

Phytoestrogens and cancer

B. C. Mathew, S. D. Reji, Al B. B. Jamal, I. W. Campbell

Assistant Professor, Lecturer, Department of Medical Biochemistry, Faculty of Medicine, El Gabal El Gharby University, Gharyan, LIBYA, Professor, Department of Social and Preventive Medicine & Dean, Faculty of Medicine, El Gabal, El Gharby University, Gharyan, LIBYA, Emeritus Professor of Medicine, Victoria Hospital, Bute Medical School, University of St Andrews, Scotland, United Kingdom.

Abstract: Phytoestrogens are a group of compounds found in plants that are structurally or functionally similar to the hormone estradiol, and act as selective estrogen receptor modulators. Epidemiological studies show an inverse correlation between consumption of a high phytoestrogen-rich diet, as seen in traditional Asiatic societies, and the incidence of certain hormone-dependent cancers such as breast and prostate cancer. Clinical studies to find a relationship between phytoestrogens, and breast and prostate cancers, have produced conflicting results. Phytoestrogens may protect against hormone-dependent cancers through their ability to lower the level of endogenous estrogens and their genotoxic metabolites, activation of estrogen receptor beta and peroxisome proliferator activated receptor gamma, inhibiting cell signaling pathways of growth factors, upregulating expression of antioxidant genes, tumor suppressor genes and immunomodulatory effects. There is little clinical evidence to suggest that phytoestrogens through their estrogenic activities will increase breast cancer risk in healthy women or worsen prognosis of breast cancer patients. Although phytoestrogens appear to hold promise as chemo preventive agents against cancer, more in-depth studies are required before definitive conclusions can be drawn.

Key words: breast cancer, chemoprevention, phytoestrogen, prostate cancer, SERMs

Introduction

Cancer causes about 13% of all deaths, and according to the American Cancer Society, 7.6 million people died from cancer in the world in 2007.¹ The significant role of complementary and alternative medicines (CAM) in the prevention, treatment, and control of cancer progression has been highlighted recently by several workers.^{2, 3} The use of nutraceuticals in cancer treatment, may reduce the high side effects of chemotherapy and is a more natural approach toward cancer prevention. Of particular interest in relation to human health are the class of compounds known as the phytoestrogens, a group of plant derived substances that are structurally and functionally similar to estradiol.² Over the last decade, the role of phytoestrogens in cancer prevention, particularly of tumors under endocrine control (breast, prostate and others), have generated considerable attention in the scientific and medical community and raised hope among cancer patients who

seek to take supplements together with standard treatment.^{4,5,6,7} However, data obtained from clinical, animal and in vitro studies are limited and consistent results have not been obtained to substantiate the beneficial effects of phytoestrogens. Concerns regarding the role of phytoestrogens to increase the risk of recurrence or stimulate the growth of existing tumors through their estrogenic activities have also been raised.^{8,9} The purpose of this review is to give a perspective of the structure and classification of the major dietary phytoestrogens, and also to provide an update on the recent clinical studies to find a link between phytoestrogens and tumors under endocrine control. The possible mechanisms of actions of the phytoestrogens in cancer chemoprevention are also discussed.

Phytoestrogen: Structure and Classification

Phytoestrogens are a broad group of biologically active plant derived phenolic compounds which are strikingly

similar in chemical structure to the mammalian estrogen, estradiol and bind to both estrogen receptors ER α and ER β with a preference for ER β in vivo.¹⁰ These phytochemicals are considered to act as selective estrogen receptor modulators (SERMs), exerting estrogen antagonist action in some tissues, such as breast and uterus and agonist action in other tissues such as bone, brain and cardiovascular cells.⁴ Five major classes of compounds are currently recognized as phytoestrogens – isoflavones (genistein, diadzein, glycitein, equol and biochanin A); the lignans (enterolactone, enterodiol); the coumestanes (coumestrol); the flavonoids (quercetin, kaempferol) and the stilbenes (resveratrol).⁵ Information on the major dietary phytoestrogens and food sources are given in **Table 1**.

