Relationship Between Soy Intake and Breast Cancer: A Non-Systematic Review

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Abstract

The growing epidemiological relevance of breast cancer has led to a large increase in studies investigating how to prevent it. The lower incidence of the disease in Asia was associated with the high soy intake of that region. Accordingly, soy contains isoflavones, which have structural similarities to estrogens and could act as agonists or antagonists. In this review, we gathered evidence on the effect of soy as a protective agent, concerning both the regular soyfood intake during life and the use of soy supplements in postmenopausal women. Current scientific knowledge appears to indicate that soy intake is a protective agent against breast cancer in premenopausal women. However, not all studies point in the same direction. Finally, the use of supplements in risk and postmenopausal patients may be more of a risk factor than a protective one.

Keywords: breast cancer, soy, isoflavones.

1. Introduction

Breast cancer has recently become a very relevant disease in industrialized countries. Nowadays, according to data from the WHO International Agency for Research on Cancer, the global prevalence rate is 181.8 cases per 100,000 inhabitants, while the incidence rate is 55.2 cases per 100,000 inhabitants (1). These rates increase if we focus on Spain, where they stand at 549.6 and 138.8, respectively (1). Meanwhile, healthy lifestyle is becoming more important in order to prevent this and other diseases (2). Globalization has allowed a wide variety of foods to be known, and they have had a widespread acceptance and media impact. Consequently, soy has become one of the most demanded foods because of its possible properties and health benefits (3). Particularly, the protective effect against breast cancer that soy and other vegetables can offer has been widely discussed (4), since countries with low breast cancer prevalence follow a diet rich in these types of food. For this reason, there has been an increase of studies in this field, trying to demonstrate this protective effect and to determine the mechanism by which it is exerted. Studies on the latter issue have focused on isoflavones, a soy component with structural similarities to estrogens. Therefore, they could bind to the estrogen receptors on breast cells (5).

Although some studies concluded that soy is a protective factor against breast cancer (6), others concluded the contrary, both in humans (7) and in experimental animals (8). However, the WHO does not even include soy as a possible carcinogen (9). Consequently, there is still a need for further work on this issue. In addition, the literature on this topic shows a lack of multi-ethnic and large-sample studies. Therefore, it is necessary to include recent publications that overcome these difficulties. Previous studies have gone in different directions: some tried to prove the ability of soy to prevent breast cancer recurrence (10), others tried to show the possibility of preventing breast cancer in risk patients through soy supplements (11), and others conducted prospective studies to evaluate cancer incidence depending on a diet rich or poor in soy (12). This disparity, both in results and in types of studies, makes it necessary to review the latest publications on the topic and to gather evidence that could explain the contradictory results obtained by high-quality studies. Moreover, it is also necessary to provide a comprehensive and joint explanation on the effects of soy on this disease, in order to make medical and non-medical recommendations concerning the intake of this product.

In conclusion, the objective of this review is to analyze the protective effect of soy intake against breast cancer on premenopausal and postmenopausal women. For this purpose, mainly observational studies and published experimental studies were consulted.

2. Relationship Between Regular Soy Intake and Breast Cancer

Attempts to demonstrate a relationship between soy intake and breast cancer prevention are not new. The lower incidence of this disease in Asian countries (1) aroused the curiosity of scientists on the lifestyle of this geographical area. Their aim was to find environmental (not genetic) factors to explain this possible relationship. In the second half of the last century, soy already began to be considered one of the possible explanations, and the first reviews attempting to unify the growing research soon appeared (13). The recent increase in publications on this topic makes a continued review of the growing evidence even more necessary.

In this sense, a prospective study published in 2014 was especially relevant (12). This study had a large sample size (84,450 women) and an extensive follow-up (13 years). Although it was conducted in the United States, its sample was multi-ethnic. This managed to avoid one of the biases that had been repeated in previous studies (i.e. a not very varied sample in terms of ethnicity), which meant that results could thus be explained by other reasons. In fact, the results of this study appeared to indicate possible differences concerning ethnicity, as soy had a higher protective effect on Asian people. However, these differences are not enough to confirm this and, in general, higher soy intake was not associated with a reduction of breast cancer incidence either.

