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Phytoestrogens and women's health: Implications for fibroids and breast cancer – a scoping review

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ABSTRACT

Background: As both uterine fibroids and breast cancer are estrogen dependent tumors, it is crucial to understand how phytoestrogen intake affects the development and progression of these conditions. Most of the research in this area has focused on soy isoflavones, yet a plethora of other phytoestrogens exist.
Objective: The aim of this scoping review was to examine the current literature to determine the relationship between phytoestrogen intake, and the development and progression of uterine fibroids and breast cancer.
Methods: The Scopus database was searched to identify relevant articles published within the past five years.
Results: A total of 5,590 articles were identified in the original search, and 22 articles were included in the final review, with a total of 218,752 female participants (>18 years) across all studies. The findings of this scoping review suggest that consuming phytoestrogen-rich foods, such as soy or flaxseeds, either has no effect on breast cancer risk, or that it may possibly decrease the risk of breast cancer Additionally, supplementation with 300-900 mg of epigallocatechin gallate (EGCG), a phytoestrogen found in green tea, shows promise as a complementary treatment for fibroids.
Conclusion: Current evidence suggests that dietary phytoestrogen intake does not increase the risk of breast cancer. Additionally, EGCG may be a future complementary treatment for reducing fibroid size, although more research is needed to confirm this finding.

Keywords: Breast cancer; EGCG; fibroids; phytoestrogens

BACKGROUND

Uterine fibroids are the most common benign pelvic tumors in reproductive aged women, affecting between 70-80% of women by age 50.[1] Risk factors for developing uterine fibroids include older age, Black race, family history of fibroids, vitamin D deficiency, nulliparity, hypertension and body mass index (BMI) ≥ 30 kg/m^2. While many cases of fibroids remain asymptomatic, in some women fibroids may cause pelvic pain, heavy menstrual bleeding, frequent urination or back pain, which can negatively impact quality of life. Furthermore, fibroids are the leading cause of hysterectomy in the United States and costs associated with fibroid treatment range from 5.9 to 34.4 billion dollars annually.[2,3] Despite the high prevalence of fibroids, treatment options are limited. Hysterectomy is the only cure for fibroids; however, this option may not be viable to women planning on starting or growing their family. Other treatments include myomectomy, uterine artery embolization and pharmacological treatments, however in many cases fibroid tumors may regrow.[4] The widespread prevalence of fibroids, the high healthcare costs associated with treating fibroids, and limited effective treatment options highlight the need for identifying ways to prevent and manage fibroids using holistic methods.

Breast cancer is the most common cancer among women in the United States; it is estimated that about 12% of American women will develop breast cancer within their lifetime.[5] Breast cancer is a significant public health concern due to the high prevalence and high mortality rate associated with it; although the 5-year survival rate in earlier stages of breast cancer is relatively high, the 5-year survival rate for stage III and stage IV breast cancer is 72% and 22% respectively. Risk factors for breast cancer include BMI ≥ 30 kg/m^2, age >50 years, exposure to radiation and mutations in the BRCA1 and BRCA2 genes.[6] Only about 5-10% of breast cancer cases can be traced back to identifiable genetic mutations, highlighting the importance of lifestyle factors, such as diet in the prevention of breast cancer.[7] Despite the wide variety of treatment options available for treating breast cancer, the risk of cancer recurrence is high, especially in more aggressive forms of breast cancer, emphasizing the need to understand measures for preventing breast cancer recurrence.

Phytoestrogens are a group of non-steroidal compounds that have weak estrogenic or anti-estrogenic activity depending on local cellular conditions.[8] Phytoestrogens are abundant in plant-based foods and include flavonoids, such as soy isoflavones (genistein and daidzein), catechins, and coumestans, as well as non-

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flavonoids, such as lignans (enterodiol and enterolactone) and stilbenes (Figure 1). As structural analogs to endogenous estrogens, phytoestrogens may exert their effects against fibroid tumors and breast cancer via interactions with the estrogen receptor (ER). There are two main isoforms of the ER including ERα and ERβ. Phytoestrogens can bind to both of these receptors although they primarily bind to ERβ, which antagonizes estrogen's proliferative effects.[8] To date only one systematic review has investigated the effects of soy intake and risk of fibroids, suggesting that high soy intake in infancy and in adulthood is associated with an increased risk of uterine fibroids.[9] Multiple systematic reviews and meta-analyses have examined the relationship between soy isoflavone intake and breast cancer risk, with results generally suggesting an inverse relationship between soy intake and risk of breast cancer.[10] While soy isoflavones are the most common type of phytoestrogens in the human diet, a plethora of other phytoestrogens exist, and their consumption may play a role in the development of fibroids and breast cancer.

