Vegetable-Fruit-Soybean Dietary Pattern and Breast Cancer: A Meta-Analysis of Observational Studies

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Summary Breast cancer is one of the most common cancers among women worldwide, and several studies have investigated the association of dietary patterns and breast cancer. However, findings of studies are inconclusive. Therefore, we aimed to conduct a meta-analysis to summarize the available data regarding the association of vegetable-fruit-soybean dietary pattern and breast cancer. A systematic literature search was conducted via PubMed, Web of Science and EMBASE to identify eligible cohort studies before February 2019. A total of 12 cohort studies were included in the meta-analysis. The summary relative risks (RR) with 95% CI were calculated with a fixed-effects model. The overall RR of breast cancer for the highest versus lowest intake of vegetable-fruit-soybean dietary pattern was 0.87 (95% CI, 0.82–0.91), with little heterogeneity (p=0.73, I²=0%). There was no obvious publication bias according to funnel plot and Begg’s and Egger’s test. In summary, the evidence from this meta-analysis indicates that vegetable-fruit-soybean dietary pattern was inversely associated with breast cancer. However, well-designed randomized controlled trials are needed to elicit the clear effect of vegetable-fruit-soybean dietary pattern and breast cancer. Women can reduce the risks of breast cancer by eating more fruits and vegetables and soybeans, which is a constructive suggestion.

Key Words plant chemicals, vitamin, isoflavones, food pattern, breast neoplasm, cohort study, systematic analysis

Globally, breast cancer is the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (1). Genetic (2), environmental (3) and dietary (4) factors may have an important role in the development of breast cancer. Data from several studies provided support for a correlation between diet and cancer rates (5–8). Furthermore, dietary factors may account for 30–35% of all cancers (9). Consumption of nutrients that contain elevated amounts of animal or caloric content, refined sugars, and alcohol increase cancer risk (10–13).

In recent years, the study of dietary factors is not limited to a single food, but to study the combination of various foods and nutrients, that is, the relationship between dietary patterns and breast cancer. A substantial amount of research used factor analysis or principal component analysis to derive dietary patterns. With the use of this approach, associations were observed between dietary patterns and breast cancer. Dietary patterns could be more representative of the various foods consumed daily than single foods. A large number of studies (14–16) have shown that some dietary patterns including vegetables, fruits and legumes have protective effects on breast cancer. Although some dietary patterns including vegetables, fruits and legumes, the vegetable-fruit-soybean dietary pattern was highly correlated with vegetables, fruits and legumes according to their factor load (the factor load is the correlation coefficient between the food item and the dietary pattern). The higher the factor load, the stronger the food item is associated with the dietary pattern). The vegetable-fruitsoybean dietary pattern can vary depending on different ethnic groups, countries, or culture (17) and the association between the dietary pattern and breast cancer is not consistent. In order to investigate the heterogeneity and obtain the average effect of each study, we aimed to conduct the present study to summarize the available data to test the hypothesis that whether a highly healthy dietary pattern is associated with decreased risk of breast cancer.

Methods

Search strategy. A systematic search was conducted in PubMed, Web of Science and EMBASE to find articles in English which were published up to February 2019 on dietary pattern and breast cancer. The following search terms (medical subject headings or keywords) were used to retrieve the relevant literature in the databases: ‘breast neoplasm’ OR ‘breast tumor’ OR ‘breast cancer’ OR ‘breast carcinoma’ OR ‘mammary cancer’ OR ‘mammary gland neoplasms’ OR ‘mammary gland neoplasms’.
Zhang L et al. focused on the association of vegetable-fruit-soybean dietary pattern and breast cancer in female: (c) reported dietary pattern identified principle component analysis (factor analysis), vegetable, fruit and soybean were in the same pattern, and their factor load ≥0.3 (the factor load is the correlation coefficient between the food item and the dietary pattern. The higher the factor load, the stronger the food item is associated with the dietary pattern (19); and (d) reported relative risks, or hazard risks, and corresponding 95% CI.

