RESEARCH ARTICLE

Post-diagnosis Soy Food Intake and Breast Cancer Survival: A Meta-analysis of Cohort Studies

Feng Chi*, Rong Wu, Yue-Can Zeng, Rui Xing, Yang Liu, Zhao-Guo Xu

Abstract

Background and Objectives: Data on associations between soy food intake after cancer diagnosis with breast cancer survival are conflicting, so we conducted this meta-analysis for more accurate evaluation. Methods: Comprehensive searches were conducted to find cohort studies of the relationship between soy food intake after cancer diagnosis and breast cancer survival. Data were analyzed with comprehensive meta-analysis software. Results: Five cohort studies (11,206 patients) were included. Pooling all comparisons, soy food intake after diagnosis was associated with reduced mortality (HR 0.85, 95%CI 0.77 0.93) and recurrence (HR 0.79, 95%CI 0.72 0.87). Pooling the comparisons of highest vs. lowest dose, soy food intake after diagnosis was again associated with reduced mortality (HR 0.84, 95%CI 0.71 0.99) and recurrence (HR 0.74, 95%CI 0.64 0.85). Subgroup analysis of ER status showed that soy food intake was associated with reduced mortality in both ER negative (highest vs. lowest: HR 0.75, 95%CI 0.64 0.88) and ER positive patients (highest vs. lowest: HR 0.72, 95%CI 0.61 0.84), and both premenopausal (highest vs. lowest: HR 0.78, 95%CI 0.69 0.88) and postmenopausal patients (highest vs. lowest: HR 0.81, 95%CI 0.73 0.91). In additioin, soy food intake was associated with reduced recurrence in ER negative (highest vs. lowest: HR 0.64, 95%CI 0.44 0.94) and ER+/PR+ (highest vs. lowest: HR 0.65, 95%CI 0.49 0.86), and postmenopausal patients (highest vs. lowest: HR 0.67, 95%CI 0.56 0.80). Conclusion: Our meta-analysis showed that soy food intake might be associated with better survival, especially for ER negative, ER+/PR+, and postmenopausal patients.

Keywords: Soy foods - breast neoplasms - survival - meta-analysis - receptor status - postmenopausal

Asian Pacific J Cancer Prev, **14 (4)**, 2407-2412

Introduction

Breast cancer is the most common malignancy affecting women and the most common cause of cancer death in the world. About 1.38 million new cases of breast cancer among women were estimated to have occurred in 2008, making it currently the second most common malignant among women worldwide (Zhang et al., 2012). It was estimated that 192,370 women would be diagnosed with and 40,170 women would die of cancer of the breast in 2009 (Li et al., 2010).

It is reported that soy food might have the potential cancer inhibitory effect in breast cancers expressing oestrogen receptor (Zhang et al., 2012). Recent meta-analyses (Qin et al., 2006; Trock et al., 2006; Enderlin et al., 2009; Dong et al., 2011) showed that soy isoflavones intake was associated with a reduced risk of breast cancer incidence. Whereas other studies have shown that isoflavones, the major component of soy, enhance the proliferation of breast cancer cells in vitro (Taylor et al., 2009), promote mammary tumor growth in rats (Helferich et al., 2008), and possibly interfere with the effectiveness of tamoxifen (Schwartz et al., 1998; Ju et al., 2008). As a result, clinicians treating women with breast cancer frequently caution them to either avoid soy foods entirely or use them in moderation (Doyle et al., 2006; Helferich et al., 2008; Velentzis et al., 2008). A cohort study of 1459 Chinese breast cancer patients who commonly eat soy foods prior to cancer diagnosis showed that there were not any association between soy food intake and disease-free breast cancer survival (Boyapati et al., 2005). And another study conducted by Fink et al (Fink et al., 2007) reported that reduced hazard ratios [hazard ratio (95% confidence interval)] for all-cause mortality were observed among premenopausal and postmenopausal women for the highest quintile of intake prior to cancer diagnosis, compared with the lowest, for isoflavones [0.52 (0.33-0.82)]. Regarding to the associations between soy food intake after cancer diagnosis and survival (mortality or recurrence), the results were not the same based on available cohort studies (Guha et al., 2009; Shu et al., 2009; Kang et al., 2010; Caan et al., 2011; Nechuta et al., 2012; Zhang et al., 2012). One meta-analysis of four prospective cohort studies (Boyapati et al., 2005; Fink et al., 2007; Guha et al., 2009; Shu et al., 2009) showed that soy isoflavones intake was inversely associated with risk

