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THE IMPACT OF SOY ON CANCER RISK AND OUTCOMES

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ABSTRACT

Aim: Soy consumption is growing globally, bringing attention to its health effects. This review aims to summarize current knowledge about the impact of soy on the risk and outcomes of various cancers.
Methods: The study is based on meta-analysis, randomized controlled trials, and systematic reviews from the PubMed database published over the past 15 years.
Key findings and Conclusions: Existing literature indicates significant health benefits associated with soy intake in the prevention of breast and prostate cancer. Studies provide moderate to weak evidence for an inverse association between soy intake and the risk of gastric, gastrointestinal, colorectal, endometrial and lung cancers. No significant relationship has been identified between soy supplementation and the risk of ovarian cancer, bladder cancer and leukemia. The exact mechanisms responsible for the anticancer properties of soy remain unknow and available research is characterized by high heterogeneity. Therefore, there is a need for larger studies concentrating on specific soy compounds.

KEYWORDS

Cancer, Soy, Isoflavones, Breast Cancer, Prostate Cancer

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1. Introduction

Soybean (Glycine max) is a widely cultivated plant used in numerous industries worldwide. Soy consumption is increasing rapidly in parallel with soybean production. For certain populations, soy is believed to promote good health, but knowledge about its properties is usually gained from the internet and least often obtained from professionals [1]. Hence, a thorough analysis of the underlying sources of soy's health-promoting effects is essential. Soybeans contain biologically active phytoestrogens, including isoflavones, coumestans, and lignans. Soy-based products such as tofu, tempeh, and soy milk contain mainly isoflavones, the most extensively studied compounds of soy. Among them, genistein, daidzein, and glycitein are the most frequently discussed. These phytochemicals, due to their structural similarity to 17-B-estradiol may influence hormone-sensitive cancers through estrogen receptors as well as other cancers in less direct, often unknown pathways. Non-isoflavone components of soy, including coumestans, lignans, saponins, protease inhibitors, lunasin, carotenoids, and dietary fiber, may also exhibit anti-cancer properties through alternative mechanisms. Although there is growing scientific interest in soy research [2,3], previous studies on the impact of soy on carcinogenesis are inconsistent and do not collectively gather data on its effect across different types of cancers. Therefore, this article focuses on the effects of soy and soy compound consumption on the risk, treatment, and prognosis of various cancers.

2. Methodology

This review is based on meta-analysis, randomized controlled trials, and systematic reviews from the PubMed database. To narrow down the results, the PubMed search tool is used. As a search term "cancer and soy" is set. We choose articles from the past 15 years, getting 148 results in total. 34 results concerned breast cancer specifically, 27 prostate cancer, 5 colorectal cancer, 4 gastric cancer, 4 endometrial cancer, 4 lung cancer, 3 ovarian cancer, 2 gastrointestinal cancer**,** 2 bladder cancer, and 2 leukemia. The rest addresses the topic more generally or is not relevant.

3. Results

3.1. Overall cancer risk and mortality

Wang et al. (2024) [4] in a meta-analysis including 52 studies indicated that high soy consumption reduced general cancer risk. Interestingly, a daily additional intake of 23 grams of soymilk was associated with a 28% reduction, and similarly intake of 100 grams of tofu with a 32% reduction of cancer risk. Other soy-derived products, such as miso soup, soy paste, and both fermented and non-fermented foods, do not appear to be associated with cancer risk. Fan et al. (2022) [5] state that an additional daily intake of 25 g of soy or 10 mg of isoflavones reduces risk of cancer by 4%, but there was no correlation between the high intake of soy products and cancer mortality. Nachvak et al. (2019) [6] find that an additional daily intake of 10 mg of isoflavones reduces cancer mortality by 7%, but an intake of soy reduces cancer mortality with marginal significance. Namazi et al. (2018) [7] also suggest no significant association between soy consumption and mortality from cancer.

3.2. Breast cancer

Genistein is an isoflavone and, as an estrogen-like chemical, binds rather to estrogen receptor beta than estrogen receptor alpha. Estrogen receptor beta may inhibit breast cancer cell proliferation in contrast to alpha-activating proliferation. Moreover, genistein promotes cancer cell apoptosis and inhibits angiogenesis. It also demonstrates anti-oxidative properties. Genistein presents individual effectiveness depending on intestinal flora composition, particularly since the metabolism of genistein occurs in the intestine. Enterohepatic circulation can affect genistein concentration as well [8].