Data extraction and quality assessment. Using a standardised data-collection form, the following data were abstracted from each study: the first author’s last name, publication year, location of study, sample size, number of cases, duration of follow-up, risk estimates with CIs, statistical adjustment for potential confounding factors. The quality assessment for each article was run according to Newcastle-Ottawa Scale adapted for cohort studies.

Statistical analysis. Relative risks (RR) was chosen as the common measure of association across this study, and hazard ratio was directly considered as RR. The degree of heterogeneity in the relationship between vegetable-fruit-soybean dietary pattern and breast cancer across studies was assessed using Q and I² statistics. Percentage of I² less than 25, about 25–50, and more than 50 was considered low, moderate, and high heterogeneity. In the presence of significant heterogeneity, a random-effects model was used to calculate the pooled effect size; otherwise, a fixed-effects model was applied. To investigate the influence of a single research on the overall RR, we made a sensitivity analysis by dropping one research in each turn. Subgroup analysis was performed to explore potential sources of heterogeneity. Publication bias was assessed by a funnel plot and Beggs’s and Egger’s tests. Two-tailed p<0.05 was considered statistically significant. All of the data were analyzed by STATA version 12.0 (Stata Corp LP, College Station, TX, USA).

**Results**

**Study characteristics**

The flow diagram describing the process of screening and excluded articles is shown in Fig. 1. A total of 12 cohort studies (20–31) focused on the association between vegetable-fruit-soybean dietary pattern and breast cancer were identified, including 15 sets of data. For the studies included, all the subjects did not have prior history of breast cancer or other cancers at baseline. And they were interviewed by quantitative food-frequency questionnaire (FFQ) to assess usual diet.

Then principal components analysis among women in the cohort was used to identify dietary patterns from the food frequency responses. Characteristics of the included studies are shown in Table 1. The sample size ranged from 10,788 to 91,779, and the number of breast cancer cases ranged from 119 to 4,140. Among them, 5 studies were conducted in Europe, 4 in Asia, 5 in North America, and 1 in Oceania. Most individual studies adjusted for a wide range of potential confounding factors, such as age, BMI, family history of breast cancer and total energy intake. The quality scores ranged from 8 to 9, and all the studies were recognized as high quality.

**Main analysis**

The forest plot of association between vegetable-fruit-soybean dietary pattern and breast cancer is indicated in Fig. 2. There was a significant inverse association between vegetable-fruit-soybean dietary pattern and breast cancer (RR=0.87; 95% CI 0.81–0.91). There was little heterogeneity (I²=0%, p=0.73) among the included studies.

**Subgroup analysis and sensitivity analysis**

Subgroup analysis revealed that differences in location had an effect on the association between vegetable-fruit-soybean dietary pattern and breast cancer. However, duration of follow-up and sample size have little impact on the results (Table 2).

To investigate the influence of a single research on the overall RR, we made a sensitivity analysis by dropping one research in each turn (Fig. 3). The RR range from 0.86 (0.81–0.91) to 0.88 (0.83–0.92).

**Publication bias**

Funnel plots (Fig. 4) revealed little evidence of asymmetry.
Table 1. Characteristics of the included cohort studies in meta-analysis.