*Department of Medical Oncology, Shengjing Hospital of China Medical University, Shenyang, China *For correspondence: chifeng71099@163.com*

of breast cancer recurrence (Dong et al., 2011). However, two (Boyapati et al., 2005; Fink et al., 2007) of them investigated whether soy intake prior to cancer diagnosis might be associated with breast cancer survival, and the rest (Guha et al., 2009; Shu et al., 2009) evaluated whether soy intake after cancer diagnosis might be associated with breast cancer survival. This meta-analysis did not conduct subgroup analysis of the time of soy foods intake (prior to cancer diagnosis vs. after diagnosis). Meanwhile, one of the four included studies focused on survival (Fink et al., 2007), and the other three focused on recurrence (Boyapati et al., 2005; Guha et al., 2009; Shu et al., 2009). So whether soy intake after cancer diagnosis might be associated with breast cancer survival (including mortality or recurrence) deserved a further meta-analysis.

Materials and Methods

We did this systematic review of the available literature in accordance with Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies [MOOSE] (Stroup et al., 2000) for the conduct of meta-analyses of observational studies.

Search Strategy

PubMed, EMBASE, ISI Web of Knowledge, and Chinese Biomedical Database were searched using (soybean or soybeans or soybean or soy beans or soy bean or soy food or soy foods or glycine max or isoflavones or isoflavone or homoisoflavones) and (breast cancers or breast cancer OR breast neoplasm or breast neoplasms OR breast tumor OR breast tumors OR breast adenocarcinoma). If possible, subject heading terms such as Medical Subject Headings terms were added in all searches. Reference lists from the meta-analysis, review articles about this topic and identified trials were hand-searched to identify further relevant citations. All the searches were conducted independently by two reviewers (Feng Chi and Rong Wu) in November 2012 without language restrictions (updated in January 2013); differences were checked by each other and resolved by discussion.

Inclusion criteria and study selection

We identified all published cohort studies that evaluated whether soy intake after cancer diagnosis affect the survival (including mortality or recurrence) in breast cancer patients. When multiple articles for a single study had been published, we used the latest publication and the most detailed data. We excluded studies which evaluated whether soy intake before cancer diagnosis affect the survival (including mortality or recurrence) in breast cancer patients. Letters, comments, editorials, practice guidelines and trials published without the outcome measures of interest were excluded. Two reviewers (Yue Can Zeng and Rui Xing) independently assessed potentially relevant citations for inclusion, disagreements were resolved involved with a third reviewer (Feng Chi).

Data abstraction

Using a standardized data extraction form by two authors (Yang Liu and Zhao Guo Xu), we collected the following baseline characteristics for cases and control groups: lead author, publication year, study design, mean age, variation in age, sex, sample size and outcomes. Any disagreement in abstracted data was resolved by a third reviewer (Feng Chi).

Data analysis

Meta-analysis was conducted by comprehensive meta-analysis software version 2.0. The percentage of variability (heterogeneity) across trials attributable to heterogeneity beyond chance was estimated with the I^2 statistic, which was deemed significant when p was less than 0.05 or I-square was more than 50%. Data was pooled using fixed-effect model if the heterogeneity is not significant and the random-effects model was also considered when there was a significant heterogeneity across trials. Subgroup analyses of different continents (Asian populations vs. Western populations), different ER status (ER- vs. ER+), different menopausal status (premenopausal vs. postmenopausal), and different doses based available data. The results for the comparisons (all doses vs. the lowest dose, the highest vs. the lowest) were both calculated. Whether soy intake could affect those people who use tamoxifen was also assessed.

Results

Search results

After comprehensive search, we got 3633 citations (Pubmed: n=398, Embase: n=15, Web of Science: n =1821, Chinese Biomedical Database: n=346, reference tracking: n=37). After duplicating 792 citations, we excluded studies that were not about soy food (n =849), not about breast cancer (n =618), not cohort studies (n=864), not about survival (n=328). After reading full-texts, we excluded reviews (n =47), experimental studies (n =88) and not about survival (n=41). Finally, five cohort studies (six citations (Guha et al., 2009; Shu et al., 2009; Kang et al., 2010; Caan et al., 2011; Nechuta et al., 2012; Zhang et al., 2012)) (11206 patients) were included.

