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Phytoestrogens and Breast Diseases: A Matter of Concern for the Gynecologist

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ABSTRACT

Background: This study is the last part of a quadruple series investigating the relationship between breast disorders and the consumption of exogenous sex hormones. Due to the structural similarity of phytoestrogens to estrogen and the confusion associated with their possible estrogenic activity in the breast, this part aims at reviewing of the literature on the relationship between phytoestrogens and breast disorders.

Methods: We carried out a thorough search of the existing literature using appropriate keywords with the aim of finding systematic reviews, reviews, cohort studies and clinical trials regarding the effects of phytoestrogens on the breast in the general population, breast cancer survivors, women at high risk of breast cancer and those with benign breast diseases.

Results: Many studies have approached the relationship between phytoestrogens and the risk of breast cancer or recurrence of the disease. Also, a few studies have considered the effects of phytoestrogens on benign breast disorders, BRCA genes, and the risk of breast cancer in high risk women. However, the variety of studies and the retrospective nature of many of them make it impossible to draw definite conclusions.

Conclusion: Existing data generally supports the safety of phytoestrogen consumption regarding the risk of breast cancer in the general population, in women with benign breast disorders, in those at risk of breast cancer, and even in survivors of the cancer. However, due to insufficient evidence, prescription of high doses of phytoestrogens is still not recommended.

Introduction

Breast disease and specifically breast cancer (BC) are affected by female sex hormones. While endogenous hormones affect the breast physiology and are involved in the pathophysiology of benign and malignant breast diseases, exogenous sex hormones may adversely affect the breast.[1,2]

Some considerations must be taken into account while prescribing hormones for various gynecologic disorders. In four consecutive studies concerning exogenous sex hormones and the breast as a matter of concern for gynecologists and other physicians who prescribe these medications, we have focused on OCP3, HRT[4], and the use of other synthetic sex hormones[5] in women without any breast lesion as well as those affected by various breast disorders. As the last part of that quadruple research, we review the literature on the effect of phytoestrogens (PEs) on BC in the present work.

The structure of PEs is similar to 17-β-estradiol (E2), and are therefore recognized as plant-derived (phyto) estrogens. Due to this similarity, PEs may bind to estrogen receptors (ER) and suppress or, conversely, prompt estrogen-dependent conditions.[6]

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There are five main classes of PE, including isoflavonoids, coumestans, stilbenes, flavonoids and lignans, which are found in various plant foods such as soybeans, chickpeas, flax, mung beans, beans and lentils.[7-9]

The issue considered in this article warrants attention from two different perspectives. First, hot flashes and other hormone-deprivation symptoms are common in BC survivors who undergo endocrine therapy or chemotherapy. Hormone replacement therapy is the most effective treatment for alleviation of these symptoms, but possible negative consequences for the cancer course prevents their use. Secondly, as PEs are often freely used by women or prescribed by physicians, the potential effects of such PE-containing foods on breast diseases and the potential risks they pose for BC need to be investigated.[10-12]

A variety of phytoestrogen-containing foods and factory-based combinations and supplements of these compounds are available. Studies of PE in various forms and supplies are innumerable, but we did not aim to systematically review all of them. Our aim was to review the effects of dietary intake or supplemental prescription of these compounds on the breast.

Methods

We aimed to find valid data concerning the effects of PE on the breast in the general population, women with benign breast disorders (BBD), high-risk women, and breast cancer survivors. We carried out a comprehensive search in Google Scholar and PubMed using combinations of these keywords: "benign breast", BRCA, "breast cancer", "breast cancer survivor", "family history", fibroadenoma, fibrocystic, flax, high-risk, isoflavonoid, isoflavone, lignan, phytoestrogen, soy, and "systematic review".

Due to the bulk of the existing literature on the subject, we focused first on systematic reviews, then on solitary cohort studies and clinical trials as well as reviews. Thus, we extracted data from all relevant studies.

Results and Discussion

1. Phytoestrogens in the general population

1.1. Phytoestrogens and their effects on the breast composition in the general population

Many estrogen compounds cause breast pain and breast edema. Whether the same changes occur secondary to the use of phytoestrogens was investigated in two studies by Dastjerdi et al.[13], and Alipour et al.[14] In these studies, placebo and isoflavone supplements were compared regarding their effects on breast exam and breast ultrasound but no significant differences were detected between the two groups in either study.

