MINI-REVIEW

Benefits and Harms of Phytoestrogen Consumption in Breast Cancer Survivors

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Abstract

Worldwide, breast cancer is the most common malignant neoplasm and the second most common cause of cancer death in women. This malignancy is recognized to be estrogen-dependent and due to this feature, hormone replacement therapy is regarded as potentially dangerous in breast cancer survivors who seek relief of their menopausal symptoms. Whereas hot flashes are detected in nearly half of postmenopausal women with a relatively high frequency and severity, botanic sources of estrogens have been proposed as an alternative treatment. Nevertheless, estrogenic properties of these compounds suggest possibility of stimulating cancer recurrence or worsening prognosis in survivors. As well, effects in improving vasomotor climacteric changes is controversial. Many studies have considered the subject, some focusing on efficacy of phytoestrogens for control of menopausal symptoms, and others discussing effects of these compounds on breast cancer outcome in terms of survival or recurrence. The present article is a concise review of the effects of consumption of phytoestrogens on menopausal symptoms, namely hot flashes, and breast cancer recurrence and mortality in survivors of the disease. Overall, the major part of the current existing literature is in favor of positive effects of phytoestrogens on breast cancer prognosis, but the efficacy on menopausal symptoms is probably minimal at the best.

Keywords: Breast - cancer - climacteric - estrogens - menopause - neoplasm - phytoestrogens - tamoxifen

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Introduction

Breast cancer is the most common female malignancy and the second cause of death due to cancer around the world (Fritz et al., 2013). Exogenous and endogenous estrogens are recognized as being associated with the etiology of breast cancer by stimulating cell growth and proliferation; higher and longer lifetime exposure to estrogens could therefore be a major risk factor for promoting or initiating breast cancer (Liu et al., 2005). As a result, apprehension has always accompanied the use of estrogenic compounds in breast cancer survivors; consumption of phytoestrogens, as a type of estrogen, is also associated with much controversy in these women.

Phytoestrogens: Structure, Types, and Functions

Phytoestrogens are secondary polyphenolic plant substances with similarities to 17-beta estradiol in chemical structure (Davis et al., 2008). These are categorized into three main classes: isoflavones, coumestans, and lignans. Isoflavone phytoestrogens are the major active component in soy products (Chen et al., 2003) and are the most widely used group of phytoestrogens consumed. Soybeans and isoflavone-containing foods are found in a variety of fruits, vegetables, and cereal products. After consumption, these substances undergo enzymatic conversion in the gut; isoflavones are metabolized into aglycones, genistein and daidzein, lignans into secoisolariciresinol diglucoside, and coumestans into coumestrol. These metabolites include a phenolic ring that competes for binding to estrogen receptors, which results in weak estrogenic activity, hence the term phytoestrogen (Bedell et al., 2014); daidzein and genistein have been mostly investigated in related studies.

Rate of consumption of these compounds varies greatly in different countries and cultures; highest rates are seen in Asian people, who use approximately 20-50 mg per day of these substances (Mense et al., 2008; Fritz et al., 2013).

Evidence has been unconvincing in providing distinct mechanisms of action of phytoestrogens. The 3-fold lower risk of breast cancer in Asian women compared with their western counterparts, as well as lower serum concentration of estrogen in the former group may be attributed to different lifestyle and diet patterns, including routine use of dietary phytoestrogens (Mense et al., 2008; Fritz et al., 2013). The observation that second- and late-generation offsprings of women who migrated from Asia to Western countries had similar breast cancer risks

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to their counterparts in the host country supported this assumption against the contribution of genetic factors (Mense et al., 2008).

Menopausal Symptoms in Breast Cancer Survivors

Menopausal symptoms (MS) are common during peri-menopausal and post-menopausal periods in women (L'Esperance et al., 2013). Some of these symptoms such as hot flashes, night sweats, insomnia, tiredness, depression, vaginal dryness, irritability, anxiety, dyspareunia, decreased libido, leuchorrhea, and vaginal bleeding can deeply and negatively affect women's quality of life (QOL) (Biglia et al., 2003; Bruno and Feeney 2006). Vasomotor hot flashes, defined as a sudden feeling of severe warmth localized particularly in face and neck areas, occurs in two thirds of postmenopausal healthy women, but there is considerable differences in intensity, frequency, and onset of time of hot flashes in different races and cultures (Loprinzi et al., 2001). Hot flushes reach intolerable levels in10%–20% of cases (Boekhout et al., 2006).

