Flavonoids and Breast Cancer Risk in Italy

Cristina Bosetti,[1] Luana Spertini,[1] Maria Parpinel,[2,3] Patrizia Gnagnarella,[4] Pagona Lagiou,[5] Eva Negri,[1] Silvia Franceschi,[6] Maurizio Montella,[7] Julie Peterson,[8] Johanna Dwyer,[9] Attilio Giacosa,[10] and Carlo La Vecchia[1,11]

[1]Istituto di Ricerche Farmacologiche ''Mario Negri'', Milan, Italy; [2]Unità di Epidemiologia e Biostatistica, Centro di Riferimento Oncologico, Aviano (PN), Italy; [3]Instituto di Igiene ed Epidemiologia, Policlinico Universitario di Udine, Udine, Italy; [4]Divisione di Epidemiologia e Biostatistica, Istituto Europeo di Oncologia, Milan, Italy; [5]Department of Hygiene and Epidemiology, University of Athens Medical School, Athens, Greece; [6]International Agency for Research on Cancer, Lyon, France; [7]Servizio di Epidemiologia, Istituto Tumori ''Fondazione Pascale'', Naples, Italy; [8]Frances Stern Nutrition Center, Tufts-New England Medical Center, Boston, Massachusetts; [9]Schools of Medicine, Nutrition, and the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts; [10]Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy; and [11]Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy

Abstract

Few epidemiologic studies have investigated the potential relation between flavonoids and breast cancer risk. We have applied recently published data on the composition of foods and beverages in terms of six principal classes of flavonoids (i.e., flavanones, flavan-3-ols, flavonols, flavones, anthocyanidines, and isoflavones) on dietary information collected in a large-case control study of breast cancer conducted in Italy between 1991 and 1994. The study included 2,569 women with incident, histologically confirmed breast cancer, and 2,588 hospital controls. Odds ratios (OR) and 95% confidence intervals were estimated by multiple logistic regression models. After allowance for major confounding factors and energy intake, a reduced risk of breast cancer was found for increasing intake of flavones (OR, 0.81, for the highest versus the lowest quintile; *P*-trend, 0.02), and flavonols (OR, 0.80; *P*-trend, 0.06). No significant association was found for other flavonoids, including flavanones (OR, 0.95), flavan-3-ols (OR, 0.86), anthocyanidins (OR, 1.09), as well as for isoflavones (OR, 1.05). The findings of this large study of an inverse association between flavones and breast cancer risk confirm the results of a Greek study. (Cancer Epidemiol Biomarkers Prev 2005;14(4):805–8)

Introduction

Flavonoids are polyphenols present in vegetables, fruit, and beverages of plant origin which have antioxidant, antimutagenic, and antiproliferative properties (1-5). They may thus have a potential protective role in various chronic diseases, including common cancers (6-9), and explain, at least in part, the well-established associations between high consumption of vegetables and fruit and reduced risk of several neoplasms (10, 11).

With reference to breast cancer, particular interest has been given to the investigation of the relation with isoflavones, contained mainly in soy products, given their antiestrogenic effects, and their consequent potential role in breast cancer prevention (12-16). A few epidemiologic studies on isoflavone intake—mainly based on urinary excretion measurements in Asian populations with high soy consumption—have suggested an inverse association with breast cancer risk (16-23). Other studies conducted in non-Asian populations with low and limited range in isoflavone intake, however, did not confirm these results (24-28).

As reliable data on the flavonoid content of foods has become available only recently, the epidemiologic evidence on the association between other flavonoids and breast cancer risk is scanty. In a cohort study from Finland (29), including 87 breast cancer cases, a nonsignificant inverse association was reported for total flavonoids (relative risk, 0.72, for the highest quintile of intake). In a subsequent follow-up of the same cohort (30), including 125 cases, a reduced breast cancer risk was found for high intake however, of quercetin (relative risk, 0.62), but not for other flavonoids. In a Greek case-control study (27) based on 820 women with breast cancer and 1,548 controls, a significant inverse association was found for the intake of flavones [odds ratio (OR), 0.87], but not for other classes of flavonoids.

