

Abstract

Background: Breast cancer is the most highly diagnosed cancer among women in the world, accounting for almost 1.7 million new cases diagnosed in 2012. The investigation of soy's role in the prevention of breast cancer arose from the significant differences in breast cancer incidence between American women and Asian women. One key difference observed between these two populations is the amount of soy consumed: Asian women are reported to consume a mean daily intake of 10-50g of soy, while American women are reported to consume a mean daily intake of 1-3g of soy. Soy isoflavones, the third main class of phytoestrogens, merit grounds for investigation in breast cancer research as they are structurally similar to estrogen hormone, estradiol, and pose agonist and antagonist effects on estrogen receptors.

Objectives: The purpose of this research is to evaluate the literature and investigate whether the ingestion of phytoestrogens found in soy products decreases a woman's risk of developing breast cancer.

Methodology: A search of the JNCI, Google Scholar, and Pubmed was conducted using search terms such as: soy, phytoestrogens, tofu, isoflavones, genistein, daidzein, premenopausal, asian, caucasian, women, and breast cancer. The final search was evaluated and narrowed down to six articles published between December 1998 and 2013, which were selected for review and use in this abstract assignment. Meta-analyses, observational studies, and experimental case-controlled studies were reviewed. Only full-length original journal articles were considered for review.

Results: Estimations of risk, levels and measures of soy, and control of confounding variables varied considerably across studies. While non-fermented soy products tended either to show no association or an inverse association with the development of breast cancer, contrasting studies showed that isoflavones, particularly genistein, in soy products stimulate the proliferation of breast tumours in premenopausal women. Fermented soy products, such as miso, showed little effect at all. While the intake of soy isoflavones among Asian populations was associated with a decreased risk of breast cancer, the opposite was true for Western populations.

Conclusions: As a result of the heterogeneity present in study designs, it is unclear whether phytoestrogens in soy have a preventative or stimulatory effect on the development of breast cancer in women. More long-term prospective cohort studies are needed to evaluate the relationship between phytoestrogens and breast cancer risk.

Research Question

Does the ingestion of phytoestrogens found in soy products decrease a woman's risk of developing breast cancer?

Introduction

Breast cancer is the most prevalent cancer among women worldwide.⁷ In Canada The investigation of soy's role in the prevention of breast cancer arose from the significant differences in breast cancer incidence between American women and Asian women. People from North America carry the highest risk of developing breast cancer, while Asians carry the lowest risk of developing breast cancer.⁴ One key difference observed between these two populations is the amount of soy consumed: Asian women are reported to consume a mean daily intake of 10-50g of soy, while American women are reported to consume a mean daily intake of 1-3g of soy. Due to the fact that genetics are only thought to account for 10-15% of breast cancer cases, the environment, particularly nutrition, is thought to play a significant role in predisposing women to breast cancer.⁹ Soybeans contain one of the three main classes of plant estrogens (phytoestrogens) called isoflavones. The two major isoflavones in soy include daidzein and genistein. Soy isoflavones merit grounds for investigation in breast cancer research as they are structurally similar to estrogen hormone, estradiol, and pose agonist and antagonist effects on estrogen receptors. Experimental research suggests that plant estrogens in soy play a potentially significant role in inhibiting the initiation and promotional processes of breast cancer development. Results from epidemiological studies and animal studies further suggest that increased soy consumption could be associated with a decreased risk of developing breast cancer. The purpose of this research is to evaluate the potential relationship between ingestion of phytoestrogens found in soy, particularly the isoflavone genistein, and the risk developing of breast cancer.