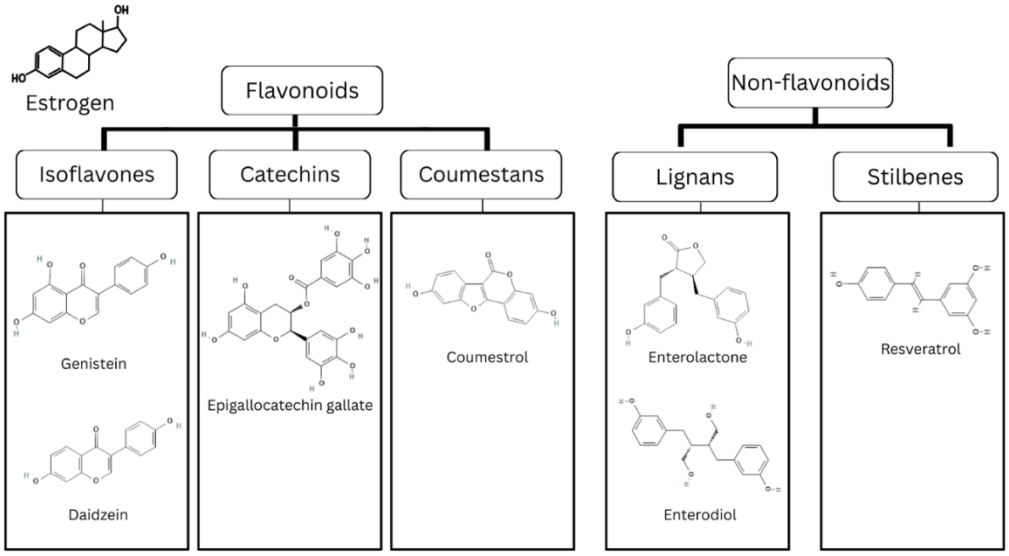


Figure 1: An Overview of Phytoestrogen Classes[11-17]

Phytoestrogens can be divided into two main classes: Flavonoids and non-flavonoids. Flavonoids can be further divided into isoflavones, catechins, and coumestans, while non-flavonoids can be divided into lignans and stilbenes. Note that phytoestrogens have a hydroxyl group in a position analogous to the para-hydroxyl group of human estrogen, which allows them to bind to human estrogen receptors.

The purpose of this scoping review is to examine the current literature to determine how phytoestrogen intake affects the risk of uterine fibroids and breast cancer, as well as to determine if phytoestrogen intake influences the risk of breast cancer recurrence and fibroid treatment. The following variables will be examined to investigate the effect of phytoestrogens on fibroids and breast cancer respectively: risk of uterine fibroids, fibroid volume/size, and quality of life; risk of breast cancer, ki67 levels (a measure of cell proliferation), mammographic density, fibroglandular breast tissue density, 2-hydroxyestrone:16-α-hydroxyestrone levels and risk of breast cancer recurrence. These parameters were defined prior to the review process to ensure methodological consistency. This scoping review aims to add novelty by specifically examining epigallocatechin gallate (EGCG), a phytoestrogen found in green tea, that has been shown to have powerful antiproliferative activity in laboratory studies. [18]

MATERIALS AND METHODS

The methods are structured according to the PRISMA Extension for Scoping Review guidelines.[19]

Search strategy

The Scopus database was used to identify relevant articles using the keywords "breast cancer" OR "fibroids" OR "leiomyomas" AND "phytoestrogens" OR "soy" OR "soy isoflavones" OR "lignans" OR "coumestans" OR "flaxseed" OR "green tea" OR "EGCG" OR "resveratrol". These keywords were chosen because they represent the phytoestrogen classes or because they refer to specific foods that contain high amounts of phytoestrogens. The database search was conducted on December 9th, 2024. In addition to the Scopus search, the reference lists of relevant articles were manually reviewed to identify additional studies.

Eligibility Criteria

The eligibility criteria for this scoping review were as follows: articles written in English, articles written between 2019-2024, and observational/experimental studies investigating the effects of phytoestrogens on either breast cancer or fibroids in human subjects. Exclusion criteria included articles not written in English, articles written before 2019, systematic reviews/meta-analyses, narrative reviews, and research including in vivo or in vitro models.