MS occurs in up to 66% of breast cancer survivors as well, because many cases of breast cancer occur in post-menopausal women, and in premenopausal cases is the result of estrogen withdrawal which happens as the most common side-effect of adjuvant therapies, including chemotherapy and hormone therapy (Biglia et al., 2003). More severe symptoms in these patients, accompanied by higher incidence, and longer time persistence compared with healthy individuals, can greatly reduce their quality of life (Biglia et al., 2003; Boekhout et al., 2006; Bruno and Feeney 2006).

Due to recent improvement in breast cancer treatment and earlier detection of the disease, number of long-term survivors is increasing (Kang et al., 2010), and MS would therefore be a greater problem. Given the importance of the issue of disturbed QOL secondary to increased MS, many studies have been conducted among breast cancer survivors regarding best treatment options (Biglia et al., 2003; Boekhout et al., 2006).

Tamoxifen and Menopausal Symptoms in Breast Cancer Survivors

Estrogens affect breast tissue via estrogen receptors by influencing cell growth and differentiation. Therefore, for its prognostic and therapeutic implications, estrogen receptor status is routinely assessed in breast cancer cells after diagnosis. Hormonal treatments are today one of the most important options in receptor positive tumors; selective estrogen receptor modulators (SERM) are a common category of drugs used for this intention in premenopausal women. These act as receptor binding competitors of estrogens; the most frequently used SERM is tamoxifen (Abdulkareem and Zurmi 2012). Former studies had definitely confirmed that a 5 years course of adjuvant tamoxifen decreased disease recurrence and mortality from breast cancer throughout the first 15 years after diagnosis in cases of estrogen receptor positive early breast cancer. Thereafter, the worldwide ATLAS trial (Adjuvant Tamoxifen: Longer Against Shorter), including 12 894 women with early breast cancer who had already received tamoxifen for 5 years, compared the effects of continuing tamoxifen for 5 other years versus stopping at 5 years. Results showed that using tamoxifen for 10 years in ER-positive disease further decreased recurrence and mortality, probably halving mortality during the second decade after diagnosis (Davies et al., 2013). However, as an opponent to estrogen in some other body tissues, tamoxifen also induces some adverse effects. As an estrogen opponent, tamoxifen provokes MS; the most common side effect of tamoxifen is hot flashes, which occurs in nearly half of cases and is generally more severe than in women with naturally occurring menopause in terms of frequency and intensity (Loprinzi et al., 2001).

Treatment Options for Menopausal Symptoms Overall

Hormone replacement therapy (HRT) with synthetic estrogen and progesterone compounds is the first line therapy for MS in healthy women; these not only have the potential to alleviate the entire range of MS, but can also partially protect the patient against osteoporosis and cardiovascular disease (Davis et al., 2008). Despite these benefits, many women prefer not to use HRT because of potential adverse effects such as an amplified risk of deep venous thrombus formation, hepatic disease, and an increased risk of cancer (Bedell et al., 2014).

Some trials have shown that a number of non-medicinal ways such as paced respiration, yoga and exercise, acupuncture and magnet therapy, or homeopathy may have some positive effects on MS (Pinkerton et al., 2009). Some other suggested treatments include selective serotonin reuptake inhibitors (paroxetine (Weber and Thacker 2014), citalopram, and venlafaxine (Handley and Williams 2014), or plant extracts with similar properties (black cohosh and licorice). As well, clonidine, gabapentin, Ginseng, evening primrose, vitamin E have all been used with different results in decreasing MS (Wong et al., 2009). Botanic products with progestogenic activities (red clover and chasteberry) or estrogenic action (phytoestrogens- soy, red clover, licorice) (Hajirahimkhan et al., 2013) are other recommended options. Overall, food sources rich in phytoestrogens, are being used as an alternative to HRT by many women. However, positive effects of phytoestrogenic compounds on MS or even bone loss have not been uniformly demonstrated (Levis et al., 2011), studies have shown that - based on type of intestinal flora, diet antibiotic use, and illness- some women can metabolize phytoestrogenic compounds into effective substances that can successfully reduce MS (Bedell et al., 2014).