Table 1. Major dietary phytoestrogens and food sources

Class	Phytoestrogens	Common food Sources
Isoflavones	Genistein, Diadzein Glycitein, Biochanin A	Soya and its processed products (Soy milk, Tofu, Soy yogurt), Red Clover.
Lignans	Secoisolariciresinol, Matairesinol, Pinoresinol, Lariciresinol	Flaxseed, Triticale, Wheat Garlic, Asparagus, Carrots
Coumestanes	Coumestrol	Soy based foods, Alfalfa, Broccoli
Flavonoids	Quercetin, Kaempferol	Onions, Apples, Curly kale, Leeks, Broccoli, Blueberries
Stilbenes	Resveratrol	Grapes, Red Wine

With the identification of several new novel estrogen-like compounds of plant origin, the number of known phytoestrogens is expanding. Although phytoestrogens have been attributed with significant therapeutic properties including a potential role in prevention of cancer, cardiovascular disease (CVD) and postmenopausal bone loss, data regarding the dietary phytoestrogen content and phytoestrogen intake in different countries are limited. Epidemiological and experimental studies have mainly focused on the health promoting effects of isoflavones, lignans (enterodiol and enterolactone) and flavonols

(quercetin).

Phytoestrogens and Hormone dependent Tumors

Clinical studies related to breast cancer

Breast cancer is the most common malignant tumor in women. It comprises 18% of all female cancers, before cervix (15%) and colon (9%) cancer. Epidemiological evidence and human interventional studies support a correlation between phytoestrogens consumption and protection towards breast and prostate cancers.⁵ The possible role of phytoestrogens as chemo preventive agents were first noted when it was observed that incidence rates of breast cancer were low in East Asian countries where soy is a predominant part of diet. It ranged from 6 per 100,000 women per year in Japan to almost 30 in the UK. This was quoted as the “Japanese phenomenon” and research identified isoflavones present in soybeans as potential chemo preventive agents.⁶ The link between isoflavones and the decreased incidence of breast cancer was further substantiated when it was observed that second- and third-generation descendants of women who immigrated to Western countries from Asia have breast cancer risks similar to those in the host country suggesting that nutrition and other environmental factors are more important than genetics.¹⁵ Furthermore, it was noted that Japanese breast cancer patients, in comparison to western women, exhibit reduced risk of breast cancer recurrence and better survival rates.⁷ The American Cancer Society in its scientific advisory 2006 regarding nutrition during and after cancer recommended that breast cancer patients can safely consume up to three servings of traditional soy foods per day, although the group advised against the use of more concentrated sources of isoflavones such as powders and supplements.¹⁶ Clinical studies conducted to observe the relationship between dietary phytoestrogens and primary prevention, treatment and control of cancer progression are mainly limited to isoflavones and lignans.

Trock et al (2006) in their meta-analysis of 18 clinical studies examined soy exposure and breast cancer risk and deduced that soy intake may be associated with a small reduction in breast cancer risk.¹⁷ They pointed that since some experimental studies suggest adverse effects from soy constituents, recommendations for high dose isoflavone supplementation to prevent breast cancer or prevent its recurrence are premature.¹⁷ Another evaluation of ten clinical studies in 2006 on the effect of enterolactone and breast cancer risk revealed conflicting results. Six studies demonstrated a protective effect due to enterolactone, specially in premenopausal women, while four studies failed to show any significant interaction.¹⁸ The inconsistent

results may be attributed partly to lack of standardization of supplemental sources and the retrospective nature of the clinical studies.¹⁹ Duffy and her colleagues (2007) analyzed 20 (14 case control and 6 cohort) studies examining phytoestrogens and breast cancer incidence and observed that most case-control studies indicated some protective effect of soy especially in premenopausal women, lending support to a current hypothesis that phytoestrogens effects are dependent on the hormonal status of the women with stimulatory effects in low-estrogen environments while, in high-estrogen environment states, they may block the effects of estrogens. In contrast, most prospective cohort studies failed to show any relationship between soy intake and breast cancer. The authors concluded that phytoestrogen-rich foods have slightly protective effects against breast cancer, but the beneficial effects may be more pronounced if consumed before puberty or during adolescence or at very high doses.⁷

Table 2. Proposed mechanisms of action of phytoestrogens in cancer

1. Depressed the activities of aromatase and 17 beta-hydroxysteroid dehydrogenase leading to lowering of endogenous estrogen levels.
2. Decreased levels of potentially mitogenic and genotoxic metabolites of estrogens by modulating expression of estrogen metabolizing Enzymes Cyp1A1 and Cyp1B1.
3. Activation of ER β and also peroxisome proliferator activated Receptor gamma (PPAR γ) induce antiproliferative effects.
4. May induce epigenetic alterations in mammary stem cells leading to changes in gene expression of tumor suppressor genes such as BRCA1 and PTEN and mammary gland morphology, thus modifying Breast cancer risk.
5. Inhibit cell signaling pathways of growth factors.
6. Modulate immune response by both estrogen receptor-dependent and independent mechanisms.
7. Upregulates the expression of antioxidant genes.