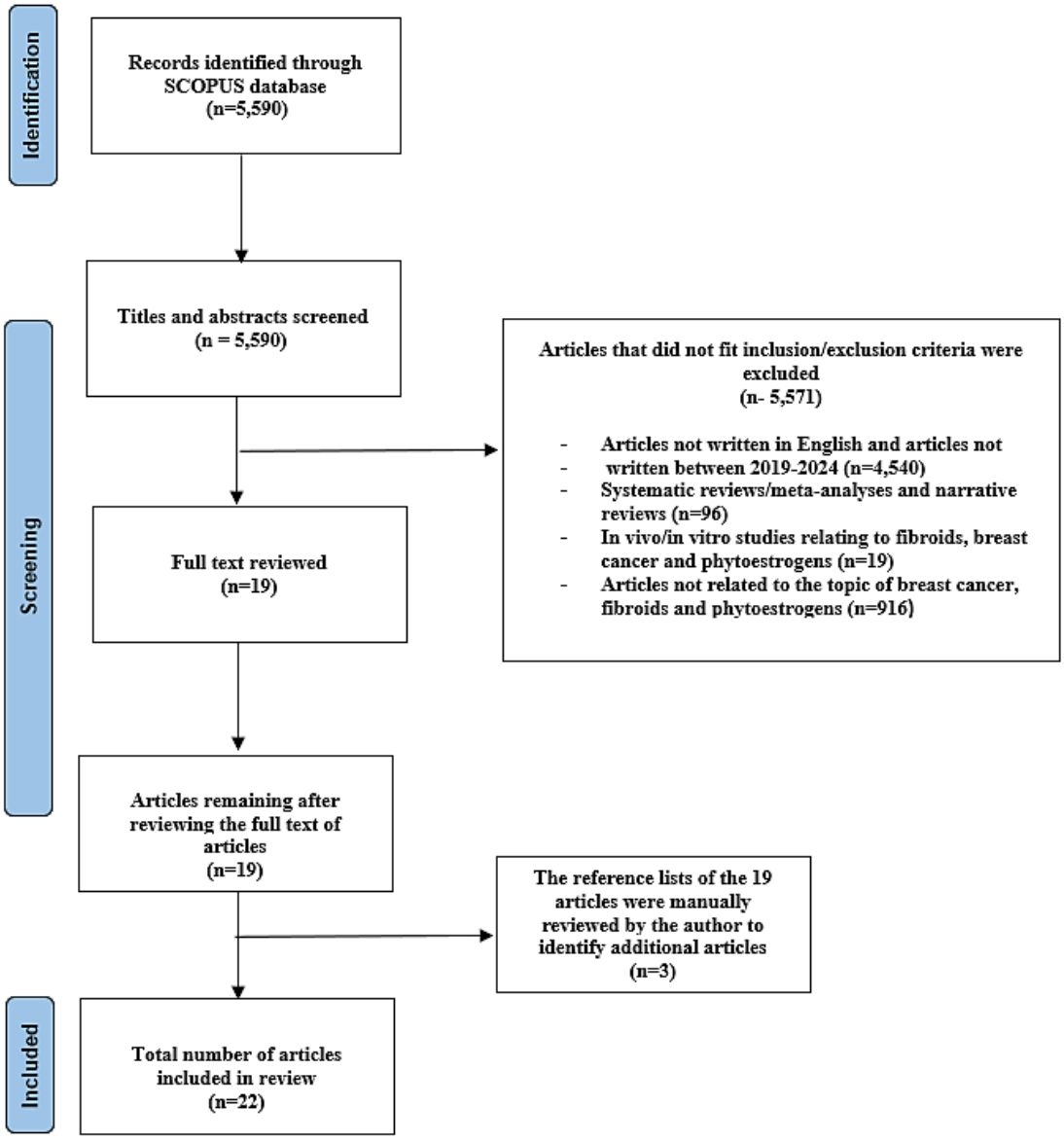


Figure 2: Overview of the Literature Search Process According to PRISMA-ScR Guidelines

Data Extraction and Charting

The full text of articles deemed to meet inclusion criteria was reviewed. The following information was extracted from each article: name of author, year of publication, country of origin, type of study, type of phytoestrogen (i.e. soy isoflavones, lignans), methods used to quantify phytoestrogen intake (i.e. food frequency questionnaire or urinary phytoestrogen excretion), measures of breast cancer and fibroid risk, dosage of phytoestrogens (where applicable), number of participants, duration of study, and results. Breast cancer risk was classified as direct risk (as reported by odds ratio, hazard ratio, etc.) or indirect risk (i.e. mammographic density, fibroglandular breast tissue density, 2-hyroxyestrone/16-α-hydroxyestrone ratio). Fibroid outcomes assessed included risk of fibroids (as reported by odds ratio, hazard ration, etc.), volume/size of fibroids and quality of life (as measured by validated questionnaires).

RESULTS

The original Scopus search yielded 5,590 results. After being restricted to articles written in English and articles written between 2019-2024, 1,050 articles remained. The titles of these 1,050 articles were screened, and 1,031 articles were further excluded due to the following reasons: systematic reviews/meta-analyses or narrative reviews (n=96), in vivo/in vitro studies (n=19), and irrelevant articles (n=916), leaving 19 articles. Irrelevant studies included articles that were not relevant to the research question (i.e. studies that examined the effects of phytoestrogen chemistry). The full text of these articles was reviewed; all 19 articles met the inclusion criteria and were thus included in this review. Four additional articles were identified after manually reviewing the reference lists of the relevant articles. Three of these articles met inclusion criteria and were included in this review, yielding a total of 22 articles. Of the 22 articles identified, 16 related to breast cancer and 6 related to fibroids. An overview of the literature review process can be found in Figure 2.

Characteristics of studies

Of the articles that related to phytoestrogens and breast cancer, two studies were cross sectional studies[20,21], two were case-control studies[22,23], five were cohort studies,[24-28] and seven were experimental studies[29-35].These articles included a diverse array of participants, including women from the United States, China, France, Japan, Korea, Malaysia, Italy and Canada. Of the articles that pertained to phytoestrogens and fibroids, 1 was a cross-sectional study[36], 1 was a retrospective cohort study[37], and 4 were experimental studies[38-41]. These articles included women from Italy, Egypt, Germany and the United States. Most studies assessed phytoestrogen intake using a food frequency questionnaire (FFQ), while some studies measured urinary phytoestrogen excretion as a proxy of phytoestrogen intake. The following sections provide an overview of the studies and key findings. A detailed description of each study can be found in Table 1.