Some studies tried to clarify the reasons why soy was found to protect against breast cancer in certain research, but not in other. The reason seems to be the sample age: while in young patients (i.e. premenopausal women) soy intake would be associated with a lower breast cancer incidence, in older patients (i.e. postmenopausal women) this association would not exist (14). An in vitro study published in 2006 (15) went even further, showing that isoflavones could act as either estrogen receptor agonists or antagonists in breast cancer cells. This duality would depend on the woman's hormonal status. In practice, they would act as antagonists in premenopausal women, but as agonists in postmenopausal women. This would be due to different estrogen concentrations in both stages of life. In a premenopausal environment, there is a high quantity of circulating estrogens. In this case, isoflavones, which have a weak estrogenic activity, would compete with them, causing a general reduction of the estrogenic effects on breast cells. However, in a postmenopausal environment there are very few circulating estrogens. Therefore, isoflavones would act as estrogenic agonists (15), having many negative effects, as it is summarized in Figure 1. This is clearly one of the possible reasons why some studies cannot demonstrate the protective effect of soy.

An observational study carried out in Shanghai (16) analyzed the relationship between breast cancer and lifestyle, taking into account different causal factors. According to the observations, a weekly soy intake was associated with early breast cancer in young women. However, this same study also stated that there was little research on young populations and that it would be adequate to conduct prospective studies. Moreover, it was mentioned that the meta-analyses conducted by Liu et al. (17) and Woo et al. (18) demonstrated that soy can be a protective factor against breast cancer. This study also analyzed, among other factors, the relationship between using animal fat for cooking and breast cancer. It was observed that women using animal fat showed a higher risk of breast cancer, as opposed to women using soybean oil for cooking, which could have a protective effect. It is also stated that these results could be useful in helping Chinese women choose a cooking oil.

With regard to soy milk intake, it was observed that replacing cow milk with soy milk reduces the risk of breast cancer in North American women (19). According to this study, cow milk was found to be a risk factor, although no evidence was found of soy acting as a protective factor against breast cancer. In addition, this research mentions the chemopreventive effects attributed to soy, since its structural similarities to estrogens enable it to block or weaken endogenous estrogens. Antiproliferative effects, anti-inflammatory effects and DNA repair systems were also attributed to soy. This study found no evidence of soy intake being a protective factor against breast cancer. However, the fact that the study involved Western population must be taken into account, since soy intake is lower than in Eastern population, so more studies on this matter are required.

Additional research (20) highlights the importance of teaching women about the existence of different modifiable risk factors for breast cancer, such as physical activity or soy intake. Moreover, it is stated that strategies to increase soy intake should be identified.

The scientific will to demonstrate the effects of soy on breast cancer in an even more empirical and accurate manner has recently led to interesting studies (21). One of them has accurately demonstrated the relationship between soy intake and the expression of certain genes and miRNA, with a view to find new ways of justifying its anticancer effect. For

that purpose, the sample consisted of patients with triple-negative breast cancer. The expression of certain genes and miRNA was analyzed and compared with the patient's soy intake during the previous year. Important differences in the expression of 14 miRNA and 24 genes between patients with higher and lower previous intake were observed. Therefore, this article provides good reasons to consider soy as a protective agent against breast cancer and describes the specific molecular pathways by which this effect could be exerted.

One of the main flaws in many of the studies published in this line of research is the small sample size. Due to this, some of the obtained results could be questioned. Moreover, this leads to contradictory results, which have impeded a correct and accurate review of the evidence. Therefore, studies with large sample sizes are considered to be noteworthy. For instance, a recent cohort study of the China Kadoorie Biobank (6) consisted of 300,000 subjects. This study found no variation in breast cancer risk between patients with high and low soy intake. As opposed to what has been described in the rest of this review, no differences between pre- and postmenopausal women were found either. However, the study found an association between a higher soy intake and a lower breast cancer incidence in women with low body mass index.