Several phytoestrogens including genistein and quercetin are reported to have a biphasic effect on cell proliferation, stimulating growth at low concentrations and suppressing growth at high concentrations.¹⁵ Wu and his colleagues in a recent meta-analysis of eight human studies (1 cohort, 7 case control), conducted in a high soy consuming Asians (e"20mg isoflavones per day), deduced a significant trend of decreasing breast cancer risk with increasing soy food

intake. In contrast, soy intake was unrelated to breast cancer in studies conducted in the 11 low-soy-consuming Western populations whose average highest and lowest soy isoflavone intake levels were around 0.8 and 0.15 mg per day, respectively. They suggested that soy food intake in the amounts consumed in Asian populations may have protective effects against breast cancer.²⁰ In a recent study in 6493 Canadian women (age 25-74 years), phytoestrogen (lignans and isoflavones) intake was associated with reduced breast cancer risk. Lignan intake was associated with a reduced breast cancer risk among all (pre-menopausal and post-menopausal) women and this reduction in risk was statistically significant only among overweight women (BMI>25). Total phytoestrogen intake was also associated with risk reduction among overweight women only.²¹ Skin and fat tissue are major sites for aromatase, an enzyme converting androgenic precursors to estrogens, and consequently obese women are able to produce more estrogens which increase their risk for breast cancer.²² Obesity is also negatively related to circulating levels of sex hormone binding globulin (SHBG), a plasma protein that binds potent estrogens like estradiol and thus leaving a higher percentage of circulating estrogens "free" to bind to estrogen receptors. Hence risk reduction in obese women related to dietary phytoestrogen intake is a significant finding and may be due to decreased estrogen levels.²²

The Japan Public Health Centre based prospective study among 24,226 women aged between 40 to 60 years found a statistically significant inverse association between plasma genistein and risk of breast cancer but no association for plasma diadzein.²³ In Dutch population, a prospective study reported that high genistein circulating levels were associated with reduced breast cancer risk whereas no effect of lignans on breast cancer risk were observed.²⁴ However, another prospective study among 58,049 postmenopausal French women examined association between the risk of postmenopausal invasive breast cancer and dietary intake of four lignans and estimated exposure to two enterolignans (enterodiol and enterolactone). It was noted that high dietary intakes of plant lignans and high exposure to enterolignans were associated with reduced risk of estrogen receptor and progesterone receptor (ER – and PR) positive postmenopausal breast cancer.²⁵

Two recent studies from Europe have produced negative results linking phytoestrogens to breast cancer. A prospective population-based cohort study was conducted among Swedish pre and postmenopausal women to evaluate the associations between phytoestrogen (isoflavones, lignans and coumestrol) intake and risk of breast cancer and whether the estrogen receptor / progesterone receptor

(ER/PR) status of the tumor influenced this relationship. The results indicate no association between intake of isoflavones or lignans and breast cancer risk.²⁶ The European Prospective into Cancer-Norfolk cohort study attempted to correlate serum and urinary phytoestrogens with breast cancer risk in 237 breast cancer patients (age 45 to 75 years). In this study no evidence of an association between phytoestrogen (daidzein, enterodiol, enterolactone, genistein, glycitein, o-desmethylnangolensin, and equol) biomarkers in serum and urine and breast cancer risk was observed. On the contrary, higher levels of some phytoestrogen biomarkers may be associated with greater risk of breast cancer.²⁷

From the above clinical studies, it can be inferred that the results obtained are inconclusive and the relationship between phytoestrogens and breast cancer prevention remains uncertain. Some studies have reported slightly protective effects mainly if consumed before puberty or during adolescence or at very high doses. The role of lignans in reducing the risk of breast cancer risk in both pre-menopausal and post-menopausal and also in obese women generate new scientific interest in this class of phytoestrogen. It has been reported that avoiding weight gain after a breast cancer diagnosis may help prevent recurrence.²⁸ Large prospective studies of dietary phytoestrogen intake in relation to breast cancer risk are still scarce and future well designed randomized trials that are of sufficient duration are warranted to further investigate the relationship between phytoestrogen consumption and breast cancer.

