ELSEVIER

Biomed Pharmacother 56 (2002) 296–301

& BIOMEDICINE PHARMACOTHERAPY

Dossier: Polyphenols: diversity and bioavailability

Cancer preventive effects of flavonoids—a review

Loïc Le Marchand *

Epidemiology Section, Etiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Suite 407, Honolulu, HI 96813, USA

Abstract

A cancer protective effect from plant-derived foods has been found with uncommon consistency in epidemiologic studies. However, it has been difficult to identify specific components responsible for this effect. Many phytochemicals have been shown to be biologically active and they may interact to protect against cancer. In recent years, experimental studies have provided growing evidence for the beneficial action of flavonoids on multiple cancer-related biological pathways (carcinogen bioactivation, cell-signaling, cell cycle regulation, angiogenesis, oxidative stress, inflammation). Although the epidemiologic data on flavonoids and cancer are still limited and conflicting, some protective associations have been suggested for flavonoid-rich foods (soy and premenopausal breast cancer; green tea and stomach cancer; onion and lung cancer). This review focuses on the biological effects of the main flavonoids, as well as the epidemiologic evidence that support their potential cancer protective properties.

1. Introduction

The scientific evidence that plant-based diets, in particular those rich in vegetables and fruits, protect against cancers of various sites has been found to be strong and consistent by a recent expert panel [1]. This effect may result from the low energy content of these diets and/or from their specific constituents. Although plant-derived foods vary in their nutritional composition profiles, they generally are good sources of important nutrients (i.e., fiber, carotenoids, vitamin C, folate, minerals) and of many less well-characterized bioactive compounds (phytochemicals). Accordingly, public health authorities have uniformly emphasized the potential benefits of fruits and vegetables in their recommendations to the public. Moreover, the identification of the specific constituents of these foods that are protective may lead to additional means of prevention, such as the fortification of the food supply (e.g., folate), the use of chemopreventive agents in high risk individuals and the engineering of “designer foods” enriched in protective compounds.

However, the identification of the protective constituents in plant-derived foods can be problematic, as illustrated by the chemoprevention research conducted with beta-carotene. This pro-vitamin A carotenoid has been found to be inversely associated with cancer risk in epidemiologic studies and showed promising results in laboratory studies [2]. Early on, this nutrient was singled out for randomized chemoprevention trials among individuals at high risk (smokers, asbestos-exposed workers) or low risk (US physicians) for lung cancer [3-5]. The results of these large beta-carotene trials have been disappointing as they showed no beneficial effect, and even, in high risk individuals, a detrimental effect, on lung cancer incidence [3-5]. However, it has been apparent for some time, that the association with beta-carotene is difficult to distinguish from that of vegetables in observational dietary studies and that, indeed, similar associations can be demonstrated between cancer and other phytochemicals. For example, in a case-control study in Hawaii, we found inverse associations of lung cancer with total intakes of vegetables and subgroups of vegetables particularly rich in other phytochemicals (dark green vegetables, cruciferous vegetables, tomatoes, carrots) that were stronger than that with beta-carotene [6]. We also found independent associations of similar magnitude with other carotenoids (lutein, alpha-carotene) [7]. These various active components may interact additively or synergistically to protect against cancer. Thus, it may be more productive to study the preventive effect of entire foods than that of single

* Corresponding author.

PII: S0753-3322(02)00186-5

Table 1
Classification of flavonoids and their food sources

Subclass	Flavonoids	Food sources
Flavones	Apigenin, luteolin	Apple skin, celery
Flavonols	Quercetin, kaempferol, myricetin	Onions, apples, tea
Flavanols	Catechin, epicatechin, epigallocatechin gallate	Tea
Flavanones	Hesperitin, naringenin	Citrus fruits, grapefruit
Anthocyanins	Cyanidin	Berries
Isoflavones	Genistein, daidzein	Soy

nutrients which may, especially at non-physiological dose, have different properties than when given as part of food matrix in a regular diet. Indeed, recent experimental studies have shown that, in some circumstances, beta-carotene may act as a pro-oxidant [8].