Phytoestrogens and Direct Risk of Breast Cancer

Three studies identified a positive association between the intake of phytoestrogens and risk of breast cancer.[20,21,27] In one cross sectional study, women in the highest tertile of urinary soy isoflavone excretion had 73% (OR: 1.73, 95% CI: 1.01-2.96) higher odds of developing breast cancer. Additionally, women in the highest tertile of lignan excretion had 88% higher odds of breast cancer (OR: 1.88, 95% CI: 1.06-3.34).[21] Specifically, higher urinary daidzein excretion were associated with 251% (OR:2.51, 95% CI:1.44-4.23) higher odds of breast cancer, and higher urinary enterodiol excretion was associated with 278% higher odds of breast cancer (OR:2.78, 95% CI:1.44-3.37).[20,21] Furthermore, one cohort study revealed that soy supplementation was associated with a 201% higher risk of estrogen receptor negative breast cancer (HR: 2.01, 95% CI: 1.41-2.86).[27] On the other hand, data from the remaining studies suggested that phytoestrogen intake either had no effect on the risk of breast cancer, or that phytoestrogen intake decreased the risk of breast cancer. In two case control studies, higher soy isoflavone and lignan intake was associated with lower odds of breast cancer.[22,23] In a cohort study of French women, soy isoflavone supplementation had no effect on overall risk of breast cancer (p=0.42), however, when analysis was stratified by breast cancer type, women taking soy isoflavone containing supplements had a 22% lower risk of estrogen receptor positive breast cancer (HR: 0.78, 95% CI: 0.60-0.99).[27]

In another cohort study, neither fermented nor non-fermented soy intake was associated with the overall risk of breast cancer, however fermented soy intake (i.e. miso) was associated with a 47% lower risk of metastatic breast cancer (HR: 0.53; 95% CI: 0.28-0.99).[25] In a different cohort study, higher soy isoflavone intake was associated with a 77% lower risk of breast cancer in those with the BRCA2 mutation (HR: 0.23, 95% CI: 0.08-0.68), and a 58% lower risk of breast cancer in non-BRCA mutation carriers with a family history of breast cancer (HR:0.42, 95% CI: 0.05-0.069). When stratified by molecular subtype of cancer, those who carried the BRCA1 mutation with the highest isoflavone intake had a 91% lower risk of triple negative breast cancer (HR:0.09, 95% CI: 0.02-0.40), while those with the BRCA2 mutation had an 86% lower risk of Luminal A breast cancer (HR: 0.14, 95% CI:0.04-0.50). Furthermore, non-carriers with a family history of breast cancer who had the highest isoflavone intake had a 73% lower risk of Luminal A breast cancer (HR:0.27, 95% CI: 0.11-0.69) and 81% lower risk of triple negative breast cancer (HR: 0.19, 95% CI: 0.05-0.69) compared to those who had the lowest intake of soy.[26] Only one study examined the effect of EGCG intake on risk of breast cancer, and this study revealed that women consuming ≥ 5 cups of green tea per day had an 18% lower risk of developing breast cancer (HR: 0.82; 95% CI: 0.70-0.99).[28]

Table 1: Results of Data Extraction

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Adham et al.[39]	Randomized control trial	Egypt	Experimental group n=35 Control group n=40	N/A	Green tea extract, 300 mg, 3x per day for four months	Women taking an EGCG containing supplement saw a decrease in fibroid volume compared to the control group ($p<0.01$).
Baharami et al.[22]	Case control study	Iran	Cases n=134 Controls n=267	168-item FFQ	N/A	Women in the highest tertile of lignan intake (>10.76 mg/day) had 49% lower odds of developing breast cancer compared to women in the lowest tertile of lignan intake (<7.61 mg/day) [OR: 0.51, 95% CI: 0.26-0.97].
Berrino et al.[29]	Randomized control trial	Italy	Experimental group n=769 Control group n=773	24-hour food frequency diary	Mediterranean diet enriched with phytoestrogen containing foods	A Mediterranean diet enriched with phytoestrogen containing foods was not associated with a decreased risk of breast cancer recurrence ($p>0.05$).
Biro et al.[38]	Interventional study	Germany	25 women	N/A	390 mg EGCG, 1x daily for six months	No significant decrease in fibroid size was observed following EGCG supplementation over a six-month period ($p>0.05$). EGCG supplementation was associated with a decrease in physical symptoms on the SF-12. ($p=0.019$).
Chang et al.[30]	Randomized control trial	Canada	Experimental group n= 48 Control group n=51	Serum enterolignan concentration	2 tbsp ground flaxseed daily for 7 weeks ($\approx 80\ mg\ SDG$)	Women who took a lignan containing supplement saw an increase in 2-hydroxyestrone levels ($p<0.002$) and an increase in the 2-hydroxyestrone: 16-α-hydroxyestrone ratio compared to the control group ($p<0.004$).