Clinical studies related to prostate cancer

Rates of prostate cancer vary widely across the world. Although the rates vary widely between countries, it is least common in South and East Asia, more common in Europe and most common in the United States. The low incidence of prostate cancer in Asia compared to Western countries such as Canada and United States have been attributed to a higher intake of phytoestrogens.²⁹ Prostate cancer is an ideal candidate for chemopreventive intervention as it is typically diagnosed in the elderly population with a relatively slower rate of progression and the potential of dietary agents to act as chemopreventive agents against it can be increasingly appreciated.³⁰ Epidemiological, animal and cell culture studies have demonstrated that dietary phytoestrogens (isoflavones and lignans) may play a protective role against prostate cancer.⁵ Recent clinical trials have provided conflicting results with regards to a clear association between prostate cancer and phytoestrogen (isoflavone and lignan) consumption .

In a Japanese prospective study in 43,509 men (age 45 to 74 years) who generally have a high intake of isoflavones, decreased risk of localized prostate cancer was observed whereas positive associations were seen between isoflavones and advanced prostate cancer.³¹ Two other studies have reported that a combination of soy isoflavones (40mg/day) and lycopene (15-40mg/day) have activity in prostate cancer patients as evident from stabilization or decrease in serum prostate specific antigen (PSA) level.^{32,33} In another phase II non randomized trial, 20 patients with rising PSA after local therapy were treated with soy milk containing 47mg of isoflavones per 8 oz serving three times per day for 12 months. It was noted that PSA had increased 56% per year before entry into the study and then only 20% per year for the 12 month period. Specifically, the slope of PSA after study was significantly lower than before the study entry in 6 patients and the slope of PSA after study entry was higher than before the study entry in 2 patients. For the remaining 12 patients, the change in slope was statistically insignificant.³⁴

Two prospective studies in Europe were conducted to study a possible association between phytoestrogen intake and prostate or colorectal cancer. In the first study in 191 patients with untreated localized prostatic adenocarcinoma, no significant link was seen between time to disease progression, adverse histology on repeat biopsy, PSA velocity and urinary levels of either daidzein, genistein, enterolactone or equol.³⁵ From the European Prospective into Cancer-Norfolk cohort (ages 45-75), serum and urine samples were analyzed for seven phytoestrogens among 193 cases of prostate cancer and 828 controls and 221 cases of colorectal cancer with 889 controls. No evidence to support an inverse association between phytoestrogen exposure and prostate or colorectal cancer was observed in this prospective study.³⁶

Von Low et al have recently reviewed all preclinical and clinical data on certain phytoestrogens including genistein in terms of their effects as potential treatment of prostate cancer. Critical assessment of data from preclinical in vitro studies with prostate cancer cells and well conducted animal experiments show a remarkable efficacy of many phytoestrogens against prostate cancer. However, it is impossible to make definite statements or conclusions on the clinical efficacy in cancer patients because of great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardized drug formulation. Although some results from clinical studies are encouraging, reliable or long-term data on tumor recurrence, disease progression and survival are unknown.³⁷

As of now, data from clinical trials are insufficient to draw

any definite conclusions on the protective role of phytoestrogens on prostate cancer. Well designed clinical trials are required to delineate the potential clinical usefulness of these agents through issues such as determining the optimal period and route of administration, systemic bioavailability, optimal dosing and toxicity of the agent and single or combinational approach. It is therefore evident that dietary intervention with phytoestrogens may have biological activity in men with prostate cancer. However, further studies with these phytonutrients in randomized clinical trials should be encouraged.