| First author/location | Breast cancer | Sample size/ follow-up years | Diet assessment | Factor ≥0.3 food items | NOS | RR  | 95% CI | Adjustment                                                                                     |
|-----------------------|--------------|------------------------------|-----------------|------------------------|-----|-----|--------|---------------------------------------------------------------------------------------------|
| Terry et al. (2001)   | 1,328        | 61,463/9.6                  | Self-administered FFQ | Vegetables (0.66), fruits (0.55), pea soup (0.30) | 9   | 0.92 | 0.76–1.13 | age, energy intake, BMI and education, family history, parity, and age at first birth       |
| Adebamowo et al. (2005) | 710         | 90,638/8                    | Interview FFQ   | Vegetables (0.70, 0.67), fruits (0.65), beans (0.59) | 9   | 0.90 | 0.68–1.18 | age at menarche, parity and age at first birth, family history of breast cancer in mother or sister, history of benign breast disease, oral contraceptive use, alcohol consumption, energy intake, current body mass index, height, smoking habit, physical activity, and use of multivitamin |
| Fung et al. (2005)    | 3,026        | 71,058/16                   | Interview FFQ   | Vegetables (0.68, 0.63 et al.), fruits (0.60), beans (0.55) | 8   | 0.62 | 0.45–0.88 | age, smoking status, BMI, multivitamin, energy intake, physical activity in METs, family history of breast cancer, history of benign breast disease, duration of menopause, age at menopause and use of hormone replacement therapy, age at menarche, parity and age at first birth, BMI at age 18, weight change since age 18, adult height and alcohol intake |
| Vellie et al. (2005)  | 1,868        | 40,559/11                   | Self-administered FFQ | Vegetables (0.53, 0.47 et al.), fruits (0.30), beans and legumes (0.39) | 8   | 1.04 | 0.87–1.26 | age, total energy intake, education, family history of breast cancer, BMI, height, parity, age at first live birth, age at menarche, menopausal hormone use, average weekday vigorous physical activity, smoking status, and alcohol use |
| Mannisto et al. (2005) | 1,127       | 62,573/7                    | Self-administered FFQ | Vegetables (0.48, 0.59 et al.), fruits (0.50, 0.51), beans (0.55) | 9   | 0.90 | 0.67–1.20 | age, body mass index, height, education, smoking, family history of breast cancer, age at menarche, age at menopause, age at first birth, ever use of oral contraceptive, ever use of hormone replacement therapy, alcohol intake and energy |
| Agurs-Collins et al. (2009) | 1,144     | 50,778/13                   | In-person FFQ   | Vegetables (0.66), fruits (0.55), pea soup (0.30) | 9   | 0.79 | 0.68–1.08 | age, public healthcare centre area, log-transformed energy intake, BMI, smoking status, leisure-time physical activity, total physical activity, age at menarche, parity, age at first birth, menopause status and use of exogenous female hormones |
| First author/location | Breast cancer | Sample size/ follow-up years | Diet assessment | Factor $\geq 0.3$ food items | NOS | RR       | 95% CI | Adjustment                                                                 |
|-----------------------|--------------|------------------------------|-----------------|-----------------------------|-----|---------|--------|---------------------------------------------------------------------------|
| Cottet et al. (2009)  | 815          | 65,374/9.7                   | Self-administered FFQ | Vegetables (0.70, 0.66), fruits (0.34), pulses (0.30) | 9   | 0.85    | 0.75–0.95 | age, educational level, region at baseline, body mass index, height, family history of breast cancer in a first- or second-degree relative, age at menarche, age at first full-term pregnancy combined with number of livebirths, menopausal hormone therapy initiated before the previous year, personal history of benign breast disease or lobular carcinoma in situ at baseline, use of oral contraceptives at baseline, lifetime duration of breastfeeding, frequency of Papanicolaou testing at baseline as an indicator of adherence to gynecologic screening, physical activity, smoking status at baseline, energy intake excluding alcohol, current use of phytoestrogen supplements, and current use of vitamin/mineral supplements |
| Butler et al. (2010)  | 629          | 34,028/12                    | Self-reported FFQ | Vegetables ($>0.3$), fruits ($>0.3$), beans ($>0.3$) | 8   | 0.82    | 0.63–1.05 | All HRs were adjusted for age at interview, dialect group, interview year, education, parity, BMI, first-degree relative with diagnosis of breast cancer, and total daily energy intake |
| Baglietto et al. (2011) | 815          | 20,967/14.1                  | Self-reported FFQ | Vegetable salads (0.37 et al.), cucumbers (0.37), fruits (0.43 et al.), green beans/peas (0.44) | 9   | 0.81    | 0.63–1.03 | country of birth, age at menarche, parity, duration of lactation, oral contraceptive use, HRT use, menopausal status at baseline, physical activity, alcohol, smoking, level of education, total energy intake and BMI. a Test for homogeneity by attained age at follow-up |
| Link et al. (2013)    | 4,140        | 91,779/15                    | Self-reported FFQ | Vegetables (0.52, 0.39), fruits (0.57, 0.55, 0.51, 0.50 et al.), beans (0.38, 0.36) | 8   | 0.85    | 0.76–0.95 | race-ethnicity/birthplace, family history of breast cancer, age at menarche, parity/age at first full-term pregnancy, average daily caloric intake, physical activity, socioeconomic status, history of a benign breast biopsy and its interaction with time-dependent age, BMI, height, menopausal status/hormone therapy use, and the other 4 dietary patterns |
| Shin et al. (2016)    | 718          | 49,552/14.6                  | Self-reported FFQ | Vegetables (0.65, 0.65, 0.56, 0.71), fruits (0.74, 0.63), beans (0.68) | 9   | 0.96    | 0.75–1.23 | age, public healthcare centre area, log-transformed energy intake, BMI, smoking status, leisure-time physical activity, total physical activity, age at menarche, parity, age at first birth, menopause status and use of exogenous female hormones |
| Kojima et al. (2017)  | 119          | 23,172/16.9                  | Self-administered FFQ | Vegetables (0.34, 0.62 et al.), fruits (0.45), beans (0.37) | 8   | 0.81    | 0.35–1.89 | age, area, tobacco smoking status, drinking status, family history of breast cancer, age at menarche, age at first birth, parity, energy intake, hormone therapy, daily walking, education, and BMI |