2. Flavonoids in the diet

Flavonoids are the most common and widely distributed group of plant phenolics [9]. Over 5000 different flavonoids have been described to date and they are classified into at least 10 chemical groups [9]. Among them, flavones, flavonols, flavanols, flavanones, anthocyanins and isoflavones are particularly common in the diet. The most-studied members of these groups are included in Table 1, along with some of their food sources.

Flavonols are the most abundant flavonoids in foods, with quercetin, kaempferol and myricetin being the three most common flavonols. Flavanones are mainly found in citrus fruit and flavones in celery. Catechins are present in large amounts in green and black tea and in red wine, whereas anthocyanins are found in strawberries and other berries. Isoflavones are almost exclusively found in soy foods.

Flavonoids are heat stable, and losses due to cooking and frying are relatively low [10]. It is usually thought that flavonoids are absorbed by passive diffusion after glycosylated flavonoids are converted to their aglycones. The colon microflora would play an important role in this conversion. The bioavailability of flavonoids is only partial with the proportion of the ingested amount that is absorbed varying from 0.2% to 0.9% for tea catechins to 20% for quercetin and isoflavones [11,12]. Thus, a large fraction remains unabsorbed and the gastrointestinal mucosa is exposed to particularly high concentrations of these compounds. After absorption, the flavonoids are conjugated in the liver by glucuronidation, sulfation or methylation or metabolized to smaller phenolic compounds [13].

Attempts to assess daily intake of flavonoids in various populations (based on food composition values for a subset of flavonoids: quercetin, kaempferol, myricetin, apigenin and luteolin) has yielded estimates that vary between 3 mg in Finland to 20 mg in Holland and the United States, and 68 mg in Japan [14]. However, tea drinkers may have a much greater intake since the average flavonoid intake from tea alone in the UK has been estimated to be 430 mg/d (based on a population average consumption of 3.3 cups of tea per day) [15]. Flavonoid intake is only weakly correlated with intakes of micronutrients, such as vitamins A and C, enabling one to study the association of flavonoids and disease in epidemiological studies without the pitfall of multicollinearity. However, the flavonoid content of foods often varies by variety, season, storage condition, method of preparation, and by part of the plant [16]. Furthermore, the bioavailability of certain flavonoids differs markedly depending on the food source. For example, the absorption of quercetin from onions has been shown to be four-fold greater than from apples or tea [17]. The limited food composition data available to date do not take these factors into account and, thus, their use may introduce significant measurement error in dietary studies. Hence, until food composition data are substantially improved, it may be preferable to focus on flavonoid food sources rather than specific flavonoids when investigating their associations with disease risk.

3. Effects of flavonoids on cancer-related biological pathways

A number of flavonoids have been shown to suppress carcinogenesis in various animal models [18]. There is currently considerable interest in these compounds as they appear to exert a beneficial effect on several key mechanisms involved in the pathogenesis of cancer. The antioxidant property of flavonoids was the first mechanism of action studied, in particular with regard to their protective effect against cardiovascular diseases. Flavonoids have been shown to be highly effective scavengers of most types of oxidizing molecules, including singlet oxygen and various free radicals [13], which are possibly involved in DNA damage and tumor promotion [19].

Flavonoids may also have a beneficial effect through their impact on the bioactivation of carcinogens. Most chemical carcinogens require transformation by phase I metabolizing enzymes into a more reactive form able to bind to DNA. If the resulting mutation is not repaired, it

may initiate or promote the carcinogenesis process. The reactive chemical group introduced by phase I enzymes (or the original carcinogen) can be detoxified through conjugation by phase II metabolizing enzymes into a water-soluble compound which can then be eliminated from the body. The flavonols quercetin, kaempferol and galangin, and the flavone apigenin have been shown to inhibit cytochrome P450 enzymes of the CYP1A family [20-23]. These enzymes play a major role in the activation of a number of suspected human carcinogens, such as polycyclic hydrocarbons and heterocyclic amines. Quercetin and naringin have also been shown to inhibit CYP3A4 and to contribute to the suppressive effect of grapefruit juice on this enzyme [23,24]. CYP3A4 is the most abundant P450 enzyme in the liver and metabolizes a significant number of carcinogens and medications. In addition, animal and in vitro studies have shown that tea catechins increase the activity of several detoxifying and antioxidant enzymes, such as glutathione reductase, glutathione peroxidase, glutathione *S*-reductase, catalase, and quinone reductase [25,26].