Characteristic of included studies

Three of them (Shu et al., 2009; Kang et al., 2010; Zhang et al., 2012) were form China and two (Guha et al., 2009; Caan et al., 2011) from USA. The total number ranges from 524 to 5042. Three of them (Guha et al., 2009; Kang et al., 2010; Zhang et al., 2012) were hospital-based and one (Shu et al., 2009) was community-based, and the last one (Caan et al., 2011) was unclear. The median follow-up ranged from 3.9 years to 7.3 years. And the other characteristics were presented in Table 1.

Results of meta-analysis

Mortality: Based on available evidence, soy protein intakes (g/day) were associated reduced mortalities in the following comparisons: 2.12-7.03 vs. < 2.12 (HR 0.73, 95%CI 0.54 0.98) and >13.03 vs. < 2.12 (HR 0.71, 95%CI 0.52 0.98). There was not an association between 7.03-13.03 g/day soy protein intake between < 2.12 g/day soy protein intake (0.71, 95%CI 0.44 1.15). Soy isoflavones

Table 1. The Characteristics of Included Studies

Study ID	Country	Setting	Total No.	No. of death	No. of recurrence	Age (years)	Menopausal status Post-/pre-	Tamoxifen use(Y/N)	ER status (+/-)	Follow-up
Zhang 2012	China	Hospital-based	616	79		45.7±6.2	326/290	350/266	378/238	52.1 (9-60) months
Shu 2009	China	Community-based	5,042	444	534	25-70	2572/2461	2622/2408	3181/1722	3.9 (0.5-6.2) years
Kang 2010	China	Hospital-based	524	154	185	29-72	276/248	438/84	447/77	5.1 years
Guha 2009	USA	Hospital-based	1954		282	-	1268/416	1517/434	1594/335	6.31 years
Caan 2011	USA	-	3088	271	448	18-70	2426/306	-	-	7.3 years

Table 2. Summary of Finding

Death	ER-	ER+				Premenopausal	Postmenopausal	Tamoxifen users	Overall
All doses	0.75 (0.66 0.85)	0.77 (0.69 0.87)				0.81 (0.72 0.90)	0.84 (0.75 0.93)	0.77 (0.58 1.01)	0.85 (0.77 0.93)
	I^2=0%, p=0.87	I^2=0%, p=0.55				I^2=40%, p=0.08	I^2=14%, p=0.31	I^2=10%, p=0.33	I^2=20%, p=0.23
Highest vs. lowest	0.70 (0.58 0.84)	0.74 (0.60 0.91)				0.78 (0.69 0.88)	0.81 (0.73 0.91)	0.26 (0.06 1.10)	0.84 (0.71 0.99)
	I^2=0%, p=0.99	I^2=44%, p=0.17				I^2=0%, p=0.82	I^2=41%, p=0.16		I^2=11%, p=0.35
Recurrence	ER-	ER+	ER-/PR+	ER+/PR-	ER+/PR+	Premenopausal	Postmenopausal	Tamoxifen users	Overall
All doses	0.72 (0.54 0.97)	0.90 (0.74 1.08)	1.08 (0.91 1.29)	1.12(0.93 1.35)	0.70 (0.60 0.80)	0.92 (0.78 1.08)	0.75 (0.67 0.84)	1.17 (0.92 1.47)	0.79 (0.72 0.87)
	I^2=0%, p=0.33	I^2=31%, p=0.23	I^2=0%, p=0.98	I^2=0%, p=0.82	I^2=0%, p=0.90	I^2=0%, p=1.00	I^2=36%, p=0.18	I^2=0%, p=0.97	I^2=0%, p=0.56
Highest vs. lowest	0.64 (0.44 0.94)	0.81 (0.63 1.04)	1.08 (0.73 1.59)	1.14 (0.80 1.63)	0.65 (0.49 0.86)	0.91 (0.72 1.14)	0.67 (0.56 0.80)	0.90 (0.48 1.67)	0.74 (0.64 0.85)
						I^2=0%, p=0.82	I^2=0%, p=0.75	I^2=54%, p=0.14	I^2=0%, p=0. 65