NOS: the Newcastle-Ottawa scale, RR: relative risk, CI: confidence interval, FFQ: food frequency questionnaire.
Discussion

Nutrients have separately shown possibly significant associations with breast cancer risk include vitamin, phytochemicals and soy isoflavones. Dietary soy consumption during early life provides protection against breast cancer (32, 33). This concept is also proved by animal studies (34, 35). Qiu and Jiang reported a systematic review about the association between soy and isoflavones consumption and breast cancer survival and recurrence (36). The conclusion was that pre-diagnosis soy and isoflavones intake was associated with a small reduction in post-menopausal breast cancer overall survival. However, there are also several conceptual limitations. People eat meals consisting of various food groups, which contain complex nutrients that are likely to be interactive. Individual foods and nutrients cannot account for the complicated interactions of components in different foods.

In comparison with the study of Qiu and Jiang our research is different. First, Qiu and Jiang collected the intake of a certain food and nutrient (soy and isoflavones) in the included study, while we collected the proportion of a certain food (fruits, vegetables, and soybean) in the diet in the included study, and classified it into a dietary pattern based on the similarity of its nutritional composition, which we summarized as the vegetable-fruit-soybean dietary pattern. The vegetable-fruit-soybean dietary pattern included high-factor loadings in fruits, vegetables, and soybean that contained plant chemicals (37-42), dietary fiber, vitamins, and soybean isoflavones. Second, Qiu and Jiang studied the relationship between a single food and nutrient and breast cancer outcomes, while the paper focused on the relationship between a dietary pattern and breast cancer risk. As a result, the aim of this article is to investigate the relationship between vegetable-fruit-soybean dietary pattern and breast cancer and draw a consistent conclusion.

In this meta-analysis, references included in the article are all cohort studies and their results are all specific. There was little heterogeneity ($I^2=0\%$, $p=0.73$)
among the included studies. The results also didn’t indicate evidence of Publication bias. The quality of evidence throughout this review regarding the vegetable-fruit-soybean dietary pattern and breast cancer risk is reliable. In this article, we find that the vegetable-fruit-soybean dietary pattern is associated with a lower risk of breast cancer. It is reported that the mechanisms are such as the intestinal reabsorption of estrogen is inhibited through the biliary system (43) and antioxidant actions (44). Included studies were done in different populations, and thus provided a conclusive answer to the assumption about the association. However, Terry et al. (20) reported that a "healthy" dietary patterns was not associated with breast cancer risk among younger or older women respectively, which usually includes high intake of vegetables, fruits, whole grains and fish. Haraldsdottir et al. (45) also reported that high rye bread consumption in adolescence and midlife may increase risk of late-life breast cancer whilst persistent consumption of oatmeal may reduce the risk, which usually includes high consumption of meat, milk, and whole grain products. In contract, several previous studies regarding dietary patterns in relation to breast cancer risk had shown an adverse association with the healthy dietary pattern (19, 26, 46, 47). This may due to the differences in research design, eating habit, social culture and the definition of “healthy” dietary patterns.