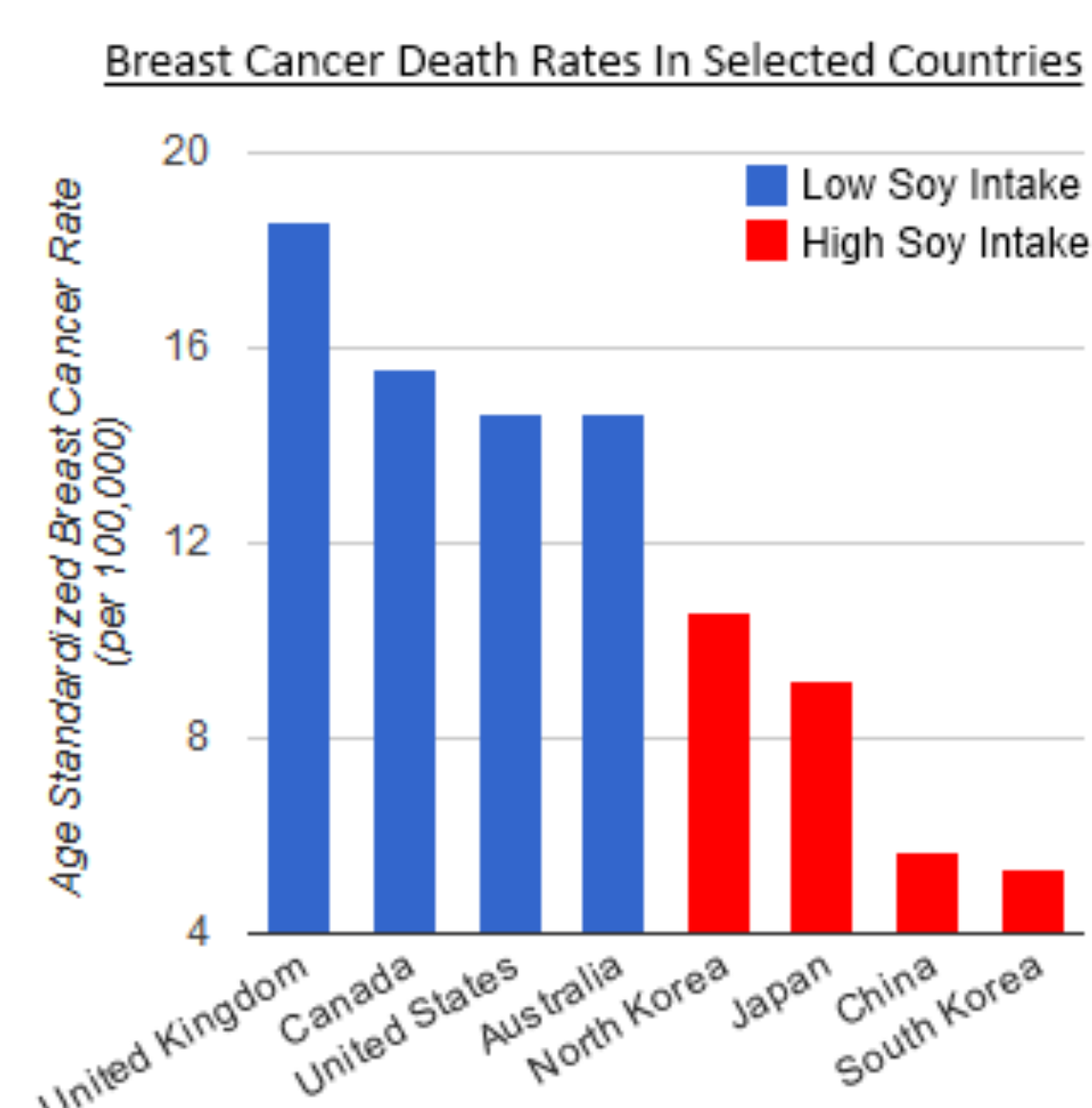


Figure 1. Comparing soy intake and breast cancer rates in select populations

Methods

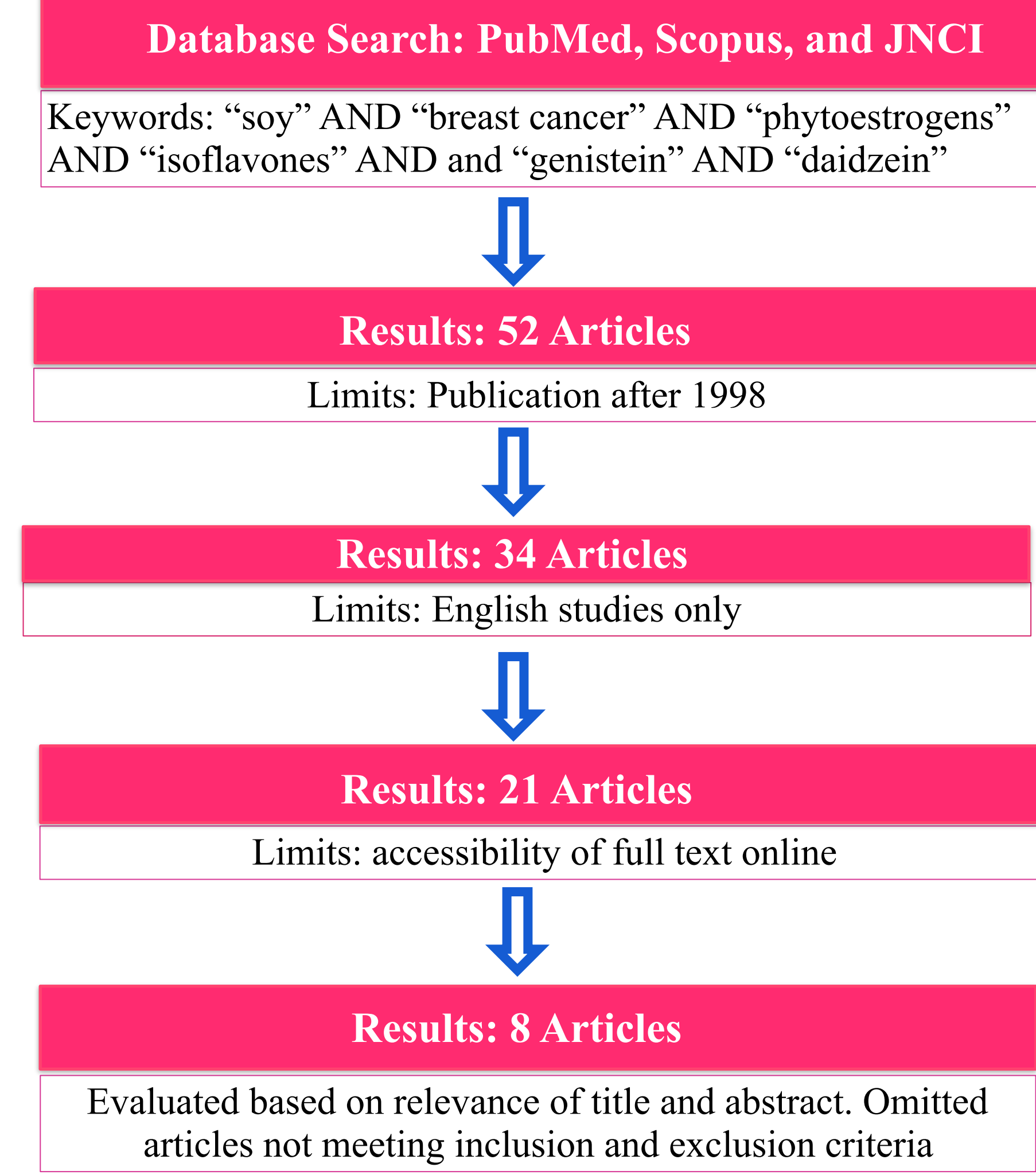


Figure 2. Methodology Flowchart Illustrating Literature Selection Process

Discussion

Findings and Structured Literature

- The search yielded 2 experimental studies, 2 observational studies, 3 meta-analysis studies, and 1 prospective study
- The literature confirms an association between high soy intake and a reduced risk of breast cancer in Asian populations, however associations of soy intake and breast cancer risk are unclear in Western populations. An increase in breast cancer risk has been noted in Asian women who emigrate to US, which is thought to be due to changes in lifestyle and dietary habits.
- Soy's protective effects against breast cancer protection in Asian women who consume a traditional diet high in soy is derived from early exposure to soy products containing isoflavones of genistein and daidzein. Experimental and epidemiological studies show that an early exposure to soy products is essential for benefits of cancer protection. Tofu contributes to the largest amount of soy intake in most Asian diets, whereas in western diet the majority of isoflavone intake comes from non-soy foods such as soy additives in baked goods, tuna or coffee.⁶ This is evident, as the daily intake of soy products in Asian populations ranges between 10-50g compared to 1-3g in the US.⁵
- Research suggests that soy products protect against cancer through multiple mechanisms:²
 - Increased mammary gland cell differentiation
 - decreased activation of pro-carcinogens to carcinogens
 - Regulation of genes in signal transduction pathways underlying tumour initiation
- Future studies should be directed towards soy isoflavones intake in Western populations

Limitations

- Articles were accessed only in the English language, published after the year 1998, and those accessible online in full text.