Other studies have focused on analyzing the relationship between soy intake and longevity. In particular, a recent meta-analysis (22) concluded that a higher soy intake is associated with increased longevity and, specifically, with lower mortality in breast cancer patients

3. Soy Suplements and Their Relationship with Cancer

Although there have been warnings about the potential risks of soy supplements in population at risk of breast cancer (23), the effects of their intake remain still unclear, and its suitability is to be proven. Though further research is hence required, previous studies may contribute to shed light on this issue. A good example is the cohort study Étude Épidémiloguique auprès de Femmes de la Mutuelle Générale de l'Éducation Nationale, focusing on women over the age of 50 (24), which asserted that results would vary depending on the type of cancer. That is to say, whereas the regular intake of soy supplements was associated with lower risk of estrogen receptor-positive (ER+) breast cancer, their intake was related to an increase in the risk of estrogen receptor-negative (ER–) breast cancer, particularly among risk patients.

3.1. Soy intake and ethnicity

The relationship between a higher soy intake of Asian women and a lower incidence of breast cancer (1) leads to think that it might be due to genetic factors (ethnicity). This would contribute to a better protective effect of soy. In a study (25) involving two groups of women who received two daily soy servings, parameters such as nipple aspirate fluid (NAF), estrogens, IGF-1, IGFBP-3, inflammatory markers —e.g. C-reactive protein (CRP) or interleukin 6 (IL-6)—, and mammographic density were measured. Of all the biomarkers analyzed, only IGF-1 and IGFBP-3 varied significantly between Asian and non-Asian populations with a soy-rich diet. Moreover, there were slight variations in CRP and NAF. Nevertheless, these findings are not enough to attribute the lower incidence of breast cancer in Asian population to the genotype (ethnicity), but to soy intake from early ages (13).

3.2. The effect of fat reduction and soy supplementation on circulating adipocytokines in postmenopausal women

The lower risk of breast cancer due to soy intake has been associated with a decrease in certain adipocytokine levels, such as the inflammatory markers TNF-alpha (TNF-α) and IL-6. In order to test this hypothesis, a two-month study was conducted in healthy postmenopausal women under no hormone therapy (10), excluding those with special diets, cancer history, diabetes or any chronic disease. Subjects were divided into three groups and were assigned three different types of diet: low-fat diet, soy-rich diet and control diet. TNF-α, IL-6, adiponectin and leptin parameters were then analyzed, though there were no significant variations in these parameters between the groups. However, a general weight loss did occur. Even though further research is needed, both studies had several limitations: (1) the small sample size, (2) measuring parameters only at the beginning and at the end of the study, (3) little rigor in diet preparation, and (4) the possibility of participants with slight chronic inflammation. This study draws the conclusion that there is no significant variation in circulating adipocytokines between a low-fat diet and a soy-rich diet, differing from the conclusions of other research (26).

3.3. The effect of soy on breast cancer using MRI and mammographic density

In general, there is a lack of studies on breast cancer using mammographic density and magnetic resonance imaging (MRI). Thus, a double-blind randomized study published in 2015 (27) may be particularly relevant. This 12-month study was conducted in a group of patients (aged 30 to 75) with breast cancer (previously treated) and another group of hi-

gh-risk patients, who were given soy supplements or placebo and who took mammography and MRI at the beginning and at the end. These techniques aim to quantify the total breast area (TBA) and the area of breast density (BD) on mammography, and to measure the total breast volume (TBV) and fibroglandular tissue volume (FTV) on MRI. Though a slight decrease in BD and FTV was observed, this was not sufficient to state that soy supplement intake induces changes in these techniques.

4. Relationship Between Soy Intake and Different Types of Breast Cancer

As mentioned above, a study in women aged over 50 focused on the relationship between soy supplement intake and breast cancer (24). This research showed that soy supplements reduced the risk of ER+ breast cancer, but increased the incidence of ER– breast cancer. Nevertheless, the study also reported that ER– breast cancer has a higher prevalence in women with family history of breast cancer in first-degree relatives.