To our knowledge, principal component analysis is used to extract the corresponding factors to define dietary patterns, but few discuss the composition ratio of various foods. We investigate the relationship between dietary patterns of specific components and breast cancer, to offer recommendations for the prevention of breast cancer. Our research has advantages. The original studies included in this article were all prospective, which greatly reduces the likelihood of recall bias and selection bias. Furthermore, they were all population-based, thereby minimizing the selection bias. At the same time, there are several potential limitations that are worthy of consideration in this meta-analysis. First, the dietary pattern may change during long-term follow-up, the association between dietary pattern and breast cancer would be wrongly estimated. Second, there are differences in the versions of FFQs in various regions, therefore, dietary pattern in each study contains different food and food groups. Third, the number of studies included in some subgroups is comparatively small, resulting in low statistical power to detect the
authentic association. Fourth, the paper only considered the researches published in English, many studies with null results were not published and the number of studies included in the paper is small, so publication bias is possible. The research is limited and other analysis is needed to resolve the problem. Finally, the components in foods have complicated interactions and factor load of vegetable, fruit and soybean in the same pattern is not 1, so this study can make possible to indicate a direct relationship between a vegetable-fruit-soybean dietary pattern and breast cancer risk but not identify the association. However, people don’t eat isolated foods and nutrients, people eat meals consisting of varieties of foods and nutrients, so the factor load of vegetable, fruit and soybean in the same pattern is usually not 1. For the research, it is inevitable.

**Conclusion**

In summary, our meta-analysis demonstrates that vegetable-fruit-soybean dietary pattern inversely associated with breast cancer. The results of this meta-analysis perhaps highlight the need for more carefully designed observational and intervention studies to clarify the role of vegetable-fruit-soybean dietary pattern and breast cancer risk.

**Search strategy**

Two investigators (Lu Zhang and Shaohua Huang) conducted a systematic search in PubMed, Web of Science and EMBASE to find articles in English which were published up to February 2019 on dietary pattern and breast cancer. The following search terms (medical subject headings or keywords) were used to retrieve the relevant literature in the databases: (1) ‘breast neoplasm’ OR ‘breast tumor’ OR ‘breast cancer’ OR ‘breast carcinoma’ OR ‘mammary cancer’ OR ‘mammary gland neoplasms’ OR ‘mammary gland cancer’: (2) ‘dietary pattern’ OR ‘food pattern’ OR ‘eating pattern’ OR ‘lifestyle pattern’ OR ‘nutrient pattern’: Additional references were also identified by manually searching the bibliographies of relevant items.

**Disclosure of state of COI**

The authors declare that there are no conflicts of interest.