Effect of Phytoestrogens on Menopausal Symptoms Overall

Some of the mostly researched alternatives to HRT have been phytoestrogens, especially soy isoflavones, although results of past studies are controversial (Secreto

et al., 2004). In 1995, Murkies et al showed a very good response of hot flushes to soy flour in comparison with wheat flour (Murkies et al., 1995). Brzezinski et al, in 1997, demonstrated significant improvement in hot flushes and vaginal dryness in women consuming a phytoestrogen-rich diet compared with controls (Brzezinski et al., 1997), and Albertazzi et al demonstrated a very good response of hot flushes to soy protein isolate in 1998 (Albertazzi et al., 1998). In 1999 Washburn et al showed that dietary soy supplementation could not only reduce vasomotor symptoms, but also affect positively the lipid profile and blood pressure in post-menopausal western women (Washburn et al., 1999). The studies of Upmalis et al (Upmalis et al., 2000) and Scambia et al (Scambia et al., 2000) in 2000 and the research carried out by Faure et al in 2002 were confirmations that isoflavones could be an appropriate alternative to HRT for hot flushes. In opposite to these results, the studies of St Germain et al in 2001 (St Germain et al., 2001) and Burke et al in 2003 (Burke et al., 2003) showed that although soy protein caused improvement in hot flushes, the elimination of isoflavone from the product did not have any consequence on this effect.

More recent works also present conflicting data. In a randomized clinical trial conducted by Levis et al in 2011, no improvement in MS was found after a 2-year period of consumption of soy isoflavone-containing tablets in 122 menopausal women in comparison with 126 controls who received placebo (Levis et al., 2011). In a review carried out by Eden et al in 2012, five meta-analyses and one review about the impact of phytoestrogens on MS were evaluated, and the overall results could not clearly show a benefit for isoflavone use in menopause; the authors conclude that if isoflavones have an impact on hot flushes, it is not much more than placebo (Eden, 2012) . However, a large systematic review was performed by taku et al in the same year, assessing the efficacy of soybean isoflavones in the relief of hot flashes in peri- and postmenopausal women. According to their very strict criteria, they could include 19 randomized controlled trials in their review, and concluded that soy isoflavones can significantly reduce hot flushes in the target groups (Taku et al., 2012). In 2014, Thomas et al conducted a systematic review focusing on trials that had studied the effect of isoflavones and amino acids on hot flushes and at least one other MS, and included 17 works in their review. They concluded that isoflavones significantly improved hot flashes and co-occurring symptoms in peri- and postmenopausal periods (Thomas et al., 2014).

Treatment Options for Menopausal Symptoms in Breast Cancer Survivors

In 1997, a consensus development conference on

Table 1. Summary of Human Studies about Effects of Phytoestrogens on Menopausal Symptoms in Breast Cancer survivors

First author- Pub year-type of study	Purpose of study: assessment of …	Number of cases	Type/ dose of PE used	Results
Quella et al. 2000 RCT, cross over design	Effect of soy PE on HF in BCS	149 BCS divided in 2 groups	soy tablets 150 mg soy/d or placebo; 2 periods of treatment for 4 w with 1 w rest in between for cross over	No significant difference between 2 groups
Van Patten et al. 2002 RCT	Effect of soy PE on HF in BCS	59 cases, 64 controls	500 mL of a soy or placebo beverage	No significant difference between 2 groups
Nikander et al. 2003 - RCT, cross over design	Effects of PE on MS and QOL in BCS	56 BCS divided in 2 groups	PE tablets 114 mg isoflavonoid/d or placebo; 2 periods of treatment for 3 m with 2 m rest in between for cross over	No significant difference between 2 groups
MacGregor et al. 2005 - RCT	Effects of soy PE on MS and QOL in BCS	33 cases, 35 controls	12 w of soy capsules (overall 70 mg/d of soy PE) or placebo	No significant difference between 2 groups
Gold et al. 2006 (WHEL*) - multicenter RCT	Association of MS with soy food, and effects of soy PE on MS, in early stage BCS	Overall 2198 BCS	Soy-rich food in cases, regular diet in controls	No association between use of PE and MS
Dorjgochoo et al. 2011 - Cohort	Association of MS with soy food	4842 Chinese BCS	Habitual dietary intake of soy foods was assessed**	No significant association between soy PE intake and MS
Pruthi et al. 2012 - RCT	Effects of flaxseed*** on HF	88 cases, 90 controls ****	Flaxseed bar (providing 410 mg of lignans) for 6 w, or placebo	No significant difference between 2 groups