Other studies, however, highlight the protective effect of soy intake against breast cancer through mechanisms other than those mentioned above. For instance, Guo et al. (21) reported the protective effect of soy intake against triple-negative breast cancer, which lacks expression of hormone receptors, and the protective effect would therefore be carried out by the miRNA mechanism already described above.

Finally, an observational study conducted in Shanghai (29) found an overall decrease in the risk of breast cancer, with greater evidence of the protective effect of soy intake in premenopausal women. In this study, cancers were classified according to their expression of ER, PR, and HER2. This study concludes that soy intake may have a protective effect against ER+ and PR+ breast cancers , but not in HER2+ breast cancers.

5. Conclusions

Apart from an obvious need for further research, regular soy intake in premenopausal women seems to have a protective effect against breast cancer — more specifically, against ER+, PR+, and triple-negative breast cancer. This is due to its net antiestrogenic effect and mechanisms related to miRNA expression. Furthermore, soy supplement intake in risk or postmenopausal women could have no effect or even be harmful because of their net proestrogenic effect. Therefore, the safety of their intake remains unclear. Likewise, the role of ethnicity on the antiestrogenic effect of soy intake is to be confirmed, as well as further exploration of other beneficial effects, such as the reduction of adipocytokines.

Statements

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Ethical concerns

This paper did not require the approval of any ethics committee.

Conflicts of interest

The authors of this paper declare no conflicts of interest.

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References

1. Global Cancer Observatory [Internet]. Lyon: International Agency for Research on Cancer (WHO); 2018 [Last access: 3 March 2020]. Available at: https://gco.iarc.fr/today/home.
2. Gandini S.; Merzenich H.; Robertson C.; Boyle P. Meta-analysis of studies on breast cancer risk and diet: The role of fruit and vegetable consumption and the intake of associated micronutrients. Eur. J. Cancer 2000, 36, 636–646.
3. Pabich M, Materska M. Biological Effect of Soy Isoflavones in the Prevention of Civilization Diseases. Nutrients. 2019; 11(7).
4. Magee PJ, McGlynn H, Rowland IR. Differential effects of isoflavones and lignans on invasiveness of MDA-MB-231 breast cancer cells in vitro. Cancer Lett. 2004;208(1):35-41.
5. Zaheer K, Humayoun Akhtar M. An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. Crit Rev Food Sci Nutr. 2017; 57(6):1280-1293.
6. Wei Y, Lv J, Guo Y, Bian Z, Gao M, Du H, Yang L, Chen Y, Zhang X, Wang T, Chen J, Chen Z, Yu C, Huo D, Li L; China Kadoorie Biobank Collaborative Group. Soy intake and breast cancer risk: a prospective study of 300,000 Chinese women and a dose-response meta-analysis. Eur J Epidemiol. 2019. [Epub ahead of print] PubMed PMID: 31754945.
7. Shike M, Doane AS, Russo L, Cabal R, Reis-Filho JS, Gerald W, Cody H, Khanin R, Bromberg J, Norton L. The effects of soy supplementation on gene expression in breast cancer: a randomized placebo-controlled study. J Natl Cancer Inst. 2014;106(9).
8. Möller FJ, Pemp D, Soukup ST, Wende K, Zhang X, Zierau O, Muders MH, Bosland MC, Kulling SE, Lehmann L, Vollmer G. Soy isoflavone exposure through all life stages accelerates 17β-estradiol-induced mammary tumor onset and growth, yet reduces tumor burden, in ACI rats. Arch Toxicol. 2016;90(8):1907-16.
9. IARC Monographs on the identification of carcinogenic hazards to humans [Internet]. Lyon: International Agency for Research on Cancer (World Health Organization); c2020. List of Classifications by cancer sites with sufficient or limited evidence in humans; 2019 [Last access: 25 March 2020] Available at: https://monographs.iarc.fr/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf
10. Braakhuis AJ, Campion P, Bishop KS. Reducing Breast Cancer Recurrence: The Role of Dietary Polyphenolics. Nutrients. 2016;8(9).
11. Malini Nadadur, Frank Z. Stanczyk, Chiu-Chen Tseng, Lila Kim & Anna H. Wu (2016) The Effect of Reduced Dietary Fat and Soy Supplementation on Circulating Adipocytokines in Postmenopausal Women: A Randomized Controlled 2-Month Trial , Nutrition and Cancer, 68:4, 554-559.
12. Morimoto Y, Maskarinec G, Park SY, Ettienne R, Matsuno RK, Long C, Steffen AD, Henderson BE, Kolonel LN, Le Marchand

