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May isoflavones prevent breast cancer risk?

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Breast cancer still represents a challenge in Brazil, as it is the most frequent malignant neoplasm with more than 14,000 deaths recorded in 2014. It is the leading cause of death in the female population[1]. It is also commonly diagnosed among women in Western countries as the second leading cause of cancer[2]. It is the sixth leading cause of mortality among women, after acute myocardial infarction, pneumonia, diabetes, stroke, and chronic obstructive pulmonary disease. Breast cancer is a heterogeneous disease and can be classified by clinical, histopathological, and molecular parameters[3]. In this classification, the estrogen receptors play an important role and seem to influence the development of breast neoplasms or response to treatment[4]. However, women with breast cancer face the consequences of hypoestrogenism due to chemotherapy treatment or being postmenopausal. Thus, several substances are being suggested to reduce the vasomotor symptoms that appear in these women.

The effects of soy isoflavones, due to their structural similarity and molecular size that resemble estrogens, have the ability to bind with greater affinity to estrogen beta-receptors; for this reason, they are called phytoestrogens[5-7]. The binding of phytoestrogen to the receptor can result in partial activation of the receptor (agonist effect) or displacement of estrogen molecules, thus reducing receptor activation (antagonistic effect)[8].

Intake of soy at high dosages may have a statistically significant reduction in breast cancer risk[9]. Epidemiological studies show that soy consumption is associated with low incidences of hormone-dependent cancers, including breast and prostate cancer in Western countries[10]. However, there are other components in soy that can also have a biological effect and there is a substitution in these countries of animal protein for soy protein. Therefore, this is still a controversial point[11].

Soy contains large amounts of isoflavones, such as genistein and daidzein. Genistein, one of the predominant soy isoflavones, may inhibit several steps involved in carcinogenesis by targeting estrogen- and androgen-mediated signaling pathways in carcinogenesis processes, in addition to its antioxidant properties showing to be a potent inhibitor of angiogenesis and metastasis[12,13]. In vivo and in vitro studies have clearly shown that genistein is a promising reagent for the chemoprevention and/or treatment of cancer. However, results are still conflicting and there is still no consensus on its effectiveness on the breast cancer risk[11,14,15].

Prospective cohort meta-analysis studies suggest that high soy intakes may statistically reduce the risk of breast cancer[9], other systematic and meta-analysis reviews conclude that there is a lack of evidence as the benefit would be small and irrelevant in clinical practice[16]. Thus, further prospective cohort studies are needed to determine the causality of this relationship, as well as to explain the mechanisms involved in the association between isoflavones and breast cancer[9].

A randomized, double-blind, placebo-controlled clinical trial conducted by Delmanto et al.[17] determined the effect of soy isoflavones on breast density and breast parenchyma assessed by mammography in 80 postmenopausal women. After 10 months of isoflavone supplementation, it was found that daily intake of 100 mg isoflavones did not affect breast density (assessed by mammography) and breast tissues (assessed by ultrasound).

Khan et al.[18] evaluated the effect of soy isoflavone supplementation on breast epithelial proliferation and other biomarkers in high-risk, healthy Western women. The breast cell proliferation is an intermediate marker of breast cancer risk generally considered more reflective of risk than mammographic density. Cells were examined for Ki-67 labeling index and atypia. The study involved 98 pre- and postmenopausal women. After 6

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months of isoflavone supplementation, the authors found that daily intake of 235 mg of isoflavones did not increase cell proliferation in pre- and postmenopausal women compared with placebo. In contrast, a hormone therapy combination increased breast cell proliferation in postmenopausal womenhan[19].

Although there is a greater consumption of soy and isoflavones worldwide, it is still too early to understand the real impact of these substances on the reduction of the risk of incidence, recurrence, and mortality from breast cancer. There is no enough evidence in the literature of serious adverse effects such as increased risk for breast cancer and cardiovascular disease with the use of isoflavones in high doses (≤100 mg)[20]. Although studies on herbal medicine are still in progress, there are only a few still many myths to overcome[21].

The extramammary benefits of soy are evident as in vasomotor symptoms[22], skin[23], bone mass[24], and genital tract[25]. However, the risk of breast cancer needs to be better explored and evaluated, mainly in the long term, and there are still risks that should be better evaluated, such as metabolic ones. In addition, the indication of isoflavone extracts should be individualized, as estroprogestative hormone therapy in the climacteric[26], guiding the patient on the benefits and risks, as well as respecting the individual preferences of postmenopausal women until new evidences in the literature.

AUTHORS' CONTRIBUTIONS

AAFC: Conceptualization, Writing – original draft, Writing – review & editing. **RSS:** Conceptualization, Resources, Validation. **GSS:** Supervision, Validation. **PAL:** Writing – original draft. **MJS:** Supervision, Writing – review & editing. **JMSJ:** Supervision, Writing – review & editing.

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