Various flavonoids (e.g., quercetin, apigenin, tea catechins) have also been shown to have anti-inflammatory activity by inhibiting cycloxygenase-2 (COX2) and inducible nitric oxide synthase [27,28]. Chronic inflammation is thought to play an important role in the etiology of a number of cancers and COX-2 inhibitors are being studied as chemopreventive agents against colorectal cancer.

A growth inhibitory activity has been demonstrated for various flavonoids on several human cancer cell lines. In estrogen-dependent tumor cells or animal models, this anti-proliferative effect has been related to the anti-estrogenic properties of certain flavonoids (e.g., isoflavonoids, quercetin) [29]. In other in vitro models, flavonoids have also been shown to affect cell-signaling and cell cycle progression. For example, tea flavonoids inhibit signal transduction pathways mediated by epidermal growth factor and platelet-derived growth factor, favorably affecting downstream events such as angiogenesis [15]. Genistein and quercetin inhibit protein tyrosine kinase which is also involved in cell proliferation [30,31]. Finally, apigenin, luteolin and quercetin have been shown to cause cell cycle arrest and apoptosis by a p53-dependent mechanism [32].

In summary, multiple mechanisms have been identified for the anti-neoplastic effects of flavonoids, including anti-oxidant, anti-inflammatory and anti-proliferative activities, inhibition of bioactivating enzymes, and induction of detoxifying enzymes. However, these effects were often obtained with concentrations which are greater than what can be achieved in humans through dietary means [18]. Furthermore, these experiments typically used the parent compounds (unconjugated flavonoids). Only limited data are available on the biological activities of the conjugated flavonoids or their downstream metabolites which are more abundant in the circulation than the parent compounds after ingestion of flavonoid-rich foods.

4. Evidence for a cancer protective effect of flavonoids

4.1. Soy products and breast cancer

Soy products are the predominant source of isoflavonoids in the diet. Many animal studies have shown a protective effect for these foods against mammary tumors [33]. Administration of genistein early in life enhances the early maturation and differentiation of the mammary gland of rats, which may be an important mechanism for the tumor inhibiting effect of soy [33]. A high isoflavone diet has also been shown to inhibit tumorigenesis in several animal models for prostate cancer [33].

Although Asian countries, such as Japan and China, differ in many potentially relevant ways from western countries, their high soy consumption and low incidence for breast and prostate cancers are consistent with the protective effect of soy foods against these cancers. Several epidemiological studies have attempted to test these hypotheses more directly. Case-control studies in Singapore and Japan have shown a reduced risk of premenopausal breast cancer in high consumers of soy products [34,35]. However, this result failed to be replicated in a 1995 case-control study in China and in a prospective study of Japanese atomic bomb survivors [36,37]. A decreased risk of breast cancer was also found in Asian American women who consumed high amounts of tofu [38]. However, this association was limited to those women who were born in Asia, suggesting that exposure during early life may be important. A recent study conducted in Shanghai examined soy intake retrospectively during adolescence, as well as in adult life, and found an inverse association for both [39]. In contrast, the case-control studies conducted among white North American women, who on the average have a much lower soy intake, have not been as suggestive as the Asian studies. Thus, overall, case-control studies have provided some support to the hypothesis, especially those conducted among Asian women. However, it is difficult to make strong inferences based on case-control studies, since they are particularly susceptible to selection and recall biases. Also, the effect observed with soy products could be due to other constituents of the Asian diet or other lifestyle factors correlated with soy intake. Additional studies, especially prospective in design, are clearly needed. Fewer studies are available on the relationship between soy intake and prostate cancer. However, frequent consumption of soy milk and tofu has been associated with lower incidence of prostate cancer in prospective studies of Seventh Day Adventists and Japanese, respectively [40,41].