Table 1: Results of Data Extraction (continue…)

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Fabian et al. [35]	Randomized control trial	USA	Experimental group n=180 Control group n=177	N/A	50 mg SDG, 1x daily for 12 months	A 44% reduction in Ki67 levels was observed among women taking a lignan containing supplement. ($p<0.001$).
Feng et al.[23]	Case control study	China	Cases n=792 Controls n=813	Serum isoflavone and lignan concentrations	N/A	Women with the highest total serum soy isoflavones had 40% lower odds of developing breast cancer compared to women in the control group (OR:0.60, 95% CI: 0.41-0.87). Among premenopausal women, higher serum daidzein concentrations were associated with a 38% lower risk of breast cancer (OR:0.62, 95% CI :0.43-0.90).
Grandi et al.[41]	Interventional study	Italy	n=16	N/A	EGCG (300 mg) and vitamin D (50 µg), 1x daily for 1.5 months	An 18% decrease in fibroid size was observed after EGCG supplementation ($p=0.015$).
Green et al.[31]	Crossover, randomized control trial	Canada	n=114	Urinary phytoestrogen excretion	Phytoestrogen containing nutraceutical	The mean 2-hydroxyestrone: 16-α-hydroxyestrone ratio increased by 4.6ng/mg creatinine after taking EstroSense® compared to placebo ($p<0.001$). The mean 2-hydroxyestrone concentration increased by 0.43 ng/mg creatinine from baseline following the use of EstroSense® ($p<0.01$).
Ho et al.[24]	Prospective cohort study	China	n=1,460	107-item FFQ, 29-item soy FFQ	N/A	Pre and post diagnosis soy intake was associated with a decreased risk of breast cancer recurrence; however, this finding was not statistically significant ($p>0.05$).

Table 1: Results of Data Extraction (continue…)

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Langton et al.[37]	Retrospective cohort study	USA	n=1,610	Early life questionnaire regarding soy formula consumption	N/A	Ever being fed soy formula was not associated with an increased risk of fibroids. (p>0.05). Being fed soy formula within the first two months of life was associated with a higher risk of developing fibroids, although this finding was not statistically significant (HR:1.24, 95% CI: 0.81-1.91). Being fed soy formula for more than 6 months was associated with a higher risk of developing fibroids in adulthood, although this finding was not statistically significant (HR:1.21, 95% CI: 0.77-1.90).
Lee et al. [21]	Cross sectional study	USA	n=22,894	152-item FFQ; Urinary phytoestrogen concentration	N/A	Women in the highest tertile of soy isoflavone excretion had 73% higher odds of breast cancer (OR: 1.73, 95% CI: 1.01-2.96). Women in the highest tertile of lignan excretion had 88% higher odds of breast cancer (OR: 1.88, 95% CI: 1.06-3.34). Women in the highest tertile of daidzein excretion had 251% higher odds of developing breast cancer. (OR 2.51, 95% CI: 1.44 -4.23). Women in the highest tertile of enterodiol excretion had 278% higher odds of developing breast cancer. (OR: 2.78, 95% CI: 1.44-5.37).

Table 1: Results of Data Extraction (continue…)

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Liu et al.[20]	Cross sectional study	USA	n=8,844	152-item FFQ; Urinary phytoestrogen concentration	N/A	Women in the third quartile of total urinary isoflavone concentration (103.28-334.21 µg/g creatinine) had 81% higher odds of developing hormone related cancers compared to women in the lowest tertile of total urinary isoflavones (<43.89 µg/g creatinine) [OR: 1.81, 95% CI: 1.20-2.73]. A positive correlation was observed between urinary concentrations of daidzein and enterodiol, and breast cancer.
Lu et al.[32]	Randomized control trial	USA	Experimental group n=97 Control group n=97	Urinary isoflavone excretion	30 mg daidzein and 30 mg genistein, 5x per week	A 19.3 cm^3 decrease in fibroglandular tissue density was observed among premenopausal women taking a soy supplement for three years. ($p<0.05$).
Miriello et al.[40]	Randomized control trial	Italy	Experimental group n=41 Control group n=54	N/A	150 mg EGCG, 25 µg vitamin D and 5 mg vitamin B6, 2x per day for 4 months	A 37.9% decrease in fibroid volume was observed after EGCG supplementation ($p<0.001$). EGCG supplementation was associated with an improvement in SF-36 scores ($p<0.001$).
Rajaram et al.[34]	Randomized control trial	Malaysia	Soy supplement group n=41 Soy food group n=38 Control group n=39	Semi Quantitative FFQ	Supplement containing 50 mg of soy isoflavones, 2x daily or two 50 mg servings of soy containing foods	Women taking a soy supplement saw a decrease in mammographic density compared to women in the soy food group and control group, however this finding was not statistically significant ($p=0.48$).

Table 1: Results of Data Extraction (continue…)

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Samavat et al.[33]	Randomized control trial	USA	Experimental group n=538 Control group n=537	124-item FFQ and urinary EGCG excretion	Supplement containing 834 mg EGCG, 1x daily for 12 months	EGCG supplementation had no significant effect on levels of circulating sex hormones.
Shirabe et al. [25]	Prospective cohort study	Japan	n=47,614	138-item FFQ	N/A	No association was observed between total fermented and non-fermented soy intake and risk of breast cancer. (p>0.05). Women in the highest quartile of fermented soy intake (53.2 mg/day) had a 47% lower risk of non-localized breast cancer compared to women in the lowest quartile (7.3 mg/day) [HR: 0.53; 95% CI: 0.28-0.99].
Sim et al.[26]	Retrospective cohort study	Korea	n=1,709	Semi Quantitative FFQ	N/A	Women with a BRCA2 mutation in the highest tertile of isoflavone intake had a 77% lower risk of breast cancer (HR: 0.23, 95% CI: 0.08-0.68). Women with a family history of breast cancer who were in the highest tertile of isoflavone intake had a 58% lower risk of breast cancer (HR:0.42, 95% CI: 0.05-0.069). Women with the BRCA1 mutation who were in the highest tertile of isoflavone intake had a 91% lower risk of triple negative breast cancer (HR:0.09, 95% CI: 0.02-0.40). Women with the BRCA2 mutation had an 86% lower risk of Luminal A breast cancer. (HR: 0.14, 95% CI:0.04-0.50).