Pub=publication, PE= phytoestrogen, RCT= randomized controlled (clinical) trial, HF=hot flashes, BCS=breast cancer survivors, d= day, w=week, MS= menopausal symptoms, QOL= quality of life, m= month. *WHEL study =Women's Healthy Eating and Living **This study included participants of the Shanghai Breast Cancer Survival Study (SBCSS) *** the richest source of lignans (one of the major classes of phytoestrogens) ****half in each group were BCS

estrogen-deficiency symptoms concluded that estrogen-replacement therapy should be avoided in patients with a history of recent breast cancer (Treatment of estrogen deficiency symptoms in women surviving breast cancer, Part 6: Executive summary and consensus statement. Proceedings of a conference held at Boar's Head Inn, Charlottesville, Virginia, September 21-23, 1997. Oncology (Williston Park) 1999;13:859-861, 865-856, 871-852). Although few trials demonstrated breast cancer progression due to HRT (Col et al., 2001; Beral et al., 2003), this treatment modality is still contraindicated in breast cancer survivors due to probable rise or acceleration in tumor cell growth (Biglia et al., 2003).

Severity of irritating symptoms especiallly hot flashes on one hand, and concern about the safety of therapies including synthetic hormones on the other, encourage these groups of patients to use simple strategies in order to alleviate their symptoms. These approaches include wearing light clothes, lowering room temperature, using air conditioners, and avoiding hot or spicy food (Boekhout et al., 2006). However, the overall efficacy of these behavioral options is modest. In the recent decade, many studies have been conducted to find an effective drug with minimal side effects and low risks to treat MS in patients surviving breast cancer, hence clinicians have been considering non-hormonal drugs to ameliorate MS (Biglia et al., 2003); serotonin reuptake inhibitors, clonidine, veralipride, gabapentin, black cohosh, primrose oil, vitamin E, and phytoestrogens are some examples which have been studied as probably effective in easing climacteric symptoms in this group (Loprinzi et al., 2001; Antoine et al., 2007).

Effect of Phytoestrogens on Menopausal Symptoms in Breast Cancer Survivors

As for the general population, improvement of MS by using phytoestrogens has been controversial in breast cancer survivors. Table 1 summarizes results of some studies about this subject. As demonstrated, efficacy of phytoestrogens in reducing MS has not been confirmed in most studies.

Effect of Phytoestrogens on Menopausal Symptoms in Tamoxifen Users

Breast cancer survivors undergoing hormone therapy must receive a symptom relief treatment that does not affect the efficacy of the regimen. Phytoestrogens can probably be a good option in these cases (Bedell et al., 2014).

In 2002 ,after implanting MCF-7 cells in ovariectomized athymic mice, Ju et al assessed interactions between genistein (as a soy isoflavone) and tamoxifen on the growth of these estrogen- dependent breast cancer cells. They found out that genistein lowered the effect of

Table 2. Summary of Human Studies about Effects of Phytoestrogens on Breast Cancer Prognosis