4.2. Tea and cancer

Tea is an important source of flavanols and flavonols. A large number of experimental studies suggest an anti-neoplastic effect for tea polyphenols [18]. Several epidemiological studies conducted in Asia have also shown a protective effect of green tea on stomach cancer, although a number of other studies have found no association [42]. In one of the most carefully conducted studies to date, Yu et al. [43] assessed the type of tea, age when tea drinking started, frequency of new batches of tea leaves per day, number of cups from each batch, duration per batch, and strength and temperature of the tea. Risk of stomach cancer in this Chinese study decreased with increasing number of batches of green tea prepared per day. In a recent case-control study reported from Japan, consumption of seven or more cups a day of green tea was associated with a 31% lower risk of stomach cancer [44]. Consistent with these data, high green tea consumption was also found to be associated with a reduction in risk of precancerous chronic atrophic gastritis [45]. Black tea was also found to be inversely associated with stomach cancer among women in a population-based case-control study in Poland [46]. However, no association was found in men in that study [46] and an absence of association between black tea and cancer was also reported in two prospective studies, respectively, conducted among postmenopausal women in Iowa [47] and men and women in the Netherlands [48]. In the latter study, site-specific analyses showed no association for lung, colorectal, breast and stomach cancers [48]. Thus, in contrast to the experimental evidence which is relatively strong, the epidemiological evidence for a protective effect of tea against cancer is weak and inconsistent, with the exception of stomach cancer for which suggestive findings have been reported. Additional studies are needed, preferentially using a prospective design and collecting detailed information on tea consumption patterns. Studies using intermediate end points may also contribute helpful data. For example, Shim et al. [49] have recently reported that the frequency of sister chromatid exchange in mitogen-stimulated peripheral lymphocytes from smokers consuming green tea (2–3 cups/d for 6 months) was comparable to that of non-smokers and significantly lower than that of smokers.

4.3. Other flavonoid-rich foods and cancer

Only limited epidemiologic data are available on the potential cancer protective effect of flavonoids other than from soy and tea. A Dutch cohort study on elderly men found an inverse association between flavonoid intake from fruit and vegetable sources and cancers of the respiratory and alimentary tracts combined [50]. A larger cohort study of 10,000 Finnish men and women followed for over 20 years also found a halving of lung cancer risk for subjects in the highest compared to the lowest quartile of flavonoid intake [51]. This association was not due to tea consumption or to confounding by smoking or intake of antioxidant vitamins (vitamin E, vitamin C, beta-carotene). The main source of flavonoids in this population (apples) was also significantly inversely associated with risk [51]. Early results from another cohort study in the Netherlands, which followed 120,852 men and women for 3 years, also were suggestive of an inverse association with onion intake [52]. However, this association was reduced after adjustment for smoking. In a population-based case-control study in Hawaii, we observed inverse associations between lung cancer risk and intakes of onions, apples, and white grapefruits, as well as of quercetin [53]. Since no clear association was found for garlic, the association with onions did not appear to be due to their high content in organosulfur compounds (also present in garlic).

5. Conclusion

The experimental data accumulated, particularly in the past three years, have demonstrated a wide variety of biological actions for flavonoids which may be beneficial against cancer. However, it is not clear whether these effects would also be present at physiological concentrations and for the metabolites that are likely to be most relevant to humans. The epidemiological evidence that would support a cancer protective effect is still limited and has so far been quite inconsistent. However, a few relationships have emerged, such as possible inverse associations between soy intake (possibly early in life) and premenopausal breast cancer, green tea consumption and stomach cancer, and onion and apple intakes and lung cancer. However, much more data are needed before any of these associations can be used to support specific health recommendations. Studies in humans that would particularly be useful include prospective studies testing the association of flavonoid intake with cancer incidence, as well as biomarker studies testing the effect of specific flavonoid-rich foods on relevant biological pathways, such as biotransformation of carcinogens, DNA damage, cell proliferation, apoptosis and inflammation.

Acknowledgements

This work was supported in part by grant 5-R01-CA85997 from the US National Cancer Institute.

References

[1] World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective. 1997.

[2] Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? Nature 1981;290:201–8.

[3] The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.

[4] Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta-carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.

[5] Hennekens CH, Burling JE, Manson JE, et al. Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996;334:1145–9.