Table 1: Results of Data Extraction (continue…)

Author	Study Design	Country	Study Population	Assessment of phytoestrogen intake (if applicable)	Intervention (if applicable)	Results
Touillaud et al.[27]	Prospective cohort study	France	n=76,442	Soy supplement use was assessed via questionnaires sent out every 2-3 years during the duration of the study.	N/A	No significant association was observed between the use of soy containing supplements and the risk of breast cancer. (p>0.05). Soy supplement use was associated with a 22% lower risk of ER+ breast cancer (HR: 0.78, 95% CI: 0.60-0.99). Soy supplement use was associated with a 201% higher risk of ER- breast cancer. (HR: 2.01, 95% CI: 1.41-2.86).
Yang and Chen[36]	Cross sectional study	USA	n=1,579	152-item FFQ; Urinary phytoestrogen concentration	N/A	Women with the highest urinary concentration of total phytoestrogen excretion had 68% higher odds of developing fibroids (OR: 1.68, 95% CI:1.12-2.51). Women with the highest urinary equol concentration (>12.98 µg/g creatine) had 92% higher odds of developing fibroids (<5.05 µg/g creatine) [OR: 1.92, 95% CI: 1.09-3.38].
Zhang et al.[28]	Prospective cohort study	USA	n=50,884	98-item FFQ	N/A	Women who consumed ≥ 5 cups of green tea per day had a 18% lower risk of breast cancer (HR: 0.82; 95% CI: 0.70-0.99).

Phytoestrogens and indirect markers of breast cancer risk

Five studies demonstrated that phytoestrogen intake is associated with a reduction in various indirect markers of breast cancer risk.[30-32,34,35] In one randomized control trial, supplementation with 30 mg daidzein and 30 mg genistein reduced fibroglandular breast tissue density by 19.3 cm^3 ($p<0.05$).[32] Furthermore, in another randomized control trial, supplementation with a pill containing 50 mg of soy isoflavones twice daily was associated with a decrease in mammographic density among perimenopausal women, as compared to women consuming dietary soy isoflavones and women not consuming soy, although this finding was not statistically significant ($p=0.13$).[34] In two other studies, both lignan supplementation and supplementation of a phytoestrogen containing nutraceutical was effective at increasing the 2-hydroxyestrone:16-α-hydroxyestrone ratio, suggesting that phytoestrogens may shift estrogen metabolism to favor the production of 2-hydroxyestrone, the less potent metabolite of estrogen.[30,31] Daily supplementation with a pill containing 50 mg secoisolariciresinol (precursor of enterolactone/enterodiol) was associated with a 44% reduction in Ki67 levels in breast tissue, suggesting that lignans may indirectly reduce the risk of breast cancer by decreasing the rate of cell proliferation ($p < 0.001$).[35]

Phytoestrogens and risk of breast cancer recurrence

Ho et al. followed a group of Chinese breast cancer survivors to determine how pre-diagnosis and post-diagnosis soy intake affected the risk of breast cancer recurrence. A slight decrease in risk of breast cancer recurrence was observed for women with moderate pre-diagnosis and post-diagnosis soy intake, however this finding was not statistically significant ($p > 0.05$).[24] The Diet and Androgen Study V trial aimed to assess the effectiveness of a Mediterranean diet enriched with phytoestrogens on reducing the risk of breast cancer recurrence. No association was observed between following a phytoestrogen-enriched Mediterranean diet and risk of breast cancer recurrence ($p > 0.05$).[29]

Fibroids and soy isoflavones

One cross sectional study found that higher urinary excretion of equol was associated with 92% higher odds of fibroids (OR: 1.92, 95% CI:1.09-3.38).[36] In a cohort study among African American women, no association was observed between ever being exposed to soy formula and risk of fibroids ($p>0.05$).[37] Being fed soy formula in the first two months of life and being fed soy formula for more than 6 months was associated with a slightly higher risk of fibroids compared to those never fed soy formula, however these findings were not statistically significant ($p > 0.05$).[37]

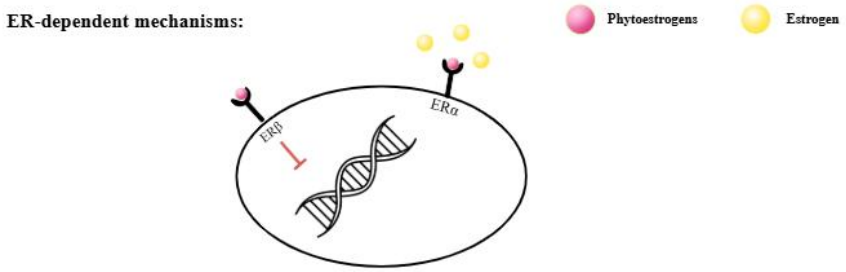
Fibroids and epigallocatechin gallate supplementation