MeBoutas et al. [9] in a 2022 meta-analysis proved that soy consumption may reduce the risk of breast cancer both in pre- and postmenopausal women and also improve the prognosis of patients with a breast cancer diagnosis. Wei et al. (2020) [10] in a prospective study of 300,000 Chinese women, investigated the influence of soy isoflavones dosage on breast cancer risk. It found that each 10 mg/day increment in soy isoflavone intake was associated with a 3% reduced risk of breast cancer, but low and moderate soy intake had no influence on breast cancer risk in Chinese women population. Moreover, more frequent soy consumption among women with a lower BMI (<24 kg/m2) led to reduced breast cancer risk in contrast to women with a higher BMI. Shin et al. (2023) [11] found that soy protein and soy isoflavone reduced breast cancer risk by 35% and 32%, while no such association was made for soy food in general. Kazemi et al. (2020) [12] established progressively decreasing risk by 3,5% for each 30 g/d of soy or soy products.

There is only limited, low-quality evidence suggesting a positive effect of soy intake on breast cancer prognosis, but there is no evidence of negative effects on prognosis either [13].

Qiu et al. (2018) [14] suggest a slight improvement in overall survival, mortality, and recurrence among postmenopausal breast cancer patients who consumed soy and isoflavones prior to diagnosis, although the evidence remains limited. There are also studies demonstrating an inverse association between soy food consumption and breast cancer survival. Even though mortality was associated with soy consumption independent of menopausal status and estrogen receptor positivity, recurrence was lower in ER-, ER+/PR+ postmenopausal patients in this research [15].

Dong et al. (2010) [16] found a 16% breast cancer recurrence reduction for patients with the highest isoflavones intake versus the lowest, especially in postmenopausal women. Van Die et al. (2023) [17] received a 26% breast cancer recurrence reduction, notably also in postmenopausal women and ER+ patients.

In terms of safety, Fritz et al. (2013) [18] concluded that there is not enough data to support concerns about the adverse effects of soy and isoflavones in breast cancer patients. Soy does not influence estradiol levels and does not negatively stimulate estrogen-sensitive tissues. It is considered safe to supplement soy during tamoxifen therapy; however, more research is needed to assess the consequences of high-dose supplementation.

3.3. Prostate cancer

Because of its slow progression over time, prostate cancer is considered an ideal candidate for chemopreventive strategies. Several studies have linked soy consumption to a reduced risk of developing prostate cancer [19,20,21,22]. The proposed mechanisms behind this protective effect include the microbial conversion of daidzein into a very active isoflavone - equol. Isoflavones are known to exert antiproliferative and anti-inflammatory effects on prostate cancer cells.

Furthermore, the chemopreventive potential of soy appears to be more pronounced in localized prostate cancer compared to metastatic forms. This observation aligns with data showing a decline in estrogen receptor beta expression as the disease progresses [23].

In a study by Huang et al. (2024) [19], prostate cancer risk tended to decrease with increasing daily soy intake, categorized as 0-50 g/day, 50-100 g/day, 100-150 g/day, and >150 g/day. However, this trend did not reach statistical significance and was only observed in participants consuming soy at least once per day. Ethnicity also appeared to influence outcomes: a protective effect was noted among African American and Latino populations, while no such association was found in Japanese, Chinese, or White populations. This study's findings are consistent with previously mentioned research [23] in demonstrating that soy consumption reduced the risk of localized, low-grade tumors but had no significant effect on non-localized and high-grade cancer. Additionally, non-fermented soy products were associated with a reduced risk, while fermented soy products showed no significant effect, except for miso, which was associated with an increased risk.

Similar results were reported by Applegate et al. (2018) [20], who found associations between reduced prostate cancer risk and intake of soy, genistein, and daidzein individually. The pattern of effectiveness was consistent across both fermented and unfermented soy products.

Van Die et al. (2014) [21] confirmed the safety of soy and isoflavones consumption, reporting no significant impact on prostate-specific antigen (PSA) level or sex hormones such as sex hormone-binding globulin, testosterone, free testosterone, estradiol, and dihydrotestosterone.