Author, year of study, type of study	Purpose of study: assessment of…	Number of cases studied	Type/ dose of PE used	Median Follow up time	Results
Shu et al., 2009 Cohort, longitudinal	Association of soy food with BC mortality and recurrence in BCS	5042 BCS	soy foods commonly used in Shanghai	3.9 y after Dx	Significant decreased mortality and recurrence with higher soy food intake
Guha et al., 2009 (LACE*) --Cohort	Association of soy food with BC recurrence in BCS	1954 BCS	Several kinds of soy-containing foods	6.31 y after enrollment	Non-significant decreased recurrence with higher soy food intake
Kang et al., 2010 Cohort	Association of soy food with BC mortality and recurrence in BCS	508 BCS under adjuvant HT	Several kinds of soy-containing foods	5.1 y after Dx	Significant decreased recurrence with higher soy food intake in postm with ER+, PR+ BC
Caan et al., 2011 following (WHEL**) study-Cohort	Effects of soy foods on BC prognosis in BCS	3088 early stage BCS	Several kinds of soy-containing foods	7.3 y after enrollment	Significant decreased mortality with higher soy food intake, but non-significant highest level of intake
Zhang et al., 2012 Cohort	Association of soy food with BC mortality and recurrence in BCS	616 BCS	Several kinds of soy-containing foods	52.1 m after Dx	Significant decreased mortality and recurrence with higher soy food intake esp. in ER+ BC
Nechuta et al., 2012 (ABCPP***)- 2 US and 1 Chinese cohort, pooled analysis	Association of soy food with BC mortality and recurrence in BCS	9514 BCS	Several kinds of soy-containing foods	7.4 y after Dx	Non-significant decreased mortality and significant decreased recurrence with higher soy food intake

Pub=publication, PE=phytoestrogen, postm= post-menopausal, BC= Breast Cancer, BCS= breast cancer survivors, y=year, Dx= diagnosis, RCT= randomized controlled (clinical) trial, PE= phytoestrogen, HT=hormone therapy, ER+=estrogen receptor positive, PR+=progesterone receptor positive, m=month, esp.=especially. *LACE = Life After Cancer Epidemiology study, **WHEL= Women's Healthy Eating and Living study***

tamoxifen on cells (Ju et al., 2002). Nevertheless, the work of Liu et al in2005 on wild-type erbB-2/neu transgenic mice showed that only low doses of isoflavones could interact with tamoxifen function, whereas higher doses intensified the inhibitory effect of tamoxifen on cancer cell growth (Liu et al., 2005) . As well, Constantinou et al demonstrated on the same year that daidzein had very good strengthening consequences on anti-breast cancer effects of tamoxifen, while genistein had opposing effects (Constantinou et al., 2005).

In human studies, Wu et al measured blood levels of tamoxifen and its important metabolites in Asian-American women and demonstrated that serum concentrations had no association with rate of soy-food consumption or serum levels of isoflavones and their main metabolites (Wu et al., 2007) . Nevertheless, in the Shanghai Breast Cancer Survival Study, where a cohort of 5042 breast cancer survivors were followed for a median time of more than 3 years by Shu et al, the protective effects of soy food intake on cancer recurrence and mortality, were seen in both tamoxifen-users and non-users (Shu et al., 2009). As well, when Guha et al followed a cohort of 1954 female breast cancer survivors for more than 6 years, they showed a significant reduction in cancer recurrence in tamoxifen-users when consuming highest levels of daidzein compared to lowest intakes. T hey concluded that isoflavones not only do not to interfere with tamoxifen efficacy, but also may increase its effects (Guha et al., 2009).

Effect of Phytoestrgens on Breast Cancer Prognosis

Some epidemiologic studies have suggested that high consumption of phytoestrogens, mostly soy and unrefined grain products, may lower the risk of some cancers such as colorectal, prostate, and breast cancer. As well, ecologic observations have confirmed that the lower incidence of breast cancer among Asian women may be related to the more frequent use of phytoestrogens among them (Mense et al., 2008). As well, mammographic density has not been shown to be affected by soy or phytoestrogen products, and recent in vitro work show either a weak proliferative effect of soy isoflavones on breast cancer cells or the blockage of proliferative effects of estradiol on these cells (Pitkin 2012). Human studies are not uniform in results regarding effects of phytoestrogens on breast cancer in survivors; Table 2 shows a summary of some studies.

Conclusion

Most of the present literature is in favor of the safety of phytoestrogens in breast cancer survivors, and even a protective effect leading to decreased breast cancer recurrence and mortality has been confirmed in a major proportion of relevant studies. Nevertheless, although administration of synthetic female sex hormones has a great efficacy in improving hot flashes and other menstrual symptoms, botanic estrogens have not been shown to exert the same positive effects in controlling these symptoms in breast cancer survivors.

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