Proposed Mechanisms of action of Phytoestrogens in Cancer

The biological processes modulated by phytoestrogens have been extensively studied, yet without leading to a clear understanding of the cellular and molecular mechanisms of action involved. Mense et al have recently reviewed the literature regarding the possible mechanisms involved in the chemopreventive role of phytoestrogens in breast cancer.¹⁵ Higher exposure to estrogens and specific genotoxic estrogen metabolites may initiate and promote hormone related cancers.^{22, 38} Local estrogen production in breast cancer tissues as a result of the interactions of various enzymes are considered to play very important roles in the pathogenesis of hormone- dependent breast carcinoma. Intratumoral aromatase (CYP19), 17 β -hydroxysteroid dehydrogenase (17 β -HSD) isoenzymes, estrogen sulfatase (STS) and estrogen sulfotransferase are key enzymes involved in the estrogen biosynthesis.³⁹ Over expression or increased activity of these enzymes are related to increase in breast cancer in postmenopausal women.^{39, 40} Suppression of estrogen synthesis has been proposed as a treatment and has yielded to improvement in prognosis for hormone sensitive cancers.⁴¹ Use of an aromatase inhibitor as initial therapy or after treatment with tamoxifen is now recommended as adjuvant hormonal therapy for postmenopausal woman with hormone-dependent breast cancer.⁴ In-vitro studies in human granulosa luteal cells, adrenocortical carcinoma cells and MCF7 cells have revealed that many phytoestrogens including genistein, diadzein, quercetin and resveratrol inhibit aromatase and 17 β HSD activities.^{15, 43} A recent study indicated that isoflavone biochanin A from red clover inhibited aromatase activity and gene expression in MCF-7 cells transfected with CYP19 and also in estrogen receptor-negative breast cancer cells SK-BR-3.⁴⁴ Estrogen metabolites are potentially mitogenic and genotoxic and are related to breast cancer. Studies in numerous cell lines have illustrated that genistein and resveratrol decrease both activity of cytochrome P450 dependent monooxygenases Cyp1A1 and Cyp1B1 which

are responsible for the metabolism of estradiol to generate 2 hydroxyestradiol (2-OHE2) and the more genotoxic 4-hydroxyestradiol (4-OHE2).¹⁵ Both are detoxified by catechol-O-methyl transferase (COMT) whereas their quinones which are formed by oxidation are inactivated by NADH-quinone-oxidoreductase (QR).⁴⁵ In rodent models, it has been reported that 2-OHE2 and 2-methoxyestradiol may protect against breast carcinogenesis, while 4-OHE2 is carcinogenic. Thus, it has been postulated that agents that increase the metabolism of estradiol by Cyp1A1 to produce 2-OHE2 may have chemoprotective properties.⁴⁶ A recent study in MCF10F breast cancer cell lines treated with quercetin at 10 and 50 μ M concentrations revealed that it produced six and eleven times greater inductions of Cyp1A1 mRNA over Cyp1B1 mRNA respectively. Quercetin significantly increased Cyp1A1 protein levels and only slightly increased Cyp1B1 protein levels indicating that phytoestrogens may exert their anti-cancer effects by modulating the expression of estrogen-metabolizing enzymes.⁴⁶ However, in another study in MCF-7 cells, genistein and diadzein inhibited the expression of Cyp1A1, COMT and QR.⁴⁵ Estrogen metabolites have also been implicated in the pathogenesis of prostate cancer. In epidemiological studies, lower excretion of urinary estradiol and lower ratio of urinary 2-hydroxy estrogens (2-OHE2) to 16 α -hydroxyestrone (2:16 OH-E1) have been reported in prostate cancer cases compared to controls. A recent study among 58 men indicated that 3 and 6 months dietary supplementation with isoflavone rich soy protein isolate (7 mg isoflavones /d) increased urinary estrogens and the ratio of 2:16 OH-E1.⁴⁷

Phytoestrogens bind to both estrogen receptors ER α and ER β with a preference for ER β in vivo.⁵ ER β may play a protective role in breast cancer development by inhibiting mammary cell growth as well as the stimulating effects of ER α .⁷ At physiological concentrations phytoestrogens may activate ER β and induce its antiproliferative effects.¹⁵ Clinical studies have indicated that consumption of soy foods or an exposure to soy isoflavone genistein during childhood and adolescence in women, and before puberty onset in animals reduces later breast cancer risk.¹⁵ It has been suggested that epigenetic alterations in mammary stem cells leading to changes in gene expression of tumor suppressor genes such as BRCA1 and PTEN and mammary gland morphology may play crucial roles in modifying breast cancer risk.⁴⁸ Alterations of breast development / morphology may be crucial in reduction of mammary sensitivity to carcinogens in adulthood.¹⁵ Peroxisome proliferator activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor superfamily comprising of three subtypes such as PPAR α ,