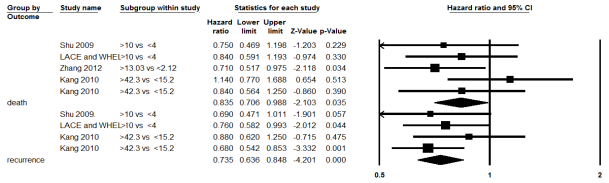

Figure 1. Meta-analysis Results of Soy Food Intake for Breast Cancer Death and Recurrence (highest vs. lowest)

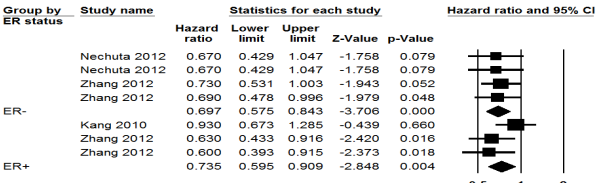

Figure 2. Subgroup Analysis Results of ER Statuses of Soy Food Intake for Breast Cancer Death (highest vs. lowest)

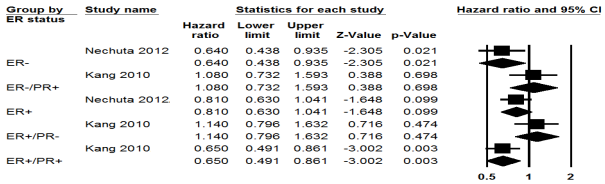

Figure 3. Subgroup Analysis Results of ER Statuses of Soy Food Intake for Breast Cancer Recurrence (highest vs. lowest)

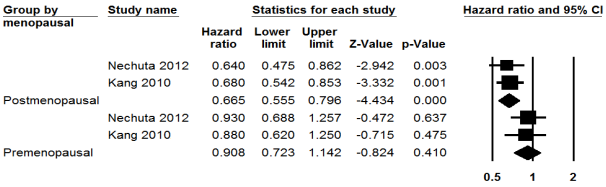

Figure 4. Subgroup Analysis Results of Menopausal Statuses of Soy Food Intake for Breast Cancer Recurrence (highest vs. lowest)

(mg/day) intakes were associated with reduced mortalities in the following comparisons: 17.32-28.83 vs. < 7.56 (HR 0.64, 95%CI 0.45 0.92) and > 28.83 vs. < 7.56 (HR 0.62, 95%CI 0.42 0.91), but not in the other comparisons: 4-10 vs. < 4 (HR 1.06, 95%CI 0.77 1.46, I^2=0%), >10 vs. <4 (HR 0.81, 95%CI 0.61 1.07), 7.56-17.32 vs. < 7.56 (HR 0.77, 95%CI 0.55 1.08), 15.3-25.4 vs. < 15.2 (HR 1.14, 95%CI 0.87 1.49, I^2=0%), 25.5-42.3 vs. < 15.2 (HR 1, 95%CI 0.75 1.33, I^2=0%), and > 42.3 vs. < 15.2 (HR 0.98, 95%CI 0.74 1.30, I^2=13%). Pooling all comparisons, soy foods intake after diagnosis was associated with reduced mortality (HR 0.85, 95%CI 0.77 0.93, I^2=20%) (Table 2). And pooling the comparisons of highest vs. lowest dose soy food intake, soy foods intake after diagnosis was also associated with reduced mortality (HR 0.84, 95%CI 0.71 0.99, I^2=11%) (Figure 1, Table 2).

Subgroup analysis of ER status showed that soy food intake was associated with reduced mortality in both ER negative patients (all comparisons: HR 0.78, 95%CI 0.70 0.85, I^2=0%; highest vs. lowest: HR 0.75, 95%CI 0.64 0.88, I^2=0%) and ER positive patients (all comparisons: HR 0.75, 95%CI 0.69 0.83, I^2=0%; highest vs. lowest: HR 0.72, 95%CI 0.61 0.84, I^2=0%) (Figure 2, Table 2). Subgroup analysis of menopausal status showed that soy food intake was associated with reduced mortality in both premenopausal patients (all comparisons: HR 0.81, 95%CI 0.72 0.90, I^2=40%; highest vs. lowest: HR 0.78, 95%CI 0.69 0.88, I^2=0%) and postmenopausal patients (all comparisons: HR 0.84, 95%CI 0.75 0.93, I^2=14%; highest vs. lowest: HR 0.81, 95%CI 0.73 0.91, I^2=41%) (Table 2).