Two interventional studies examined the effect of EGCG supplementation (ranging from 390-900 mg) on fibroid size/volume, with one of these trials observing a decrease in fibroid size after EGCG supplementation.[38,39] Two trials examined the combined effect of EGCG supplementation with other micronutrients involved with estrogen metabolism. In one trial, supplementation with 300 mg EGCG and 50 µg vitamin D resulted in an 18% reduction in fibroid volume ($p=0.015$).[41] Additionally, combined supplementation with 150 mg EGCG, 25 µg vitamin D and 5 mg vitamin B6 twice daily, resulted in a 37.9% decrease in fibroid volume after four months ($p < 0.001$).[40] Two of these studies also found that EGCG supplementation improved quality of life. [38,40]

DISCUSSION

Among the studies examined in this scoping review, most studies suggest that consuming soy isoflavones and lignans either has no effect on breast cancer risk, or that it may possibly decrease the risk of breast cancer. Although two cross-sectional studies and one cohort study observed an increased risk of breast cancer among women with higher urinary soy isoflavone concentrations, the other case-control and cohort studies, and all interventional trials (which provide strongest evidence), found either no association, or decreased risk of breast cancer among women who consumed soy isoflavones. Similarly, while in two cross sectional studies higher urinary lignan concentration was associated with an increased risk of breast cancer, case-control, cohort and interventional studies (which provide stronger evidence) observed a decreased risk of breast cancer among women consuming lignans. These findings are in line with a recent meta-analysis by Boutas et al. who observed a negative correlation between soy isoflavone intake and risk of breast cancer in both premenopausal and postmenopausal women.[9] Furthermore, a 2010 meta-analysis by Buck et al. found that higher lignan intake was associated with reduced risk of breast cancer among postmenopausal women.[42]

Only two studies investigated the effect of phytoestrogen intake and risk of breast cancer recurrence, and neither study found an association between phytoestrogen intake and risk of breast cancer recurrence. This finding is not in line with a recent meta-analysis by van Die et al. where a 26% lower risk of breast cancer recurrence was observed among breast cancer survivors who had a high intake of soy isoflavones.[43] Regarding fibroids, only six articles were identified, of which four focused on EGCG. There was a common consensus that EGCG is effective at reducing the size/volume of uterine fibroids, and two studies found that EGCG may be effective at increasing quality of life among women with fibroids.[38-41]. Supplementation with EGCG doses ranging from 300-900 mg appeared to be effective at reducing fibroid size, and to be well tolerated by study participants.[39-41]



Phytoestrogens can bind to the ERα receptor, thus preventing stronger estrogens from binding and exerting their proliferative effects. Phytoestrogens also bind to the ERβ receptor which has anti-estrogen activity.

Figure 3: Suggested ER-dependent mechanisms of phytoestrogens

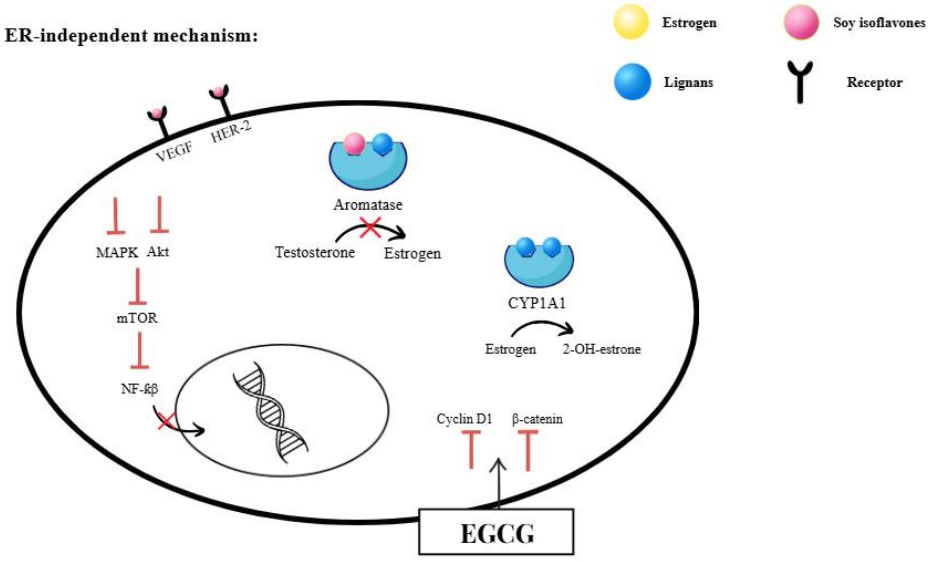


Figure 4: Suggested ER-independent mechanisms of phytoestrogens.

Soy isoflavones may exert their effects though inhibiting the aromatase enzyme, suppressing the expression of tyrosine kinases (VEGF, HER-2) and inhibiting various effectors of cell signaling pathways, including the PI3K/Akt/mTOR, MAPK, and the NF-ĸβ pathways. Lignans have also been shown to inhibit the aromatase enzyme and to promote the production of 2-hydroxyestrone, the less potent estrogen metabolite via interactions with the CYP1A1 enzyme. EGCG may exert its effects through blocking the effectors of pathways involved with ECM deposition, such as the Wnt/β-catenin pathway, or though downregulating the production of cyclin D1, an important regulator of the cell cycle.