We have thus applied recently published data on the composition of foods and beverages in terms of the six principal classes of flavonoids (i.e., flavanones, flavan-3-ols, flavonols, flavones, anthocyanidines, and isoflavones; refs. 31, 32) on dietary information collected in the context of a large multicentric case-control study of breast cancer from Italy.

Materials and Methods

Data were derived from a case-control study of breast cancer conducted between 1991 and 1994 in six Italian areas: the greater Milan area, the province of Pordenone, the urban area of Genoa, the province of Forlì, the province of Latina, and the urban area of Naples (33). Briefly, cases were 2,569 women with incident, histologically confirmed breast cancer (median age 55, range 23-74 years), admitted to major teaching and general hospitals of the study areas and controls were 2,588 women (median age 56, range 20-74 years) with no history of cancer, admitted to the same hospitals for acute, non-neoplastic, nongynecological conditions, unrelated to hormonal or digestive tract diseases or to long-term modifications of diet. Among controls, 22% had traumas, 33% other orthopedic diseases, 15% acute surgical condition, 18% eye diseases, and 12% other miscellaneous diseases. Less than 4% of cases and controls approached for interview refused to participate.

Cases and controls were interviewed in the hospital by centrally trained interviewers, using a standard structured questionnaire. This included information on sociodemographic factors, anthropometric variables, tobacco smoking, alcohol drinking, and other life-style habits, physical activity,

Received 11/15/04; revised 12/24/04; accepted 1/4/05.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: This work was conducted with the contribution of the Italian Association for Cancer Research and the Italian League Against Cancer.

Requests for reprints: Cristina Bosetti, Istituto di Ricerche Farmacologiche ''Mario Negri'', Via Eritrea 62-20157 Milan, Italy. Phone: 39-2390-14526; Fax: 39-2332-00231. E-mail: bosetti@marionegri.it

obstetric, gynecologic and a selected medical history, and history of breast cancer in first-degree relatives. A validated (34) and reproducible (35) food frequency questionnaire was used to assess the patients' usual diet in the previous 2 years, including 78 foods or food groups, plus questions aimed at assessing fat intake and general dietary habits. Subjects were asked to indicate their average weekly consumption of single food items or food groups. Intakes lower than once a week, but at least once per month were coded as 0.5 per week.

Energy was computed using an Italian food composition database, appropriately checked and supplemented with other published data (36). Food and beverage content in terms of six classes of flavonoids (i.e., flavanones, flavan-3-ols, flavonols, flavones, anthocyanidines, and isoflavones) was obtained from the U.S. Department of Agriculture (31, 32), further integrated with other sources (37-39). Major flavonoids included in these classes were hesperitin and narigerin for flavanones, epicatechin and catechin for flavan-3-ols, quercetin, myricetin and kaempferol for flavonols, apigenin and luteolin for flavones, cyanidin and malvidin for anthocyanidines, and genistein and daizeina for isoflavones. In our population, flavanones come mainly from oranges and other citrus fruits, flavan-3-ols from red wine, grapes, and other fruits, flavonols from various common vegetables and fruits, flavones from aromatic herbs, anthocyanidines from onion and garlic, and isoflavones from pulses.

ORs and 95% confidence intervals (CI) were estimated by multiple unconditional logistic regression models (40), including terms for age (quinquennia), study center, years of education (<7, 7-11, ≥12 years), parity (0, 1, 2, 3, ≥4 births), alcohol consumption (tertiles), and nonalcohol energy intake (quintiles). Flavonoids were included in the models as quintiles based on the distribution of controls. Models including the residuals of the regression of flavonoids on energy (41) yielded similar results; thus, only the former estimates were presented. Tests for trend for quintiles of flavonoids were based on the likelihood ratio test between the models with and without a linear term for flavonoid quintile. Flavonoids were also included into the models as continuous variables, with a measurement unit equal to the difference between the upper cutpoint of the fourth quintile and that of the first.