Soy food intake was not associated with reduced mortality in breast cancer patients who used tamoxifen (all comparisons: HR 0.77, 95%CI 0.58 1.01, I^2=10%; highest vs. lowest: HR 0.26, 95%CI 0.06 1.10) (Table 2).

Recurrence: Soy isoflavones (mg/day) intakes were associated with reduced recurrences in the following comparisons: 15.3-25.4 vs. < 15.2 (HR 0.82, 95%CI 0.68 0.98, I^2=0%), 25.5-42.3 vs. < 15.2 (HR 0.76, 95%CI 0.62 0.94, I^2=0%), >10 vs. <4 (HR 0.74, 95%CI 0.59 0.92, I^2=0%) and > 42.3 vs. < 15.2 (HR 0.73, 95%CI 0.61 0.89, I^2=32%), but not in 4-10 vs. < 4 (HR 1, 95%CI 0.78 1.28, I^2=0%). Pooling all comparisons, soy foods intake after diagnosis was associated with reduced recurrence (HR 0.79, 95%CI 0.72 0.87, I^2=0%) (Table 2). And pooling the comparisons of highest vs. lowest dose soy food intake, soy foods intake after diagnosis was also associated with reduced recurrence (HR 0.74, 95%CI 0.64 0.85, I^2=0%)

(Figure 1, Table 2).

Subgroup analysis of ER status showed that soy food intake was associated with reduced recurrence in ER negative patients (all comparisons: HR 0.72, 95%CI 0.54 0.97, I^2=0%; highest vs. lowest: HR 0.64, 95%CI 0.44 0.94) and ER+/PR+ patients (all comparisons: HR 0.70, 95%CI 0.60 0.80, I^2=0%; highest vs. lowest: HR 0.65, 95%CI 0.49 0.86), but not in ER positive patients (all comparisons: HR 0.90, 95%CI 0.74 1.08, I^2=31%; highest vs. lowest: HR 0.81, 95%CI 0.63 1.04), ER-/PR+ (all comparisons: HR 1.08, 95%CI 0.91 1.29, I^2=0%; highest vs. lowest: HR 1.08, 95%CI 0.73 1.59) and ER+/PR- (all comparisons: HR 1.12, 95%CI 0.93 1.35, I^2=0%; highest vs. lowest: HR 1.14, 95%CI 0.80 1.63) (Figure 3, Table 2).

Subgroup analysis of menopausal status showed that soy food intake was associated with reduced mortality in postmenopausal patients (all comparisons: HR 0.75, 95%CI 0.67 0.84, I^2=36%; highest vs. lowest: HR 0.67, 95%CI 0.56 0.80, I^2=0%), but not in premenopausal patients (all comparisons: HR 0.92, 95%CI 0.78 1.08, I^2=0%; highest vs. lowest: HR 0.91, 95%CI 0.72 1.14, I^2=0%) (Figure 4, Table 2).

Soy food intake was not associated with reduced recurrence in breast cancer patients who used tamoxifen (all comparisons: HR 1.17, 95%CI 0.92 1.47, I^2=0%; highest vs. lowest: HR 0.90, 95%CI 0.48 1.67) (Table 2).

Discussion

Summary of finding: Based on available evidence, soy food intake might be associated with lower mortality and recurrence. Subgroup analyses showed that soy food intake was associated with lower mortality regardless of ER and menopausal statuses. However, soy food intake was associated with lower recurrence in ER negative, ER+/PR+, and postmenopausal patients. This means ER and menopausal statuses might not affect the association of soy food intake with mortality, but they could influence the association of soy food intake with recurrence.