Zhang et al. (2016) [22] observed a reduced prostate cancer risk associated with soy, soy-based foods, daidzein, genistein, and tofu specifically among Asian and Caucasian populations, though not among Africans.

In secondary prevention, a group of patients with high-grade prostatic intraepithelial neoplasia (HGPIN), in order to prevent the progression to invasive prostate cancer, received a supplement containing 20 g of soy, 400 U of vitamin E, and 100 μg of selenium twice a day for 3 years. This intervention did not produce significant clinical benefits [24].

In vitro studies demonstrated that isoflavones and curcumin reduced PSA levels and androgen receptor expression in LNCaP prostate cancer lines. In a parallel clinical arm, men with negative prostate biopsies took a supplement containing isoflavones and curcumin for 6 months, resulting in a significant PSA reduction [25].

Hackshaw-McGeagh et al. (2015) [26] conducted trials involving prostate cancer patients. In a single-factor intervention, supplementation with 30 mg/d of genistein for 3-6 weeks before prostatectomy led to significant changes in PSA level, cell behavior, and proliferation; however, this study was rated as having high or unknown risk of bias. In contrast, a well-controlled study using 60mg/day of genistein found no effect on PSA levels. Multi-factor interventions that included isoflavones demonstrated significant improvements in PSA and free-total PSA levels.

There remains a clear need for further large-scale, long-term studies that specifically investigate the effects of individual isoflavones - particularly genistein - on prostate cancer risk and progression [27].

3.4. Gastrointestinal cancer in general

The intake of soy products seems to reduce the incidence of gastrointestinal cancer in general, gastric cancer, but not colorectal cancer. If a study group is divided into sex categories, risk is reduced for women, but not for men [28]. From 22 studies in this analysis, 7 reported an association between soy intake and gastrointestinal cancer mortality, but the estimated summary risk for mortality was not confirmed. Tse et al. (2014) [29] for soy received only slight risk reduction with stronger evidence in colon cancer and colorectal cancer. For isoflavone intake, a significant decrease in risk was observed. Differences between the sexes were slight or even absent. These two meta-analyses alone reveal inconsistencies in the results, highlighting the need for further research that accounts for the overlapping influence of multiple external factors.

3.5. Colorectal cancer

Soy products also demonstrate protective activity against colorectal cancer, especially in the Asian population [30,31]. Soy isoflavones may reduce colorectal cancer risk by 16% or 23% [32,30]. Dose-response analysis pointed to an 8% risk reduction for every 20 mg/d increase of isoflavones intake in the Asian population [33]. Not only isoflavones but also lignans turn out to exhibit a cancer-preventive effect in colorectal neoplasm [33]. On the other hand, Yan et al. (2010) [32] did not reveal such an association for soy in the general population neither for colorectal cancer nor for colon and rectal cancer alone. Instead, the study found a difference between the female and male populations, suggesting a 21% colorectal risk reduction in women consuming soy and no association in the men group. Chapelle et al. (2020) [34] also suggest no protective effect of soy products. Despite data pointing significant decrease in colon cancer risk, certainty of evidence was very low in this study.

3.6. Gastric Cancer

Three independent meta-analyses [35,36,37] proved that soy food intake is inversely associated with gastric cancer risk, reducing the risk by up to 36 %. However, this is mainly due to non-fermented soy products, because fermented products increase the risk of gastric cancer [35,38]. The immune modulation in gastric cells by non-fermented soy is suspected of its positive properties. Soy may also amplify the humoral and cellular immune responses [35]. On the contrary, in fermented soy products, factors such as high salt content, the formation of carcinogenic nitrites during storage, high processing temperature, and exposure to high serving temperatures may increase the risk of gastric cancer. These conditions can damage gastric epithelial cells and diminish the concentration of protective, anti-cancer compounds [35]. Miso soup as a product consisting of fermented soybeans is thoroughly studied for its potential pro-carcinogenic activity. High intake of miso soup may be linked to a higher risk of gastric cancer [36,37]. Such an effect can be observed in males consuming 1-5 cups of miso soup per day [36]. Isoflavones alone seem not to demonstrate anti-cancer properties against gastric cancer significantly in presented studies [35].