L, Wilkens LR. Dietary isoflavone intake is not statistically significantly associated with breast cancer risk in the Multiethnic Cohort. Br J Nutr. 2014;112(6):976-83.
13. Messina MJ, Persky V, Setchell KD, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr Cancer. 1994;21(2):113-31.
14. Hidaka BH, Carlson SE, Kimler BF, Fabian CJ. Dietary Associations with a Breast Cancer Risk Biomarker Depend on Menopause Status. Nutr Cancer. 2016;68(7):1115-22.
15. Hwang CS, Kwak HS, Lim HJ, Lee SH, Kang YS, Choe TB, Hur HG, Han KO. Isoflavone metabolites and their in vitro dual functions: they can act as an estrogenic agonist or antagonist depending on the estrogen concentration. J Steroid Biochem Mol Biol. 2006;101(4-5):246-53.
16. Li Ping RN, Huang Jialing RN, Wu Huina RN, Fu Cuixia RN, Li Yun RN, Qiu Jiajia MSN. Impact of lifestyle and psychological stress on the development of early onset breast cancer. Medicine: 2016; 9(50)-5529.
17. Liu D, Chen L, Zhang YN, et al. System evaluation on intake of soybean products and the risk of breast cancer. J Mod Oncol 2012;20:290–2.
18. Woo HD, Park S, Oh K, Kim HJ, Shin HR, Moon HK et al. Diet and cancer risk in the Korean population: a meta-analysis. Asian Pac J Cancer Prev 2014;15:8509–19.
19. Gary E Fraser, Karen Jaceldo-Siegl, Michael Orlich, Andrew Mashchak, Rawiwan Sirirat, Synnove Knutsen. International Journal of Epidemiology. 2020.
20. Tan M-M, Ho W-K, Yoon S-Y, Mariapun S, Hasan SN, Lee DS-C, et al. (2018) A case-control study of breast cancer risk factors in 7,663 women in Malaysia. PLoS ONE 13(9): e0203469.
21. Guo X, Cai Q, Bao P, Wu J, Wen W, Ye F, Zheng W, Zheng Y, Shu XO. Long-term soy consumption and tumor tissue MicroRNA and gene expression in triple-negative breast cancer. Cancer. 2016; 122(16):2544-51.
22. Nachvak SM, Moradi S, Anjom-Shoae J, Rahmani J, Nasiri M, Maleki V, Sadeghi O. Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. J Acad Nutr Diet. 2019;119(9):1483-1500.e17.
23. Enderlin CA, Coleman EA, Stewart CB, Hakkak R. Dietary soy intake and breast cancer risk. Oncol Nurs Forum. 2009; 36(5):531-9.
24. Touillaud M, Gelot A, Mesrine S, Bennetau-Pelissero C, Clavel-Chapelon F, Arveux P, Bonnet F, Gunter M, Boutron-Ruault MC, Fournier A. Use of dietary supplements containing soy isoflavones and breast cancer risk among women aged >50 y: a prospective study. Am J Clin Nutr. 2019; 109(3):597-605.
25. Gertraud Maskarinec, Dan Ju, Yukiko Morimoto, Adrian A. Franke, and Frank Z. Stanczyk. Soy Food Intake and Biomarkers of Breast Cancer Risk: Possible Difference in Asian Women? Nutr Cancer. 2017; 69(1): 146–153.
26. Wu SH, Shu XO, Chow WH, Xiang YB, Zhang X, et al.: Soy food intake and circulating levels of inflammatory markers in Chinese women. J Acad Nutr Diet 112, 996– 1004, 1004 e1-4, 2012.
27. Anna H. Wu, Darcy Spicer, Agustin Garcia, Chiu-Chen Tseng, Linda Hovanessian-Larsen, Pulin Sheth, Sue Ellen Martin, Debra Hawes, Christy Russell, Heather McDonald, Debu Tripathy, Min-Ying Su, Giske Ursin, and Malcolm C. Pike. Double-blind randomized 12-month soy intervention had no effects on breast MRI fibroglandular tissue density or mammographic density. Cancer Prev Res (Phila). 2015; 8(10): 942–951.
28. American Cancer Society: Estado del receptor hormonal del cáncer de seno. Atlanta [Last access: 24 March 2020]. Available at: https://www.cancer.org/
29. Michelle L. Baglia, Wei Zheng, Honglan Li, Gong Yang, Jing Gao, Yu Tang Gao et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int. J. Cancer. 2016; 139 (4): 742-748.