Soy isoflavones in the soy food are the most important constituents, which are structurally similar to 17β-estradiol, the primary endogenous estrogen (Guha et al., 2009). Some studies (Trock et al., 2006; Taylor et al., 2009; Zhang et al., 2012) showed it played a competitive role with endogenous estrogens for binding of estrogen receptors in the breast and stimulate cell proliferation. Depending on the estrogen environment, isoflavones could act as ER antagonists by attenuating the estrogenic response of 17β-estradiol or as ER-agonists when there is a greater chance of binding to ERs (Guha et al., 2009). This would increase synthesis of sex hormone binding globulin (thus lowering the biological availability of sex hormones), inhibit 17β-hydroxysteroid dehydrogenases (thus reducing estrogen synthesis), and increase clearance of steroids from the circulation (Trock et al., 2006; Taylor et al., 2009; Zhang et al., 2012). Soy isoflavones also act independently of the ER: they exhibit anti-proliferative, anti-oxidant, and anti-inflammatory properties in vivo and in vitro (Guha et al., 2009). However, soy isoflavones exhibit only weak estrogenic activity: daidzein has 10-4 the activity per mole as 17β-estradiol (Wang et al., 1996; Santell et al., 1997). These anti-estrogenic effects by soy food intake may play a positive role in the better breast cancer outcomes (Shu et al., 2009; Zhang et al., 2012). This might explain why soy food intake might be associated with lower mortality and recurrence. However, there is large inter-individual variability in isoflavone metabolism, which primarily depends on intestinal flora and genetic polymorphisms (Moon et al., 2006; Nechuta et al., 2012). Thus, the mechanism and role of soy in breast carcinogenesis remains unresolved.

After menopause, despite the loss of ovarian hormones, most estrogens are formed in the peripheral tissues and exert their effects locally in a paracrine or intracrine manner (Nakata et al., 2003). Among postmenopausal women, the concentration of 17β-estradiol in breast tumors is at least 20-fold higher than that in the circulation, but among premenopausal women with breast cancer, this difference was only five-fold (Pasqualini et al., 2005). In vitro experiments also have shown that isoflavones inhibit the activity of aromatase and 17β-hydroxysteroid dehydrogenases involved in the synthesis of estradiol from circulating androgens and estrones (Brooks et al., 2005; Lacey et al., 2005). So it is said that soy isoflavones may have a protective effect in terms of initiation or progression of breast cancer because they inhibit the local production of estrogens from circulating precursors in breast tissue (Kang et al., 2010). Postmenopausal women may take soy-based supplements as an alternative to hormone replacement therapy because they are a natural source of exogenous estrogen (Morris et al., 2000; Harris et al., 2002). This may explain the beneficial effects of soy isoflavones on postmenopausal patients. And this might be the reasons that soy food intake was associated with lower recurrence in postmenopausal patients from our meta-analysis.

Tamoxifen is an anti-estrogen widely prescribed to women with ER positive (ER+) tumors as a long-term adjuvant therapy to prevent recurrences (Moon et al., 2006). Experimental studies suggest that soy isoflavones may interact with tamoxifen therapy (Messina et al., 2001), with some studies showing a potential benefit of combined dietary isoflavone intake and tamoxifen therapy use on the inhibition of breast tumor growth (Constantinou et al., 2001; Tanos et al., 2002), whereas other studies have reported a reduction in the anticancer effects of tamoxifen on breast tissue due to competing for binding to estrogen receptors (Jones et al., 2002; Liu et al., 2005; Ju et al., 2008). Therefore, physicians in the United States caution women who have received tamoxifen therapy against consuming soy foods and supplements (Constantinou et al., 2005). However, our meta-analysis did not identify any good or bad effects on mortality and recurrence for those breast cancer patients who use tamoxifen.

Strength and limitations: To our knowledge, this is the first meta-analysis of available prospective cohort studies focusing on the associations between soy food intake post-diagnosis and breast cancer survival. Our meta-analysis used the strict conducting methods according to the Cochrane handbook recommended criteria: search as many resources as possible, independently select studies

and abstract data and assess the quality. However, this meta-analysis still has limitations. First, this meta-analysis only searched English and Chinese databases. This means that those studies might fulfill inclusion criteria in other languages might be missed. Due to few studies we included (five cohort studies), publication bias analysis could be conducted. So we could not judge whether there was publication biases in this meta-analysis. That is to say, selective bias might exist in this meta-analysis. Second, we retrieved data based on published results and we did not contact authors for raw data. This makes conducting a dose-response relationship between soy foods intake and breast cancer survival difficult. Third, indeed there were a lot of instruments for assess the quality of cohort studies, such MINOR, NOS, but none of them could reflect the quality of cohort studies adequately. So we did not evaluate the quality in our meta-analysis, which might be an important flaw in this study.