3.7. Endometrial cancer

Mechanisms responsible for cancer-preventive features of soy against endometrial cancer are probably estrogen receptor inhibition, epigenetic regulation, tyrosine kinase inhibition, angiogenesis inhibition, and some others. The risk of endometrial cancer may be decreased by soy intake by 22% in Asian countries and by 18% in other countries. It can be due to higher soy consumption in Asia – in China 142,3 g/day versus low intake in Wester counties - <5 g/day in the USA. Notably, there is a growing trend of phytoestrogen supplementation in Western countries, particularly aimed at managing menopausal symptoms [39,40]. Unfortunately, the dosage of phytoestrogens causing metabolic and ultrasound changes in the endometrium has not been established yet [39]. Endometrial thickness, especially in postmenopausal women is an important indicator of endocrine disturbances and potential endometrial cancer. Quaas et al. (2013) [40] found no statistically significant data proving isoflavone soy protein reduces the risk of endometrial cancer or endometrial hyperplasia in postmenopausal women. Although compliance in this study was high and participants consumed 25 g of soy per day for 3 years, the rate of hyperplasia and malignancy was not significantly higher in the study group than in the placebo group. Liu et al. (2016) [41] also did not find a significant alteration in the endometrial thickness measured by transvaginal ultrasound after isoflavone intake. Only daily isoflavone intake of more than 54 mg could reduce endometrial thickness by 0,26 mm. Moreover significant decrease of 0,23 mm could be achieved in groups from North America and on the contrary, a 0,23 mm increase was observed in Asian participants. The conclusion may point to genetic or dietary variations between these two groups. Zhang et al. (2015) [42] conducted an analysis based on a more geographically diverse population, including 5 studies in the USA, 1 in Australia, 1 in Italy, 1 in China, and 2 in Japan. A 19% reduction in endometrial cancer was observed comparing the higher and the lowest intake of soy. This effect is particularly evident in postmenopausal women, both in Asian and non-Asian populations, especially for unfermented soy food.

3.8. Lung cancer

Although the influence of soy or more specifically phytoestrogen intake on preventing breast and prostate cancer is quite clear, more high-quality studies are needed regarding lung cancer [43,44,45]. The mechanism suspected for anticancer properties against lung cancer is not only estrogen receptor signaling but also estrogen-independent epidermal growth factor receptor (EGFR) signaling via inhibiting EGFR kinase and amplifying EGFR-tyrosine kinase inhibitors. The first meta-analysis examining the relationship between soy intake and the risk of lung cancer proved 23% less risk for the highest observed intake of soy compared to the lowest intake of soy [44]. This effect is especially seen among women, the Asian population, and never-smokers. Such an outcome was also observed with an intake of unfermented soy food, while fermented ones showed no association with reduced lung cancer risk. This study has some limitations including other health-related factors like smoking, drinking and eating fruit, and vegetables. Additionally, it did not use standardized common measures, and the amount of soy consumed was not comparable across studies. Therefore, a meta-analysis using a standardized common measure was conducted in order to estimate the association between the daily exact amount of soy protein intake in grams and lung cancer risk [45]. It does not provide strong data in general but shows a significant association with nonsmokers. Authors explain that again other health behaviors may differ significantly between groups, for example, nonsmokers could probably lead a healthier life in general than smokers. Yang et al. (2012) [46] in their research including 71,550 Chinese women managed to provide a significant association between increasing soy-food intake and reduced lung cancer risk.

Moreover, this association was not affected by other lung cancer risk factors and health-related behaviors, mainly thanks to high group homogeneity – 97,2% of participants were never smokers. The study also found that this association is stronger for aggressive lung cancer and could be influenced by endogenous estrogens. Women with a history of long and high estrogen exposure may benefit more from soy product intake. It emphasized the importance of the anti-estrogenic mechanism of soy in lung cancer prevention, but there was no evidence of superior efficacy of phytoestrogens in lung cancer prevention than that demonstrated by soy.