1.2. Phytoestrogens and the risk of breast cancer in the general population

Due to the high rate of PE consumption by Asians and the low incidence of BC among them, the possibility of a protective effect for these compounds against BC has been put forward.[11] Many studies have considered the effect of PE on BC risk. However, the designs of these studies and their findings are so diverse that conclusive results and definitive conclusions cannot be easily obtained.

Some researchers have considered the risk of BC as a function of the rate of consuming PE-containing foods and supplements. Some studies have studied one specific type of PEs while some others have considered all or multiple forms of PEs. Several works have investigated the association between PE consumption and specific subtypes of BC, while others have considered pre- versus post-menopausal BC.

Flaxseed which contains a large amount of lignans has been the subject of multiple studies. Calado et al. have reviewed the relevant literature and found several studies on mice, all of which showed a decrease in tumor load or growth in animals fed with flaxseed.[15] Also, human studies have showed a reduced risk of breast cancer in women consuming higher amounts of flaxseed. This effect was more prominent in postmenopausal BC under certain conditions, and limited to postmenopausal ER+ tumors in one study. The researchers concluded that further research and especially clinical trials considering flaxseed and BC risk need to be conducted to confirm the association.

Peeters et al. carried out a review of 18 articles containing analytical epidemiological data about the effect of dietary PE on BC risk, showing that PE intake had no protective effect against BC, except for the use of PE in very high doses or in adolescence.7 Dong et al. systematically reviewed prospective studies on the potential relationship between soy isoflavone intake and BC incidence.[16] Their meta-analysis suggested an indirect association only in Asians but failed to show any dependence on the dose of PE intake. Fritz et al. [17] carried out a thorough review of the effect of PE on BC, reporting no increase in BC risk with the use of dietary PE. They also found that amounts of PE intake comparable to traditional Japanese food may have a protective role against the cancer. Nagata et al. reviewed all epidemiological studies investigating the effects of dietary soy on incidence of BC among Japanese women and mortality associated with it. They considered five cohorts and six case–control studies, the results of which varied from no effect to a strong inverse association between dietary soy and BC risk. They concluded that soy intake may cause BC risk reduction in the Japanese population.[18] Zhao et al. carried out a systematic review of all prospective cohort studies on the association between dietary isoflavones and BC risk. They conducted a meta-analysis of 16 eligible studies, showing no significant association.[19]

Apart from these studies, two population-based

case-control studies in 2004 reported a reduced risk of premenopausal BC due to high levels of dietary lignan [20] and high intakes of isoflavonoids (for ER+ tumors).[21] Two other population-based case-control studies carried out in Canada in 2006 [22] and 2013 x compared the effects of consuming PE during adolescence, reporting a reduced risk of BC in adults with a higher intake. This effect was limited to postmenopausal BC, mainly ER+ BC in the latter.

2. Phytoestrogens in BC survivors

Phytoestrogens have been investigated in managing menopausal symptoms and particularly hot flashes in breast cancer survivors, although their beneficial effect in the general population is still uncertain. Two earlier clinical trials in 2000 [11] and 2002 [12] compared the effects of dietary PE in soy to placebo on managing hot flashes in BC survivors, detecting no significant differences. A systematic review by Flower et al. [24] assessed the positive effects of flaxseed on menopausal symptoms, finding a non-significant reduction in hot flashes. In addition, a review of clinical trials in 2016 comparing PE with placebo for the treatment of hot flashes in BC survivors did not find any significant effect for PE.[9] Moreover, a recent review of different types of management of the symptoms in these patients did not find PE as an effective therapy.[25]

An important issue which is still controversial is the safety of PE in BC prognosis. While some studies suggest the possibility of worsening BC by consuming PE due to its similarity to estrogens, many others support its protective role.[15,26,27]

In 2011, Dong et al. reviewed prospective studies examining the effect of soy isoflavones on the recurrence of BC among the survivors. They failed to observe a clear relationship, although a reduction in recurrence was more likely to be associated with the use of PE.[16] In 2013 Fritz et al. performed a thorough review of all observational studies as well as randomized and uncontrolled trials concerning the association between dietary isoflavones and recurrence of BC in survivors. They showed that dietary use of soy was safe for BC survivors independent of tamoxifen use, possibly decreasing the rate of recurrence and mortality. However, they recommended against the consumption of high doses of soy in this population due to insufficient evidence.[17] In another concurrent systematic review by Chi et al., a systematic review and meta-analysis of five cohort studies showed a diminished rate of recurrence in BC survivors and lower mortality in postmenopausal women. These results were applicable to both hormone receptor-positive and negative tumors. However, a recent systematic review and meta-analysis of observational studies by Qiu et al. showed different results. They detected a slightly decreased survival in post-menopausal women with BC who were PE consumers before the disease, whereas PE consumption following the disease had no effect on survival. They also demonstrated a lower recurrence rate in BC survivors who used dietary PE before or after the diagnosis.[28]

3. Phytoestrogens in high-risk women

Prospective studies on the use of PE in high risk women for breast cancer have not been performed, and thus we cannot be certain whether the use of PE would have a protective or stimulating effect in this group. However, this can be indirectly inferred by considering some existing studies.