Implications to the research and practice: In all included studies, the dose categories were not different. That is why we failed to conduct dose-response relationship between soy food intake and breast cancer survival. In order to better evaluate the relationship between soy food intake and breast cancer survival, standardized dose categories of soy food intake should be developed for the future studies to follow. Few included studies did not evaluate whether PR status affect the relationship between soy food intake and breast cancer survival or not. That is why it is hard for us to meta-analyze the affections of PR status on the relationship between soy food intake and breast cancer survival. So in the future, studies focusing on this topic should be conducted.

Our meta-analysis showed that soy food intake might be associated with lower mortality and recurrence. Subgroup analyses showed that soy food intake was associated with lower mortality regardless of ER and menopausal statuses. However, soy food intake was associated with lower recurrence in ER negative, ER+/PR+, and postmenopausal patients. So Based on available evidence, soy food intake should be encouraged in order to avoid mortality and recurrence, especially for ER negative, ER+/PR+, and postmenopausal patients.

In conclusion, our meta-analysis showed that soy food intake might be associated with lower mortality and recurrence. Subgroup analyses showed that soy food intake was associated with lower mortality regardless of ER and menopausal statuses. However, soy food intake was associated with lower recurrence in ER negative, ER+/PR+, and postmenopausal patients.

References

Boyapati SM, Shu XO, Zhi XR, et al (2005). Soyfood intake and breast cancer survival: A followup of the Shanghai Breast Cancer Study. *Breast Cancer Res Treat*, **92**, 11-7.

Brooks JD, Thompson LU (2005). Mammalian lignans and genistein decrease the activities of aromatase and 17beta-hydroxysteroid dehydrogenase in MCF-7 cells. *J Steroid Biochem Mol Biol*, **94**, 461-7.

Caan BJ, Natarajan L, Parker B, et al (2011). Soy food consumption and breast cancer prognosis. *Cancer Epidemiol Biomarkers Prev*, **20**, 854-8.

Constantinou AI, Lantvit D, Hawthorne M, et al (2001). Chemopreventive effects of soy protein and purified soy isoflavones on DMBA-induced mammary tumors in female Sprague-Dawley rats. *Nutr Cancer*, **41**, 75-81.

Constantinou AI, White BEP, Tonetti D, et al (2005). The soy isoflavone daidzein improves the capacity of tamoxifen to prevent mammary tumours. *Europ J Cancer*, **41**, 647-54.

Dong JY, Qin LQ (2011). Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. *Breast Cancer Res Treat*, **125**, 315-23.

Doyle C, Kushi LH, Byers T, et al (2006). Nutrition and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices. *CA Cancer J Clin*, **56**, 323-53.

Enderlin CA, Coleman EA, Stewart CB, et al (2009). Dietary soy intake and breast cancer risk. *Oncol Nurs Forum*, **36**, 531-9.

Fink BN, Steck SE, Wolff MS, et al (2007). Dietary flavonoid intake and breast cancer survival among women on Long Island. *Cancer Epidemiol Biomarkers Prev*, **16**, 2285-92.

Guha N, Kwan ML, Quesenberry Jr CP, et al (2009). Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: The Life after Cancer Epidemiology study. *Breast Cancer Res Treat*, **118**, 395-405.

Harris PF, Remington PL, Trentham-Dietz A, et al (2002). Prevalence and Treatment of Menopausal Symptoms Among Breast Cancer Survivors. *Journal of Pain and Symptom Management*, **23**, 501-9.

Helferich WG, Andrade JE, Hoagland MS (2008). Phytoestrogens and breast cancer: a complex story. *Inflammopharmacology*, **16**, 219-26.

Jones JL, Daley BJ, Enderson BL, et al (2002). Genistein inhibits tamoxifen effects on cell proliferation and cell cycle arrest in T47D breast cancer cells. *Am Surg*, **68**, 575-7; discussion 577-8.