[6] Le Marchand L, Yoshizawa CN, Kolonel LN, Hankin JH, Goodman MT. Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii. J Natl Cancer Inst 1989;81:1158–64.

[7] Le Marchand L, Hankin JH, Kolonel LN, Beecher GR, Zhao LP. Intake of specific carotenoids and lung cancer risk. Cancer Epidemiol Biomarkers Prev 1993;2:183–7.

[8] Mayne ST, Handelman GJ, Beecher G. Beta-Carotene and lung cancer promotion in heavy smokers–a plausible relationship? J Natl Cancer Inst. 1996;88:1513–5.

[9] Harbone JB, editor. The flavonoids. Advance in research since 1986. London: Chapman & Hall; 1993.

[10] Hertog MG, Hollman PCH, Katan MB, et al. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. Nutr Cancer 1993;20:21–9.

[11] Hollman PCH, de Vries JHM, van Leeuwen SDD, Mengelers MJB, Katan MB. Absorption of dietary quercetin in healthy ileostomy volunteers. Am J Clin Nutr 1995;62:1276–82.

[12] Lee M- J, Wang ZY, Li H, et al. Analysis of plasma and urinary tea polyphenols in human subjects. Cancer Epidemiol Biomarkers Prev 1995;4:393–9.

[13] Bravo L. Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. Nutr Rev 1998;11:317–33.

[14] Hertog MGL, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med 1995;155:381–6.

[15] Wiseman S, Nulder T, Rietveld A. Tea flavonoids: bioavailability in vivo and effects on cell signaling pathways in vitro. Antioxidants Redox Signaling 2001;3:1009–21.

[16] Hermann K. Flavonols and flavones in food plants: a review. J Food Technol 1976;11:433–42.

[17] Hollman PC, Trijp van JM, Buysman MN, Gaag van der MS, Mengelers MJ, Vries de JH, et al. Relative bioavailability of the antioxidant flavonoid quercetin from various foods in man. FEBS Lett 1997;418:152–6.

[18] Yang CS, Landau JM, Huang M- T, Newmark HL. Inhibition of Carcinogenesis by dietary polyphenolic compounds. Annu Rev Nutr 2001;21:381–406.

[19] Cerutti PA. Prooxidant states and tumor promotion. Science 1985;227:375–81.

[20] Lautraite S, Musonda AC, Doehmer J, Edwards GO, Chipman JK. Flavonoids inhibit genetic toxicity produced by carcinogens in cells expressing CYP1A2 and CYP1A1. Mutagenesis 2002;17:45–53.

[21] Ciolino HP, Daschner PJ, Yeh GC. Dietary flavonols quercetin and kaempferol are ligands of the aryl hydrocarbon receptor that affect *CYP1A1* transcription differentially. Biochem J 1999;348:715–22.

[22] Kang ZC, Tsai SJ, Lee H. Quercetin inhibits benzopyrene-induced DNA adducts in human Hep G2 cells by altering cytochrome *P*-450 1A1 gene expression. Nutr Cancer 1999;35:175–9.

[23] Muto S, Fujita K- I, Yamazaki Y, Kamataki T. Inhibition by green tea catechins of metabolic activation of procarcinogens by human cytochrome P450. Mutation Res 2001;479:197–206.

[24] Ho PC, Saville DJ. Inhibition of human CYP3A4 activity by grapefruit flavonoids, furanocoumarins and related compounds. J Pharm Pharmaceut Sci 2001;4:217–27.

[25] Khan SG, Katiyar SK, Agarwal R, Mukhtar H. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. Cancer Res 1992;52:4050–2.

[26] Valerio Jr LG, Kepa JK, Pickwell GV, Quattrochi LC. Induction of human NAD(P)H:quinone oxidoreductase (NQO1) gene expression by the flavonol quercetin. Toxicol Lett 2001;119:49–57.

[27] Raso GM, Meli R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sci 2001;68:921–31.

[28] Mutoh M, Takashi M, Fukuda K, Komatsu H, Enya T, Masushima-Hibiya Y, Mutoh H, Sugimura T, Wakabayashi K. Suppression by flavonoids of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells: structure-activity relationship. Jpn J Cancer Res 2000;91:686–91.

