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The role of soy in development of breast, ovarian, endometrial and prostate gland cancer

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Abstract

Introduction and purpose

Soy as a rich source of isoflavones has become a focus of interest because of its positive health benefits on numerous diseases, particularly hormone-related cancers. The aim of this study was to present the current state of knowledge on the role of soy in the development of breast, ovarian, endometrial, and prostate gland cancer.

A brief description of the state of knowledge

Soy components reduce inflammation, stress oxidative and inhibit proliferation of breast, ovarian, endometrial, and prostate cancer cells. Isoflavones such as genistein, daidzein, S-equol via activation of estrogen receptors, inhibit aromatase synthesis and may decrease the risk of estrogen-dependent cancers. Moreover, soy food products have the potential to regulate molecular pathways of AR and reduce testosterone levels. It leads to a reduced risk of prostate cancer. Furthermore, increased consumption of soy protein and isoflavones decreased the risk of mortality from cancers.

Conclusions

Soy foods and their isoflavones are associated with reduced carcinogenesis. A higher amount of soy intake can have positive benefits for prevention of cancers including breast, prostate gland, endometrial and ovarian cancer.

Key words : soy; soy isoflavones; breast cancer; ovarian cancer; endometrial cancer; prostate cancer

Introduction and purpose

Soybeans have been grown as a commercial crop in Eastern countries for thousands of years [1]. Soy and soy-based food products constitute a source of vitamins, minerals, high amounts of fat, protein as isoflavones – genistein, daidzein, glycitein, which makes soy considered as a common nutritional product with health benefits [2,3]. According to studies, soy compounds may prevent chronic diseases such as atherosclerosis, coronary heart disease, osteoporosis, cognitive decline, dementia, and some cancers [1,2,4,5]. Previous studies report that soy isoflavones, particularly genistein, have antioxidant and anti-inflammatory properties, which can alleviate oxidative stress induced by chemotherapy [3]. It has been evidenced that soy isoflavones have the potential to affect cell progression, induce apoptosis, inhibit angiogenesis, which results in inhibition of cancer development, growth, and apoptosis [3,5].

Additionally, some studies suggest that soy consumption prevents some gynecologic cancers or prostate cancer via binding to estrogen receptors. Soy isoflavones – genistein and daidzein due to similar structure to estradiol can bind to estrogen receptors (ERs) [4]. It has been evidenced that soy isoflavones as agonists or antagonists can have estrogenic and antiestrogenic properties [5], with an impact on endocrine homeostasis and reproductive system both in females and males. What is more, in countries with high soy intake such as China and Japan breast and prostate cancer are noted less frequently than in Europe – where soy is consumed much less [3]. Due to the increasing incidence of cancers worldwide, it is important to identify dietary interventions with cancer-preventive effects.

The objective of the study is to present the current state of knowledge on the role of soy in development of breast, ovarian, endometrial and prostate gland cancer. The newest publications from the last 5 years available on the Pubmed database were taken into account.

State of knowledge

Breast cancer

Several modifiable and unmodifiable risk factors are involved in the pathogenesis of breast cancer (BC) – the most frequent cancer in women [6]. Unmodifiable factors include physical activity and diet. Due to antioxidative, antiproliferative properties, soy is supposed to play an important role in the carcinogenesis of the breast [7]. What is more, soy isoflavones are structurally similar to estrogens and can bind to the ERs, which results in inhibition of aromatase activity and a decrease in natural estrogen production [8]. Furthermore, ERβ has been suggested to have an antiproliferative effect on breast cancer cells and suppress tumor growth [9].

Feng et al. reported an association of higher daidzein levels with reduced risk of BC in premenopausal women [10]. Previous cohort studies in Asian populations revealed the

reducing effect of high consumption of soy isoflavones on breast cancer incidence [6]. Fraser et al. indicated that replacing dairy milk with soy milk can decrease the risk of breast cancer among postmenopausal women. In a meta-analysis performed by Kazemi et al., they found an association between an increase in soy consumption and decreased risk of BC [11]. The results of this study are in line with another meta-analysis – performed by Zhao et al [8]. Authors found a significant relationship between the intake of isoflavones and reduced risk of BC (RR = 0.87, p = 0.048). Interestingly, supplementation of soy isoflavones initiated after diagnosis decreased recurrence of BC among Chinese and American populations (HR: 0.75, 95% CI, 0.61–0.92) [7]. Furthermore, Nachvak et al. noted that an increase in intake of soy protein and isoflavones decreased the risk of mortality from all cancers and also breast cancer [5].

Ovarian cancer

There is currently little data about the effect of soya on the development of ovarian cancer which is the second most deadly gynecological cancer [12]. The high mortality rate and poor prognosis are related to difficulties with diagnosis and treatment caused by the lack of early-stage markers, late-onset symptoms, resistance to chemotherapy, frequent recurrence, and inflammation related to stress oxidative in the organ. In the study on laying hens, genistein reduced levels of proinflammatory biomarkers – tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and vascular endothelial growth factor (VEGF) ($p < 0.001$). As described, VEGF is a protein engaged in the process of lymphangiogenesis and metastasis as a target of bevacizumab – a monoclonal antibody used in the treatment of neoplasms. Besides inflammation, the important risk factors of ovarian cancer are high gonadotropin levels, resulting in stimulation ovulation and DNA damage. Moreover, genistein repressed glycogen synthase kinase-3 (GSK-3) expression in the ovaries. It has been hypothesized that activated GSK-3 gen signaling is involved in the development of ovarian cancer.