Ju YH, Doerge DR, Woodling KA, et al (2008). Dietary genistein negates the inhibitory effect of letrozole on the growth of aromatase-expressing estrogen-dependent human breast cancer cells (MCF-7Ca) in vivo. *Carcinogenesis*, **29**, 2162-8.

Kang X, Zhang Q, Wang S, et al (2010). Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. *CMAJ*, **182**, 1857-62.

Lacey M, Bohday J, Fonseka SM, et al (2005). Dose-response effects of phytoestrogens on the activity and expression of 3beta-hydroxysteroid dehydrogenase and aromatase in human granulosa-luteal cells. *J Steroid Biochem Mol Biol*, **96**, 279-86.

Li L, Li J, Yang K, et al (2010). Ixabepilone plus capecitabine with capecitabine alone for metastatic breast cancer. *Future Oncol*, **6**, 201-7.

Liu B, Edgerton S, Yang X, et al (2005). Low-dose dietary phytoestrogen abrogates tamoxifen-associated mammary tumor prevention. *Cancer Res*, **65**, 879-86.

Messina MJ, Loprinzi CL (2001). Soy for breast cancer survivors: a critical review of the literature. *J Nutr*, **131**, 3095S-108S.

Moon YJ, Wang X, Morris ME (2006). Dietary flavonoids: Effects on xenobiotic and carcinogen metabolism. *Toxicol In Vitro*, **20**, 187-210.

Morris KT, Johnson N, Homer L, Walts D (2000). A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. *Am J Surg*, **179**, 407-11.

Nakata T, Takashima S, Shiotsu Y, et al (2003). Role of steroid sulfatase in local formation of estrogen in post-menopausal breast cancer patients. *J Steroid Biochem Mol Biol*, **86**, 455-60.

Nechuta SJ, Caan BJ, Chen WY, et al (2012). Soy food intake after diagnosis of breast cancer and survival: an in-depth analysis of combined evidence from cohort studies of US and Chinese women. *Am J Clin Nutr*, **96**, 123-32.

Pasqualini JR, Chetrite GS (2005). Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer. *J Steroid Biochem Mol Biol*, **93**, 221-36.

Qin LQ, Xu JY, Wang PY, et al (2006). Soyfood intake in the prevention of breast cancer risk in women: a meta-analysis of observational epidemiological studies. *J Nutr Sci Vitaminol (Tokyo)*, **52**, 428-36.

Santell RC, Chang YC, Nair MG, et al (1997). Dietary genistein exerts estrogenic effects upon the uterus, mammary gland and the hypothalamic/pituitary axis in rats. *J Nutr*, **127**, 263-9.

Schwartz JA, Liu G, Brooks SC (1998). Genistein-mediated attenuation of tamoxifen-induced antagonism from estrogen receptor-regulated genes. *Biochem Biophys Res Commun*, **253**, 38-43.

Shu XO, Zheng Y, Cai H, et al (2009). Soy food intake and breast cancer survival. *JAMA*, **302**, 2437-43.

Stroup DF, Berlin JA, Morton SC, et al (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*, **283**, 2008-12.

Tanos V, Brzezinski A, Drize O, et al (2002). Synergistic inhibitory effects of genistein and tamoxifen on human dysplastic and malignant epithelial breast cells in vitro. *Eur J Obstet Gynecol Reprod Biol*, **102**, 188-94.

Taylor CK, Levy RM, Elliott JC, et al (2009). The effect of genistein aglycone on cancer and cancer risk: a review of in vitro, preclinical, and clinical studies. *Nutr Rev*, **67**, 398-415.

Trock BJ, Hilakivi-Clarke L, Clarke R (2006). Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst*, **98**, 459-71.

Velentzis LS, Woodside JV, Cantwell MM, et al (2008). Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know. *Eur J Cancer*, **44**, 1799-806.

Wang TTY, Sathyamoorthy N, Phang JM (1996). Molecular effects of genistein on estrogen receptor mediated pathways. *Carcinogenesis*, **17**, 271-5.

Zhang YF, Kang HB, Li BL, et al (2012). Positive effects of soy isoflavone food on survival of breast cancer patients in China. *Asian Pac J Cancer Prev*, **13**, 479-82.