Results

Table 1 gives the median daily intake of six major classes of flavonoids among controls, and the ORs of breast cancer according to quintile of intake. The median daily intake was 33.7 mg for flavanones, 36.4 mg for flavan-3-ols, 15.6 mg for flavonols, 0.5 mg for flavones, 10.4 mg for anthocyanidins, and 21.7 μg for isoflavones. After allowance for major confounding factors and energy intake, a reduced risk of breast cancer was found for increasing intake of flavones (OR, 0.81, for the highest versus the first quintile; P-trend, 0.02), and of flavonols (OR, 0.80; P-trend, 0.06). No meaningful association emerged for other flavonoids, including flavanones (OR, 0.95), flavan-3-ols (OR, 0.86), anthocyanidins (OR, 1.09), as well as for isoflavones (OR, 1.05). The continuous ORs for an increment equal to the difference between the upper cutpoint of the fourth quintile and that of the first were 0.95 for flavanones, 0.93 for flavan-3-ols, 0.94 for flavonols, 0.90 flavones, 1.06 for anthocyanidins, and 0.97 for isoflavones. The estimates were not substantially changed after mutual adjustment of the various classes of flavonoids.

In Table 2, the relation between the six classes of flavonoids and breast cancer risk were analyzed in strata of selected covariates. The estimates were consistent across strata of menopausal status, body mass index, and parity.

Discussion

The results of the present study indicate that flavones are inversely related to breast cancer risk. An inverse—although not significant—association was also found for flavonols, whereas no evidence that other flavonoids, including isoflavones, had a major role on breast cancer risk was found. These findings are in agreement with those of another case-control study from Greece (27), which found a protective effect of flavones on breast cancer risk.

The Italian population of our study is characterized by a high and varied consumption of vegetables (42), including herbs and aromatic plants rich in flavones (2). Thus, our results indicate that these substances could be, at least in part, responsible for the potential beneficial properties of vegetables in breast cancer risk (43, 44). Some recent studies

Table 1. OR of breast cancer among 2,569 cases and 2,588 controls, and corresponding 95% CI according to daily intake of flavonoids (Italy, 1991-1994)

Flavonoids	Median*	Quintile of intake					χ^2 Trend	OR[†,‡] continuous
		1	2	3	4	5		
Flavanones								
Upper cutpoint (mg)	33.7	11.5	29.1	37.7	62.2			
OR[†] (95% CI)		1.00	1.19 (1.00-1.43)	1.11 (0.92-1.33)	1.15 (0.96-1.38)	0.95 (0.79-1.15)	0.48 (0.49)	0.95 (0.87-1.04)
Flavan-3-ols								
Upper cutpoint (mg)	36.4	18.1	30.3	44.1	79.7			
OR[†] (95% CI)		1.00	0.98 (0.82-1.18)	0.80 (0.66-0.98)	1.01 (0.83-1.23)	0.86 (0.71-1.05)	1.28 (0.26)	0.93 (0.87-0.99)
Flavonols								
Upper cutpoint (mg)	18.6	12.6	16.4	21.5	29.9			
OR[†] (95% CI)		1.00	0.81 (0.67-0.98)	1.00 (0.83-1.21)	0.82 (0.67-1.00)	0.80 (0.66-0.98)	3.52 (0.06)	0.94 (0.88-1.01)
Flavones								
Upper cutpoint (mg)	0.5	0.2	0.3	0.5	0.6			
OR[†] (95% CI)		1.00	0.94 (0.79-1.13)	0.97 (0.81-1.17)	0.86 (0.71-1.04)	0.81 (0.66-0.98)	5.41 (0.02)	0.90 (0.83-0.97)
Anthocyanidins								
Upper cutpoint (mg)	10.4	3.7	7.9	14.3	20.5			
OR[†] (95% CI)		1.00	1.03 (0.86-1.25)	1.16 (0.95-1.40)	1.11 (0.90-1.37)	1.09 (0.87-1.36)	0.76 (0.38)	1.06 (0.96-1.17)
Isoflavones (μg)								
Upper cutpoint	21.7	13.4	19.0	25.2	34.7			
OR[†] (95% CI)		1.00	1.05 (0.87-1.27)	1.00 (0.83-1.22)	1.02 (0.84-1.24)	1.05 (0.86-1.29)	0.08 (0.78)	0.97 (0.91-1.04)

*Median intake among controls.
[†]Estimates from multiple logistic regression models including terms for age, study center, education, parity, alcohol consumption, and nonalcohol energy intake.
[‡]OR for a difference in intake equal to the difference between the upper cutpoints of the fourth and that of the first quintile.