PPAR γ and PPAR δ / β .⁴⁹ PPAR γ agonists inhibit the growth of many types of cancers.⁵⁰ Studies have illustrated that isoflavones including genistein and biochanin A can act as ligands for PPAR gamma.⁵¹

Phytoestrogens modulate many signaling cascades in various cell types involving MAP kinase and NF-kappa B signaling pathways, AP-1-mediated signaling, cell cycle regulation, apoptosis and other nuclear-mediated signaling.⁵ It has been suggested that genistein inhibit human cancer cell growth by modulation of genes that are related to the control of cell cycle and apoptosis. Genistein inhibits the activation of NF-kappaB and Akt signaling pathways, both of which are known to maintain a homeostatic balance between cell survival and apoptosis. Moreover, genistein antagonizes estrogen and androgen mediated signaling pathways in the processes of carcinogenesis.⁵² Recent evidence suggests that soy isoflavones modulate immune response by both estrogen receptor-dependent and independent mechanisms which may contribute to its overall effectiveness as an anti-carcinogenic agent.⁵³

Genomic microarray analysis in conjunction with quantitative real-time PCR and western blot analysis in prostate cancer cells have indicated the immunomodulatory and anti-inflammatory properties of flavonoids which empower them with properties as effective chemopreventive agents.⁵⁴

Most chemopreventive agents are antioxidant in nature and the usefulness of dietary antioxidants for chemoprevention of breast, prostate and other cancers are well documented.⁵⁵ Oxidative stress, including alterations in the activity of antioxidant enzymes glutathione peroxidase and superoxide dismutase were detected in mammary and tumor tissue of experimental animals as a function of estrogen exposure.⁵⁶ A recent study indicated that the prevention of tumorigenesis in prepubertal rats by the phytoestrogen Biochanin A may be attributed to its antioxidant properties and intake of this phytoestrogen at an early stage may help in the lowering of mammary tumor.⁵⁷ Studies have also demonstrated the antioxidant and related effects of the phytoestrogen quercetin and other structurally related phenolic compounds.^{58,59}

Genistein and diadzein upregulates the expression of antioxidant genes and are shown to be potent inhibitors of angiogenesis and metastasis.^{52, 60, 61} Table 2 gives the key points about the proposed mechanisms of action of phytoestrogen in cancer.

Phytoestrogens as safe functional ingredients

Phytoestrogens have anticarcinogenic potential but they also have significant estrogenic properties. Estrogens are

well known component of numerous hormone related cancers including breast and they have been included in the list of known human carcinogens.¹⁵ Epidemiological evidence indicates that prolonged lifetime exposure to estrogen is associated with elevated breast cancer risk in women. Rodent and cell culture model studies have demonstrated that certain phytoestrogens like genistein and resveratrol not only reduce but also stimulate estrogen dependent growth such as uterine and breast cancers depending on dose and timing of exposure.⁵ Concerns regarding the role of phytoestrogens to increase the risk of recurrence or stimulate the growth of existing tumors through their estrogenic activities have also been raised.^{8, 9, 62} This controversy carries considerable public health significance because of increasing popularity of soy foods and commercial availability of isoflavone supplements. Recent analysis and review into the safety aspect of phytoestrogens have indicated that there is little clinical evidence to suggest that isoflavones will increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients.⁶³

Furthermore, consuming soy products such as tofu, soymilk or soy flour as part of a balanced diet low in saturated fats and high in fruits and vegetables is likely safe and even beneficial.⁷ However, supplementary intake or augmentation of dietary phytoestrogen sources cannot be recommended at this time.

Conclusion

Interest in the role of phytoestrogens in cancer prevention, particularly of tumors under endocrine control (breast, prostate and others) has increased dramatically over the last decade. The limited clinical studies so far in humans clearly confirm that phytoestrogens exert slightly protective effects against both breast and prostate cancer. However, the results are inconsistent and available data do not appear to unequivocally support the beneficial effects of phytoestrogens against cancers and warn against their wide use as dietary supplements in the absence of satisfactory clinical findings. The role of phytoestrogens as protectors or perpetrators against cancer can only be resolved by more well-designed clinical trials and an in-depth investigation into their mechanisms of action. Till then, it would be prudent to say that the debate on phytoestrogens and cancer still continues.

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