[29] Miodini P, Fioravantio L, Di Fronzo G, Cappelletti V. The two phyto-oestrogens genistein and quercetin exert different effects on oestrogen receptor function. Br J Cancer 1999;80:1150–5.

[30] Akiyama T, Ishida J, Nikagawa H, Watanabe S, Itoh N, Shibuy AM, Fukamo Y. Genistein. A specific inhibitor of tyrosine-specific protein kinases. J Biol Chem 1987;262:5592–5.

[31] So FV, Guthrie N, Chambers AF, Moussa M, Carroll KK. Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices. Nutr Cancer 1996;26:167–81.

[32] Plaumann B, Fritsche M, Rimpler H, Brandner G, Hess RD. Flavonoids activate wild-type p53. Oncogene 1996;13:1605–14.

[33] Messina MJ, Persky V, Setchell KD, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr Cancer 1994;21:113–31.

[34] Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE. Dietary effects on breast cancer risk in Singapore. Lancet 1991;337:1197–200.

[35] Hirose K, Tajima K, Hamajima N, Inoue M, Takezaki T, Kuroishi T, et al. A large-scale, hospital-based case-control study of risk factors of breast cancer according to menopausal status. Jpn J Cancer Res 1995;86:146–54.

[36] Yuan JM, Wang QS, Ross RK, Henderson BE, Yu MC. Diet a breast cancer in Shanghai and Tianjin, China. Br J Cancer 1995;71:1353–8.

[37] Key TJ, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, et al. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. Br J Cancer 1999;81:1248–56.

[38] Wu AH, Ziegler RG, Horn-Ross PL, Nomura AM, West DW, Kolonel LN, et al. Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol Biomarkers Prev 1996;5:901–6.

[39] Shu XO, Jin F, Dai Q, Wen W, Potter JD, Kushi LH, et al. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. Cancer Epidemiol Biomarkers Prev 2001;10:483–8.

[40] Severson RK, Nomura AMY, Grove JS, et al. A prospective study of demographics, diet and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res 1989;49:1857–60.

[41] Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (. United States). Cancer Causes Control 1998;9:553–7.
[42] Bushman JL. Green tea and cancer in humans: a review of the literature. Nutr Cancer 1998;31:151–9.
[43] Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, Jin TH. Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China. Cancer Causes Control 1995;6:532–8.
[44] Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. Cancer Causes Control 1998;9:209–16.
[45] Shibata K, Moriyama M, Fukushima T, Kaetsu A, Miyazaki M, Une H. Green tea consumption and chronic atrophic gastritis: a cross-sectional study in a green tea production village. J Epidemiol 2000;10:310–6.
[46] Chow WH, Swanson CA, Lissowska J, Groves FD, Sobin LH, Nasierowska-Guttmejer A, Radziszewski J, Regula J, Hsing AW, Jagannatha S, Zatonski W, Blot WJ. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. Int J Cancer 1999;81:871–6.
[47] Zheng W, Doyle TJ, Kushi L, et al. Tea consumption and cancer incidence in a prospective study of postmenopausal women. Am J Epidemiol 1996;144:175–82.
[48] Goldbohm RA, Hertog MGL, Brants HAM, et al. Consumption of black tea and cancer risk: a prospective cohort study. J Natl Cancer Inst 1996;88:93–100.
[49] Shim JS, Kang MH, Roh JK, Roberts C, Lee IP. Chemopreventive effect of green tea (*Camellia sinensis*) among cigarette smokers. Cancer Epidemiol Biomarkers Prev 1995;4:387–91.
[50] Hertog MGL, Feskens EJM, Hollman PCH, et al. Dietary flavonoids and cancer risk on the Zutphen elderly study. Nutr Cancer 1994;22:175–84.
[51] Knekt P, Jarvinen R, Seppanen R, et al. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997;146:223–30.
[52] Dorant E, den Brandt P, Goldbohm RA. A prospective cohort study on Allium vegetable consumption, garlic supplement use, and the risk of lung carcinoma in the Netherlands. Cancer Res 1994;54:6148–53.
[53] Le Marchand L, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN. Intake of flavonoids and lung cancer. J Natl Cancer Inst 2000;92:154–60.