Table 2. OR and corresponding 95% CI according to intake of flavonoids in strata of menopausal status, body mass index, and parity (Italy, 1991-1994)

Flavonoids	OR*,† (95% CI)					
	Menopausal status		Body mass index (kg/m^2)		Number of births	
	Pre/Peri (987/842)‡	Post (1,579/1,746)‡	<25 (1,399/1,353)‡	≥25 (1,170/1,235)‡	0-1 (998/884)‡	≥2 (1,571/1,704)‡
Flavanones	0.98 (0.85-1.13)	0.93 (0.82-1.05)	0.90 (0.79-1.02)	0.99 (0.87-1.12)	0.87 (0.75-1.02)	0.99 (0.89-1.11)
Flavan-3-ols	0.94 (0.85-1.05)	0.92 (0.84-1.00)	0.94 (0.86-1.03)	0.94 (0.85-1.04)	0.94 (0.84-1.06)	0.93 (0.86-1.01)
Flavonols	0.90 (0.80-1.02)	0.97 (0.89-1.05)	0.92 (0.83-1.01)	0.98 (0.89-1.08)	0.96 (0.86-1.07)	0.93 (0.85-1.02)
Flavones	0.87 (0.76-0.99)	0.90 (0.81-1.00)	0.93 (0.83-1.04)	0.87 (0.77-0.98)	0.90 (0.79-1.03)	0.88 (0.79-0.98)
Anthocyanidins	1.14 (1.00-1.31)	1.04 (0.93-1.17)	1.06 (0.95-1.20)	1.10 (0.97-1.25)	1.09 (0.95-1.26)	1.08 (0.97-1.20)
Isoflavones	1.01 (0.90-1.15)	0.96 (0.88-1.03)	0.96 (0.89-1.04)	1.00 (0.89-1.11)	1.05 (0.93-1.19)	0.93 (0.85-1.01)

*Estimated using multiple logistic regression models, adjusted for age, study center, education, parity, alcohol consumption, and nonalcohol energy intake.
†OR for a difference in intake equal to the difference between the upper cutpoints of the fourth and that of the first quintile.
‡Cases/controls.

have challenged the inverse association of vegetable intake with breast cancer risk (45). Observational studies, however, are susceptible to the negative confounding likely to be generated by the fact that health-conscious women, who tend to consume more vegetables and fruits, also tend to undergo mammographic examinations more frequently and hence are more easily diagnosed with subclinical breast cancer.

With respect to isoflavones, our data did not confirm the results from other studies, mainly from Asian populations (17, 18, 20, 21). The absence of any meaningful association with isoflavone intake in our study may be due to the extremely limited intake of soya or soya products—and consequently of isoflavonoids—in the Italian population. It is also possible that an association between isoflavones and breast risk may not be captured through a dietary intake study, but only through measurement of urinary excretion (46). Thus, the association between isoflavones and breast cancer risk remains unclear, with several studies reporting no relation (15, 16).

The usual strengths and weaknesses of hospital-based case-control studies should be considered (40). Dietary recall can be influenced by recent diagnosis of cancer. However, the information collected refers to the habitual diet in the 2 years before the diagnosis or hospital admission. Furthermore, potential recall bias in the intake of flavonoids should be limited, given the limited appreciation by the lay population in Italy of a link between vegetable and fruit intake and breast cancer risk. The dietary habits of hospital controls may differ from those of the general population, but we took great care to include as controls only patients admitted to hospital for acute conditions not related to major changes in diet and other life-style factors. Moreover, the same interview setting and catchment areas for cases and controls, and the almost complete participation rate are reassuring. The well recognized risk factors for breast cancer (including age at menarche, age at menopause, parity, family history, alcohol drinking, body mass index, etc.) were consistently observed in the present data (47, 48). Among the strengths of this study are the uniquely large dataset, the high intake of fruit and vegetables in the population, the satisfactory reproducibility and validity of the food frequency questionnaire (34, 35), and the ability to control for total energy intake and major potential confounding factors. Among the limitations of the study are the questions concerning the adaptability of U.S. flavonoid food composition tables to the Italian diet, and the fact that the questionnaire was not specifically designed to investigate flavonoids.