3.1. Positive family history of breast cancer

In order to investigate the risk of BC in regard to PE consumption in women with a positive family history, Powles et al. designed a prospective study including either three-year consumption of red clover or placebo in healthy women with a family history of BC. They measured mammographic density as a risk marker for BC, finding no significant difference in the two groups.[29]

Other studies focused on the association between PE and BC by evaluating the mediating role of family history. For example, in a population-based case–control study by Thanos et al., a possible reverse association was found between PE intake during adolescence and future risk of BC. A family history of BC did not significantly affect this result.[22] Also, the lack of association between PE intake and BC detected in the prospective population-based cohort study of Hedelin et al.[30] was not affected by a family history of BC. In addition, in a nested case-control study (out of a large multiethnic cohort study) by Goodman et al., where PE levels were measured in pre-diagnosis urine specimens in postmenopausal BC cases and controls, the indirect association found between high PE use and BC was not mediated by any potential confounder, including family history of BC.[31]

3.2. BRCA mutation careers

The effect of PE on BC risk in genetically positive women has been rarely investigated. In our review, we found only one study which had considered the subject among gene-positive women.

The Korean Hereditary Breast Cancer Study (KOHBRA) was designed to evaluate nutritional issues in BRCA mutation carriers. Among various dietary elements, Ko et al. found out that the use of soy-containing food lowered the risk of BC in gene-positive participants.[32]

We also found a few animal studies or in vitro works on the effect of PE on the gene itself at the cellular-molecular level. Bernard et al. investigated the effect of daidzein and genistein, two isoflavones, on BRCA2 in BC cell lines, observing a down-regulation in some gene expressions, suggesting a possible preventive effect for these compounds.[33]

Bosviel et al. studied whether genistein and daidzein could affect DNA methylation in mutated BRCA1 and BRCA2 genes in BC cell lines, reporting that these can de-methylate DNA and bring back the oncosuppressor expression of the genes.[34] In a recent study on mice bred with BRCA1 gene, Donovan et al. fed animals with genistein-rich food from birth to 50 days. They found a decrease in methylation of BRCA1, suggesting that dietary genistein might have a therapeutic role.[35]

4. Phytoestrogens in benign breast disorders

BBD is frequent as many women refer to gynecology or breast clinics for breast pain, where fibrocystic changes (FCC) are the most common finding among them.36 In addition, fibroadenomas (FA) are among the most common benign breast lumps.[37] In our review, we found a few clinical trials regarding the effects of PE on BBD. Wu et al. examined whether the rate of FCC was affected by soy products, finding a non-significant reduced risk of FCC with proliferation and FCC with atypia.[38] Mirghafourvand et al. compared the effect of flaxseed on cyclical mastalgia, finding a significantly reduced mastalgia in the case group compared to controls after two months.[39] Atkinson et al. measured the levels of equol, a bacterial metabolite of daidzein, in plasma of women with FCC and controls. However, they did not find any evidence in favour of a positive association between these conditions.[40] Kişakeviç et al. investigated the effects of a 6-month use of phytoestrogens on breast pain and ultrasound-detected breast structure in perimenopausal and early-menopausal women with and without FCC. They detected a lowered ultrasound-detected tissue density and a reduced number of cysts and a decreased size after 3 months, as well as a decrease in severity and frequency of mastalgia in the case group after 6 months.[41]

In conclusion, PE has been broadly explored regarding its relation with BC, and to a lesser extent with other breast conditions. Studies are largely different in their designs and definitions, and the type, amount, and timing of PE consumption, in addition to ethnic dissimilarities in study cases preclude conclusive results. Nevertheless, the existing data are mostly in favor of the safety of these compounds in the general population as well as in women with BC or at risk of the disease. Due to insufficient evidence, prescription of high doses of PE for the latter two groups is still not recommended.

Conflict of Interest

None.

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