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**Author contributions**

Lu Zhang conceived the strategy of the literature search. Lu Zhang and Shaohua Huang screen the date and finish the manuscript. Lina Cao, Miaomiao Ge and Yuanhong Li participated in partial statistical analysis. All authors contributed to and reviewed the manuscript. Lu Zhang and Shaohua Huang contributed equally to this work.
major dietary patterns and the risk of breast cancer. *Cancer Epidemiol Biomark* 10: 1281–1285.
21) Agurs-Collins T, Rosenberg L, Makambi K. 2009. Dietary patterns and breast cancer risk in women participating in the Black Women’s Health Study. *Am J Clin Nutr* 90: 621–628.
22) Shin S, Saito E, Inoue M. 2016. Dietary pattern and breast cancer risk in Japanese women: the Japan Public Health Center-based Prospective Study (JPHC Study). *Br J Nutr* 115: 1769–1779.
23) Baglietto L, Krishnan K, Severi G. 2011. Dietary patterns and breast cancer risk in women participating in the Black Women's Health Study. *Br J Cancer* 104: 524–531.
24) Kojima R, Okada E, Ukawa S. 2017. Dietary patterns and breast cancer risk in a prospective Japanese study. *Breast Cancer* 24: 152–160.
25) Butler LM, Wu AH, Wang RW. 2010. A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. *Am J Clin Nutr* 91: 1013–1019.
26) Adebamowo CA, Hu FB, Cho E. 2005. Dietary patterns and the risk of breast cancer. *Am J Epidemiol* 161: 789–795.
27) Fung TT, Hu FB, Holems MD. 2005. Dietary patterns and the risk of postmenopausal breast cancer. *Int J Cancer* 116: 116–121.
28) Cottet V, Touvier M, Fournier A. 2009. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. *Am J Epidemiol* 170: 1257–1267.
29) Vellig EM, Schairer C, Flood A. 2005. Empirically derived dietary patterns and risk of postmenopausal breast cancer in a large prospective cohort study. *Am J Clin Nutr* 82: 1308–1319.
30) Link LB, Canchola AJ, Bernstein L. 2013. Dietary patterns and breast cancer risk in the California Teachers Study cohort. *Am J Clin Nutr* 98: 1524–1532.
31) Mannisto S, Dixon LB, Balder H. 2005. Dietary patterns and breast cancer risk: results from three cohort studies in the DIETSCAN project. *Cancer Cause Control* 16: 725–733.
32) Shu XO, Jin F, Dai Q. 2001. Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiol Biomark* 10: 483–488.
33) Wu AH, Yu MC, Tseng CC. 2009. Dietary patterns and breast cancer risk in Asian American women. *Am J Clin Nutr* 89: 1145–1154.
34) Hilakivi-Clarke L, Onojaife I, Raygada M. 1999. Prenatal exposure to zearalenone or genistein reduces mammary tumorigenesis. *Br J Cancer* 80: 1682–1688.
35) Fritz WA, Coward L, Wang J. 1998. Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. *Carcinogenesis* 19: 2151–2158.
36) Qiu S, Jiang C. 2018. Soy and isoflavones consumption and breast cancer survival and recurrence: a systematic review and meta-analysis. *Eur J Nutr*. Advance Publication, doi: 10.1007/s00394-018-1853-4.
37) Liu RH. 2004. Potential synergy of phytochemicals in cancer prevention: Mechanism of action. *J Nutr* 134: 3479s–3485s.
38) Messina M, Barnes S, Setchell KD. 1997. Phyto-oestrogens and breast cancer. *Lancet* 350: 971–972.
39) Surh YJ. 2003. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer* 3: 768–780.
40) Rajendran P, Ho E, Williams DE. 2011. Dietary phytochemicals, HDAC inhibition, and DNA damage/repair defects in cancer cells. *Clin Epigenetics* 3: 4.
41) Anantachoke N, Lomarat P, Praserttitrachai W. 2016. Thai fruits exhibit antioxidant activity and induction of antioxidant enzymes in HEK-293 cells. *Evid-Based Compl Alternat Med* 2016: 6083136.
42) Ziaei S, Halaby R. 2017. Dietary isoflavones and breast cancer risk. *Medicines* 4: 18.
43) Goldin BR, Adlercreutz H, Gorbach SL. 1982. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *New Engl J Med* 307: 1542–1547.
44) Willett WC. 2001. Diet and breast cancer. *J Internal Med* 249: 395–411.
45) Haraldsdottir A, Torfadottir JE, Valdimarsdottir UA. 2018. Dietary habits in adolescence and midlife and risk of breast cancer in older women. *PloS One* 13: e0198017.
46) Sieri S, Krogh V, Pala V, Muti P, Micheli A, Evangelista A, Tagliafuore G, Berrino F. 2004. Dietary patterns and risk of breast cancer in the ORDET cohort. *Cancer Epidemiol Biomarkers Prev* 13: 567–572.
47) Sant M, Allemani C, Sieri S. 2007. Salad vegetables dietary pattern protects against HER-2-positive breast cancer: a prospective Italian study. *Int J Cancer* 121: 911–914.