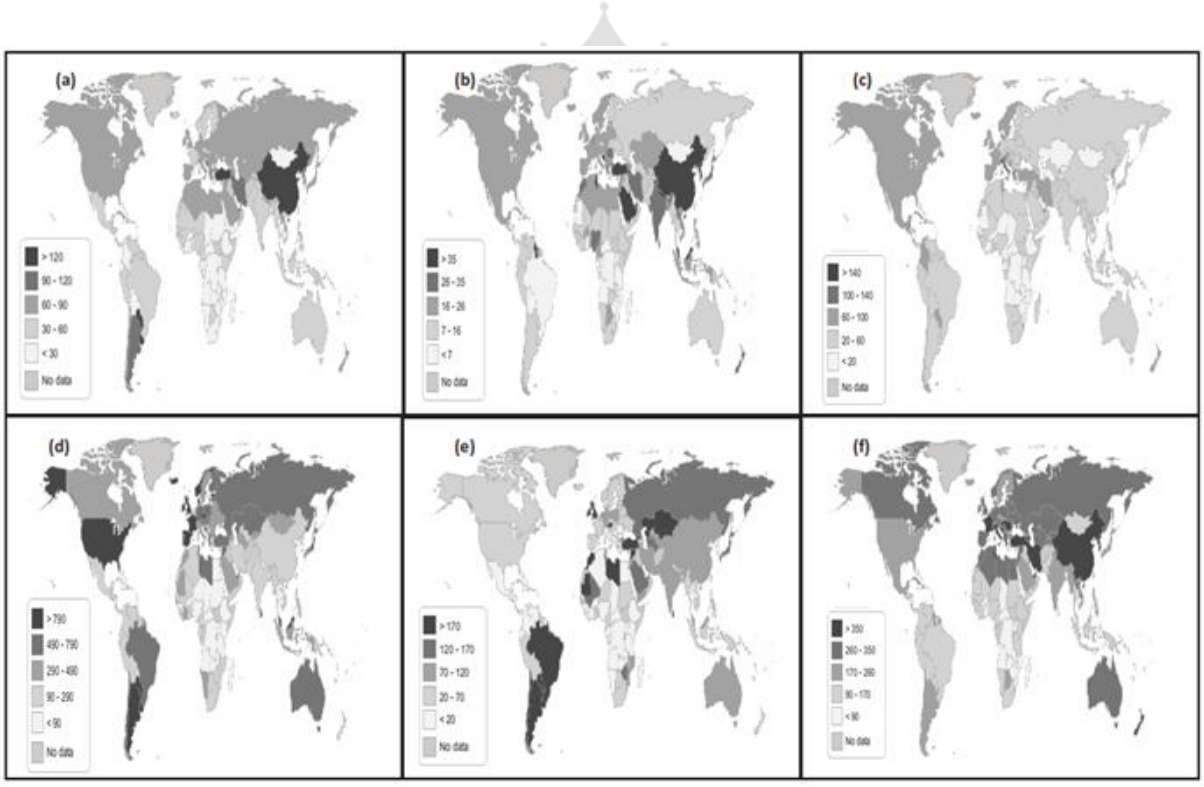

Figure 2. Global flavonoid consumption patterns (mg per person per day) from 2006-08. (a) flavonol; (b) flavone; (c) flavanone; (d) flavan-3-ol; (e) theaflavin and (f) anthocyanidin

DISCUSSION

Estimation of flavonoid intake from dietary sources has been conducted since the USDA released their database in 2003. Since that time, several studies have estimated the flavonoid intake in various populations or subgroups[21,22,23]. However, information is very limited on the worldwide flavonoid intake. This study provides the first global estimation of flavonoid intake for 162 countries (Figure 2). The worldwide of total flavonoids consumption was composed of mainly flavan-3-ols (47.7 %), anthocyanidins (27.8%), theaflavin (9.9%), flavonols (6.5 %), flavanones (5.8%), and flavones (2.4 %).

Flavan-3-ols were the top subclass of flavonoids consumed worldwide, which was strongly influenced by tea and cocoa consumption. The most significant positive correlations of flavan-3-ol consumption were with incidence rates of following cancers: colorectum, prostate and melanoma of skin. The present study does not support the previous findings of a 12 month follow-up study suggesting that green tea catechins consumption has a negative association with the prostate cancers risk[24]. However, our study is a multivariable adjusted model of all flavonoids subclasses, while Bettuzzi et al.[24] only studied the association of green tea catechins with prostate cancer. The Netherlands Cohort Study failed to find any relationship between catechin consumption and the risk of colorectum cancer[25]. However, the present study shows a slight positive correlation between flavan-3-ol consumption and the above cancers incidence rates. Conversely, flavan-3-ols consumption has been negatively related to liver cancer in a cohort study from 10 Western European countries [26] and in *in vitro* model[27], which seem to be consistent with the present study.