Annex I: Figures

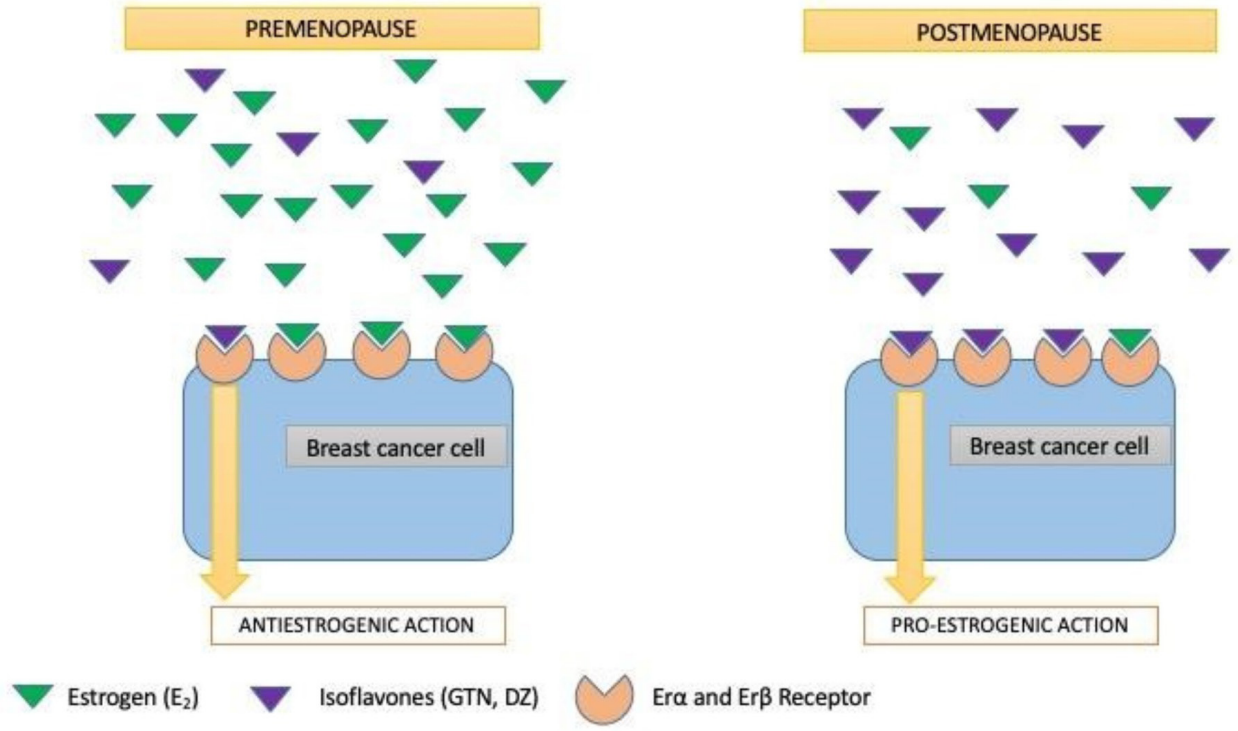

Figure 1. Duality of the estrogenic activity of isoflavones depending on the patient's estrogenic status. Designed by the authors based on data from (15).