3.9. Ovarian cancer

One of the main mechanisms of action of soy-derived food in protection against ovarian cancer is the influence of the phytoestrogens on estrogen receptor beta-dependent signaling, as previously mentioned. Other mechanisms include modulation of GnRH, FSH, LH, and EGRF receptors. Genistein, as an isoflavonoid, may also affect proteins involved in the cell cycle, such as Akt, Caspace-3, and Raf. It appears that phytoestrogens, as a more specific subgroup, offer greater protection against ovarian cancer than soy food. This protective effect is particularly pronounced in the Asian population and among groups consuming higher amount of phytoestrogens. A higher amount could be linked to around 30% more reduction of ovarian cancer risk than a lower amount. [47] There is little data on the effect of soy on ovarian cancer risk in the European population. Hedelin et al. (2011) [48] focus on the association between eating soy compounds such as isoflavones, lignans, coumestrol, and fiber and ovarian cancer risk in 47,140 Swedish women population. The results differ from the previously described study. There was no statistically significant relationship between intake of isoflavones and lignans and ovarian cancer risk. Coumestrol and fiber appear to have some protective effects against one subtype of ovarian cancer – borderline ovarian cancer, but not against invasive ovarian cancer. It needs to be emphasized that the intake of soy products in the examined population was 10 times lower than the lowest quartile among the analogic Chinese population. In addition to isoflavonoids, lignans, and fiber soy also contains carotenoids. In vitro studies have shown that carotenoids present antioxidant properties and could inhibit cancer cell growth. Paxton et al. (2011) [49] study a population of women with stages II-IV ovarian cancer. This research examines serum alpha- and beta-carotene concentration after 6 months of low fat, high-fiber diet or a special diet with soy-based beverages and encapsulated fruit and vegetable juice concentrates. Beta-carotene levels rose significantly in both groups but grew more in the group with soy powder. This research may suggest some role of soy supplementation in order to provide a high level of cancer-protective carotene.

3.10. Bladder cancer

It is hypothesized that genistein inhibits EGFR phosphorylation. In preclinical in vitro studies, genistein appears to exert inhibitory effects on urothelial cancer development. Messing et al. (2012) [50] examined the influence of 300 or 600 mg/d genistein intake among patients with presurgical bladder cancer on changes in the molecular pathways in a postoperative material after transurethral resection of a bladder tumor and cystectomy. A study focuses on EGFR phosphorylation, Ki67, active caspase-3, and many other signaling molecules. The results show a significant reduction in EGFR phosphorylation staining in the study group administered 300 mg/d genistein and dose combined group, but no significant reduction in 600 mg/d group. This research confirms previous findings and shows an intriguing dose-dependent effect of soy isoflavone on bladder cancer. Within the same study, researchers aimed to evaluate the Soy Food Frequency Questionnaire as a diagnostic tool for estimating genistein levels in plasma and urine, but there was no significant correlation between actual genistein level and questionnaire results [51]. Thus, to facilitate the use of isoflavones in cancer prevention and treatment, a reliable and cost-effective tool for measuring their concentrations in blood and urine is essential.

3.11. Leukemia

No study found using our methodology investigated the relationship between soy consumption and the risk of leukemia, but two of them investigated using soy as supportive therapy for leukemia. Acute leukemia is often accompanied by cachexia and severe morphological abnormalities. 30 g/d soy seems to reduce fatigue and improve red blood cell parameters and nutritional status in children with B-cell acute lymphoblastic leukemia in the maintenance phase of chemotherapy [52]. Ingestion of 1.5 g/day/kg body weight of a 1:1 soy-whey protein blend in patients with acute leukemia before transplantation increases muscle mass, griping power, serum total protein, and above all shortens the time to stem cell engraftment [53]. Although there is no research about the relationship between soy consumption and the incidence of leukemia, these findings indicate a need to investigate whether the supportive role of soy in leukemia treatment is purely nutritional or if it also contributes to leukemia suppression through its anticancer properties and it may potentially be used in the prevention of leukemia.

4. Conclusions

Soy and isoflavone supplementation appears to be effective, affordable, and widely available chemoprevention for multiple types of cancer. Stronger evidence supporting this strategy is found in breast cancer and prostate cancer. Moderate to weak evidence is reported for gastric, gastrointestinal, colorectal, endometrial and lung cancer. Little or no data have confirmed a reduced risk of ovarian cancer, bladder cancer, or leukemia with soy supplementation. Due to the high heterogeneity of current research, especially considering geographic, lifestyle, diet, and gender factors, there is a pressing need for larger and better-quality studies. Rising soy research should be conducted with international and intersectoral cooperation including sustainability and impact on public health. Considering growing nutritional awareness and the increasing need for plant-derived proteins it is crucial to evaluate the health consequences of higher soy product intake.

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