The next rank subclass of flavonoid intake was anthocyanidins, which was strongly influenced by vegetables and fruits consumption. Frankenfeld et al.[28] concluded in their case-control study that high anthocyanidin and other flavonoids consumption is associated with decreased risks for non-hodgkin lymphoma cancer. An *in vitro* study by Rugină et al.[29] demonstrated anthocyanidin's anticancer effects on cell lines of cervix and uteri cancers. Reddivari et al.[30] were also able demonstrate the same effects on prostate cancers using *in vitro* and *in vivo* models. Our study conclusions are consistent with these observations.

Our study has discovered that consumption of theaflavins, a major class of flavonoids found in tea, was inversely correlated with the incidence rates of several cancers. These observations are generally consistent with studies in the literature. These studies includes a

breast cancer cell culture study[31], ovary cancer *in vitro* model[32], prostate cancer studies using animals and humans[33,34], melanoma animal study[35], thyroid cancer cell culture study[36] and lung and leukaemia cell culture study[37].

In this study, the strongest positive correlations were between flavonol, which was strongly influenced by vegetable consumption, and the incidence rates of colorectum and lung cancers. This is inconsistent with what were reported in literature. A multicentric Italian case-control study[25] and Netherlands cohort study[25] found no association with the risk of colorectal cancer. In addition, two Finland studies found negative correlations between consumption of flavonol and lung cancer risks[38,39]. It is not known why these inconsistencies exist. It is possible that these other studies were on a single population while our study was international in nature.

Our study has discovered that consumption of flavanones, which were strongly influenced by citrus fruits consumption, were inversely correlated with the incidence rates of pharynx and stomach cancers. These findings were in general agreement with studies in the literature. An Italian case-control study by Rossi et al.[40] found negative correlation between flavanones consumption and the risk of pharynx cancer. A Greek case-control study by Lagiou et al.[41] also found the same correlation with stomach cancer. However, our study showed that flavanone consumption was positively correlated with prostate cancer incidence rates. This finding is inconsistent with some studies in the literature. Rajkapoor et al.[42] concluded in *in vitro* model study that isolated flavanone may offer protective effects against human tumor cell lines including prostate cancer. Conclusions are often not comparable between an epidemiological study and an *in vitro* study. So far, no other epidemiological studies on the effects of flavanones on prostate cancer are in the literature.

Flavones, where spices serving as the largest contributor, were negatively correlated with the cancer incidence rates of melanoma, liver, pancreas, bladder and prostate. These findings are generally consistent with the studies in the literature. An animal study by Birt et al.[43] found similar effects of flavones on melanoma. A Greek case-control study and a cohort study from 10 Western European countries also found similar effects on liver cancer[44,26]. Similar findings were from an *in vivo* study on pancreas cancer[45] and an *in vivo* study on bladder cancer[46]. Shukla et al. [47] also found that increased intake of apigenin, a flavone, decreased tumor volumes of the prostate in *in vivo* model.

This study has several limitations. First, the difference between availability and consumption since dietary intake data from FAO estimated the national availability of food. However, these differences exist among all nations and the nutrient estimates are valid. Secondly, although all cares were taken to ensure the accuracy of flavonoid intake estimation, the true intakes for each country are subject to errors. These errors are caused by several factors including differences in growing conditions influenced by geographic location and potential flavonoid retention differences caused by different cooking/processing methods influenced by cultures. Finally, these associations discovered by this study do not necessarily indicate the causation relationships between flavonoids and cancers because of genetic and environmental factors involving.

CONCLUSION

In summary, our study with global statistics has confirmed the important roles of flavonoids in cancer development. European and part of South American countries tend to have higher consumption of total flavonoids and flavan-3-ols. The higher flavone consumption was among Asian and Middle Eastern countries, theaflavin among South American countries, flavanone among Central American countries, anthocyanidin among Asian, European and Middle Eastern countries and flavonol among South American, Asian, European and Middle Eastern countries. Our study demonstrated that incidence rates of most cancers were positively correlated with the consumption of flavonols. The same was true for flavan-3-ols, but to a lesser degree. However, incidence rates of most cancers were negatively correlated with the consumption of flavone. The same was true for theaflavin but to a lesser degree. A similar negative correlation existed between cervix uteri cancer and the consumption of anthocyanidin. Flavanones were positively correlated to prostate and lip with oral cavity cancers, whereas flavones were positively related to lip with oral cavity and pharynx cancers. This global study agreed that theaflavin, flavones and anthocyanidin intakes are associated with a reduced risk of most cancers. Despite previous studies findings, our data did not suggest the protective effect of flavonol and flavan-3-ol in most cancers. Our findings suggest that low flavonol and flavan-3-ol, high theaflavin and flavone diets are desirable for prevention of most cancers. However, cancers of lip with oral cavity and pharynx *vs.* flavone and liver *vs.* flavan-3-ol are exceptions to this rule. It is premature to make public health recommendations at this time. These important relationships established here will provide

further support to public health efforts aiming to reduce the incidence of cancer around the world.

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