Although the exact mechanism of how phytoestrogens may exert their effects is unknown, phytoestrogens may act through both estrogen receptor (ER) dependent and ER independent pathways. As mentioned earlier, phytoestrogens can bind to estrogen receptors; phytoestrogens may compete with endogenous estrogens for binding to the ER, thereby preventing endogenous estrogens from exerting their proliferative effects. Additionally, phytoestrogens may bind to ERβ, which antagonizes estrogen's effects. [8] Although this mechanism is plausible, the interaction of phytoestrogens with the ER may be more complex

and depend on the concentration of ERα to ERβ in a particular cell. In cells with high ratios of ERα to ERβ, genistein has been shown to stimulate cell proliferation, while in cells with low ratios of ERα to ERβ, genistein demonstrated antiproliferative activity.[44] The following sections will discuss the proposed ER independent mechanisms by which soy isoflavones, lignans and EGCG may exert their effects.

Soy isoflavones

A variety of cell signaling pathways including the PI3K/Akt/mTOR pathway, the MAPK pathway, and the NF-ƙβ pathway, are often upregulated in breast cancer. Soy isoflavones have been shown to downregulate effectors of these pathways, thereby preventing abnormal cell proliferation. In addition to modulating cell signaling pathways, soy isoflavones have been shown to inhibit aromatase activity, which helps prevent the conversion of androgens to estrogens.[45] Additionally, soy isoflavones have been shown to suppress the expression of tyrosine kinases such as Human Epidermal Growth Factor Receptor-2 (HER-2), potentially slowing the progression of HER2-positive breast cancer.[46] Furthermore, soy isoflavones have been shown to inhibit vascular endothelial growth factor (VEGF), which reduces blood supply to the tumor and prevents tumor growth.[44]

Lignans

Lignans may exert their effects via interactions with CYP450 enzymes in the liver, such as CYP1A1, which favors the production of 2-hydroxyestrone over the more potent metabolite, 16-α-hydroxyestrone.[47] Similarly to soy isoflavones, lignans have also been shown to inhibit aromatase, which in turn lowers the levels of circulating estrogen. [45] Lignans can also act as potent antioxidants by directly binding to reactive oxidative species or enhancing the activity of endogenous antioxidants, such as superoxide dismutase. Ironically, at high concentrations lignans may also exert prooxidant activity, which leads to the generation of large amounts of free radicals that activate apoptotic pathways.[48]

EGCG

The anti-tumor effects of EGCG may be attributed to epigenetic mechanisms. Meeran et al. demonstrated that EGCG can induce demethylation and deacetylation of the promoter region of human telomerase reverse transcriptase, thereby reducing the length of telomeres and inducing apoptosis of tumor cells.[49] Additionally, aberrant extracellular matrix (ECM) deposition is a hallmark of uterine fibroids, and in vivo studies have demonstrated that EGCG may downregulate pathways involved with ECM deposition, including the Wnt/β-catenin and Hippo/Yap pathways. Finally, EGCG may also decrease cyclin D1 levels, which prevents abnormal cell proliferation by blocking progression through the cell cycle.[50]

Strengths and limitations

This scoping review had many strengths including the use of articles that included women from diverse ethnicities, which increases the generalizability of the results. Additionally, about half of the studies included in this review were experimental studies, thereby providing a closer link to causality. Furthermore, this is the first scoping review to explore the link between the use of EGCG containing supplements in fibroid treatment. Finally, the use of validated FFQs or biomarkers in most studies enhanced the accuracy of estimating phytoestrogen intake. Despite these strengths, this scoping review had limitations. First, while some studies directly assessed breast cancer risk by determining if participants developed breast cancer, some studies looked at indirect measures of breast cancer risk. While elevated indirect measures of breast cancer risk may suggest that a person will develop cancer, these markers are not always a reliable indicator of breast cancer risk. Second, although it is ideal to obtain phytoestrogens from diet alone, it can be challenging to consume sufficient amounts of phytoestrogens needed to observe physiologic effects from food alone. For this reason, studies that examined the effects of phytoestrogens from food sources and supplements were included in this scoping review. It is crucial to note that this approach has limitations because phytoestrogen containing foods are made up of thousands of chemicals, making it difficult to discern whether the observed effects were due to phytoestrogens or other components of the foods. As a result, direct comparison between food-based sources of phytoestrogens and phytoestrogen supplements was not possible in this review. Future reviews should consider investigating the effects of phytoestrogens on breast cancer and fibroids from food sources and supplements separately. Third, the use of FFQs to assess phytoestrogen intake may be subject to recall bias. Also, sampling bias may have occurred since women elected to participate in the studies. Finally, some studies, especially the studies regarding phytoestrogen intake and fibroids, had small sample sizes, which limited the power of the studies.

CONCLUSIONS

In summary, consuming phytoestrogen-rich foods does not increase the risk of breast cancer, and it may possibly reduce the risk of breast cancer. Additionally, EGCG supplementation (300-900 mg) may be a safe and affordable complementary treatment for fibroids alongside conventional medical therapy, although large, randomized controlled trials are necessary to confirm this finding. It is crucial to note that soy isoflavone intake and lignan should primarily come from food sources, as further research is needed to establish safe soy isoflavone and lignan supplement dosages.

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