In conclusion, we found evidence of an inverse association of flavones and—to a lesser extent—flavonols with breast cancer risk, which may, at least in part, explain the inverse association of vegetable consumption with breast cancer risk in this population (33).

References

1. Kandaswami C, Perkins E, Drzewiecki G, Soloniuk DS, Middleton E Jr. Differential inhibition of proliferation of human squamous cell carcinoma, gliosarcoma and embryonic fibroblast-like lung cells in culture by plant flavonoids. Anticancer Drugs 1992;3:525–30.
2. Peterson J, Dwyer J. Flavonoids: dietary occurrence and biochemical activity. Nutr Res 1998;18:1995–2018.
3. Franke AA, Cooney RV, Custer LJ, Mordan LJ, Tanaka Y. Inhibition of neoplastic transformation and bioavailability of dietary flavonoid agents. Adv Exp Med Biol 1998;439:237–48.
4. Takahashi T, Kobori M, Shinmoto H, Tsushida T. Structure-activity relationships of flavonoids and the induction of granulocytic- or monocytic-differentiation in HL60 human myeloid leukemia cells. Biosci Biotechnol Biochem 1998;62:2199–204.
5. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 2001;74:418–25.
6. Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary flavonoids and cancer risk in the Zutphen Elderly Study. Nutr Cancer 1994;22:175–84.
7. Hollman PC, Hertog MG, Katan MB. Role of dietary flavonoids in protection against cancer and coronary heart disease. Biochem Soc Trans 1996;24:785–9.
8. Lagiou P, Samoli E, Lagiou A, et al. Flavonoid intake in relation to lung cancer risk: case-control study among women in Greece. Nutr Cancer 2004;49:139–43.
9. Lagiou P, Samoli E, Lagiou A, et al. Flavonoids, vitamin C and adenocarcinoma of the stomach. Cancer Causes Control 2004;15:67–72.
10. La Vecchia C, Decarli A, Pagano R. Vegetable consumption and risk of chronic disease. Epidemiology 1998;9:208–10.
11. Trichopoulou A, Naska A, Antoniou A, Fiel S, Trygg K, Turrini A. Vegetable and fruit: the evidence in their favour and the public health perspective. Int J Vitam Nutr Res 2003;73:63–9.
12. Stoner GD, Mukhtar H. Polyphenols as cancer chemopreventive agents. J Cell Biochem Suppl 1995;22:169–80.
13. Barnes S, Sfakianos J, Coward L, Kirk M. Soy isoflavonoids and cancer prevention. Underlying biochemical and pharmacological issues. Adv Exp Med Biol 1996;401:87–100.
14. So FV, Guthrie N, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-positive MCF-7 human breast cancer cells by flavonoids in the presence and absence of excess estrogen. Cancer Lett 1997;112:127–33. Erratum in: Cancer Lett 1997;120:245.
15. Adlercreutz H. Phyto-oestrogens and cancer. Lancet Oncol 2002;3:364–73.
16. Peeters PH, Keinan-Boker L, van der Schouw YT, Grobbee DE. Phytoestrogens and breast cancer risk. Review of the epidemiological evidence. Breast Cancer Res Treat 2003;77:171–83.
17. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. Lancet 1997;350:990–4.
18. Zheng W, Dai Q, Custer LJ, et al. Urinary excretion of isoflavonoids and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:35–40.
19. Murkies A, Dalais FS, Briganti EM, et al. Phytoestrogens and breast cancer in postmenopausal women: a case control study. Menopause 2000;7:289–96.
20. Dai Q, Franke AA, Jin F, et al. Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. Cancer Epidemiol Biomarkers Prev 2002;11:815–21.
21. Yamamoto S, Sobue T, Kobayashi M, Sasaki S, Tsugane S; for the Japan Public Health Center-Based Prospective Study on Cancer Cardiovascular Diseases (JPHC Stdy) Group. RE: Soy, isoflavones, and breast cancer risk in Japan. J Natl Cancer Inst 2003;95:906–13.
22. Linseisen J, Piller R, Hermann S, Chang-Claude J. German Case-Control Study. Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case-control study. Int J Cancer 2004;110:284–90.