It has been evidenced that genistein might prevent ovarian cancer by modulating mechanisms of cell cycle [13]. High concentrations of this isoflavone promoted apoptosis in ovarian cancer cells. Antiproliferative, anti-inflammatory, antioxidant properties of formononetin – a soy isoflavone – were observed in Park's study in epithelial (ES2 and OV90) ovarian cancer cells [14]. The findings demonstrate that formononetin inhibited ovarian cell proliferation and promoted cell cycle arrest through PI3K/AKT and ERK1/2 pathways inactivation. However, this soy compound disrupts mitochondrial depolarization and increases the synthesis of ROS.

As described, ERβ can inhibit tumor growth due to antiproliferative properties [9]. Furthermore, loss of estrogen receptor beta (ERβ) expression is associated with metastasis, resistance to chemotherapy, and poor prognosis. It has been hypothesized that ovarian cancer cells express ERβ. It suggests ERβ may be represented as a target for new therapeutic agents – agonists ERβ in the treatment of ovarian cells. Liu et al. assessed S-equol – agonist ERβ isolated from soy isoflavone daidzein in the therapy of ovarian cancer. They observed reduced cell viability and survival of ovarian cancer cells. Moreover, increased activity of caspase 3/7 indicated induced apoptosis. S-eqol caused reduced migration, invasion, and

inhibited metastasis, which was confirmed by photomicrographs of migrated and invasive cells. Moreover, ERβ agonist via downregulation of the NF-κB pathway inhibited the growth of therapy-resistant ovarian cancer model cells. Additionally, S-eqol induced response of ovarian cancer cells to chemotherapy including cisplatin and paclitaxel.

Endometrial cancer

The development of endometrial cancer is related to increase in estrogen exposure – early age at menarche, late-onset menopause, obesity, and use of tamoxifen [15]. It was supposed that soy via activating ERs, inducing synthesis of estrogen hormone-binding globulin, and inhibiting aromatase synthesis may decrease estrogens levels and risk of endometrial cancer. Cytotoxicity, modulation of the activity of enzymes involved in steroid hormone metabolism, inhibiting angiogenesis are considered as other mechanisms by which soy prevents carcinogenesis in the endometrium. Previous studies revealed that supplementation of isoflavone soy protein did not have a significant impact on endometrial thickness or risk of endometrial cancer in postmenopausal women [1]. It is interesting because isoflavones and soy extracts have the potential to ameliorate vasomotor symptoms of menopause. This might support the hypothesis that intake of soy foods could be beneficial for women with menopausal syndrome. Furthermore, in a meta-analysis conducted by Zhong et al., they noted that high consumption of soy products including isoflavones decreased risk of endometrial risk in age from 30 to 79 years [15].

Prostate cancer

Prostate cancer is the second most common cancer worldwide in men (15%) [16]. Due to the high incidence rate of cancer and its long latency period, there is a need to identify effective and safe prophylactic methods including dietary interventions to prevent carcinogenesis [17]. Anticancer activity of soy has been observed not only in gynecological tumors but also in the prostate gland.

Applegate et al. found that soy consumption was associated with decreased risk of prostate cancer ($p < 0.001$) [16]. Interestingly, unfermented soy food products – soy milk, tofu, and soybeans were related to reduced risk of prostate cancer ($p < 0.001$), but fermented soy products did not have a significant impact on the development of this cancer ($p = 0.281$).

Soy isoflavones have positive effects on hormone-related cancers including prostate gland cancer by affecting the androgen receptor (AR) signaling pathway [18]. Androgen receptors (ARs) play a crucial role in prostate cancer development. In addition, increased expression of AR in prostate cancer tissue can lead to resistance to androgen antagonists used as anticancer drugs. Soy isoflavones are supposed to regulate molecular pathways of AR, promote AR degradation, and inhibit nuclear binding to androgen response elements. AR activity can be evaluated by prostate-specific antigen (PSA) expression. Additionally, PSA is a well-known, nonspecific marker of prostate cancer. However, previous studies report inconsistent results about the impact of soy and soy isoflavones on the PSA level. In addition, it has been evidenced that soy reduced testosterone biosynthesis and the level of this androgen.

The next mechanism by which soy products affect carcinogenesis in the prostate gland is binding to ER. Activation of ERβ induced by soy isoflavones results in repression of cell proliferation and inhibition of tumor growth. Moreover, soy isoflavones might concentrate in the prostatic gland, which can lead to direct cytotoxic effects on cancer cells. Genistein promoted apoptosis, modulated by the cell regulation via upregulation of p21 and p27, p53 in prostate cancer cells [18]. What is more, cytotoxicity was a result of the reduced expression of cyclin B1 – a regulatory protein involved in mitosis and cell proliferation. It was also reported that daidzein inhibited prostate cell proliferation while its metabolite – equol, has been acted as an antioxidant.

A summary of the effect of soy on the development of breast, ovarian, endometrial, and prostate gland cancer is presented in the table below (Tab. 1.).

Tab. 1. Impact of soy on development of described cancers

	Effects of soy on carcinogenesis
Breast cancer	● replacing dairy milk with soy milk can decrease the risk of breast cancer among postmenopausal women ● increase of soy consumption decreased the risk of breast cancer
Ovarian cancer	● soy isoflavones reduced proliferation, invasion, and induced apoptosis *in vivo* and *in vitro*
Endometrial cancer	● high consumption of soy products including isoflavones decreased risk of endometrial risk
Prostate cancer	● unfermented soy food products were associated with decreased risk of prostate cancer

Summary

Soy components exhibited antioxidative, antiinflammatory, antiproliferative properties in carcinogenesis of breast, ovarian, endometrial, and prostate cancer. Soy isoflavones via activation of ERβ can modulate various pathways involved in the pathogenesis of these cancers. It is supposed that soy could be consumed in prevention as a combination therapy with anticancer drugs. Nevertheless, further studies are necessary to evaluate the precise mechanism of action and effects of soy used in the prevention against cancers or therapy.

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