23. dos Santos Silva I, Mangtani P, McCormack V, Bhakta D. Phyto-oestrogen intake and breast cancer risk in South Asian women in England: findings from a population-based case-control study. Cancer Causes Control 2004;15:805–18.
24. den Tonkelaar I, Keinan-Boker L, Veer PV, et al. Urinary phytoestrogens and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:223–8.
25. Horn-Ross PL, John EM, Lee M, et al. Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am J Epidemiol 2001;154:434–41.
26. Horn-Ross PL, Hoggatt KJ, West DW, et al. Recent diet and breast cancer risk: the California Teachers Study (USA). Cancer Causes Control 2002;13:407–15.
27. Peterson J, Lagiou P, Samoli E, et al. Flavonoid intake and breast cancer risk: a case-control study in Greece. Br J Cancer 2003;89:1255–9.
28. Keinan-Boker L, van Der Schouw YT, Grobbee DE, Peeters PHM. Dietary phytoestrogens and breast cancer risk. Am J Clin Nutr 2004;79:282–8.
29. 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.
30. Knekt P, Kumpulainen J, Järvinen R, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002;76:560–8.
31. U.S. Department of Agriculture. Iowa State University database on the isoflavone content of foods, Release 1.3, 2002. Beltsville (MD): U.S. Department of Agriculture; 2002.
32. U.S. Department of Agriculture. USDA database for the flavonoid content of selected foods. Beltsville (MD): U.S. Department of Agriculture; 2003.
33. Franceschi S, Favero A, La Vecchia C, et al. Influence of food groups and food diversity on breast cancer risk in Italy. Int J Cancer 1995;63:785–9.
34. Decarli A, Franceschi S, Ferraroni M, et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 1996;6:110–8.
35. Franceschi S, Negri E, Salvini S, et al. Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. Eur J Cancer 1993;29A:2298–305.
36. Salvini S, Gnagnarella P, Parpinel MT, et al. The food composition database for an Italian food frequency questionnaire. J Food Compost Anal 1996;9:57–71.
37. Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA, Bingham SA. Daidzein and genistein contents of vegetables. Br J Nutr 2000;84:717–25.
38. Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA, Bingham SA. Daidzein and genistein content of fruits and nuts. J Nutr Biochem 2000;11:326–31.
39. Liggins J, Mulligan A, Runswick S, Bingham SA. Daidzein and genistein content of cereals. Eur J Clin Nutr 2002;56:961–6.
40. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case–control studies. IARC Sci Publ 1980;32:5–338.
41. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
42. Agudo A, Slimani N, Ocke MC, et al. Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. Public Health Nutr 2002;5:1179–96.
43. World Cancer Research Fund in association with the American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): World Cancer Research Fund; 1997.
44. Bosetti C, Altieri A, La Vecchia C. Diet and environmental carcinogenesis in breast/gynaecological cancers. Curr Opin Obstet Gynecol 2002;14:13–8.
45. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA 2001;285:799–801.
46. Grace PB, Taylor JI, Low YL, et al. Phytoestrogen concentrations in serum and spot urine as biomarkers for dietary phytoestrogen intake and their relation to breast cancer risk in European prospective investigation of cancer and nutrition—Norfolk. Cancer Epidemiol Biomarkers Prev 2004;13:698–708.
47. Tavani A, Braga C, La Vecchia C, Negri E, Russo A, Franceschi S. Attributable risks for breast cancer in Italy: Education, family history, and reproductive and hormonal factors. Int J Cancer 1997;70:159–63.
48. Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S. Population attributable risk for breast cancer: Diet, nutrition, and physical exercise. J Natl Cancer Inst 1998;90:389–94.