- Studies assessed did not talk about soy intake in women who already have breast cancer and whether it reduces progression of the disease. Future studies may wish to be evaluated in this area.

- Intake of soy was not measured homogeneously across all studies, therefore effects of soy intake and risk breast cancer cannot be generalized to other populations.
- The risk of breast cancer in women was primarily addressed in these studies, even though men also have the ability to develop breast cancer.
- The mechanisms behind metabolism of soy and its effect on the development of breast cancer were lacking in some of the studies reviewed.

Implications

- The majority of the studies revealed an inverse relationship between high soy intake and breast cancer risk in Asian populations. As such, it may be advised that Asian women continue to consume their typical diets high in soy, particularly those who are genetically susceptible to developing breast cancer, to reduce their risk of developing the disease.
- Interventions should be placed on early detection of breast disorders and describe options available to women at high genetic risk for breast cancer.
- Ultimate goal of early diagnosis is to identify women at risk and predicting response to different therapies.
- Cancer surveillance is important to determine how many people are developing breast cancer attributable to high or low intakes of phytoestrogens.

Future Considerations

- Few long-term studies were conducted, particularly in Western populations. As such, more research is needed to evaluate the relationship between intake of soy and breast cancer risk.
- More research is needed to understand why soy intake during early life may both reduce breast cancer risk and risk of recurrence.
- Future studies are necessary to be conducted to clarify the relationship between soy intake in premenopausal women compared to soy intake in postmenopausal women and the associated risk of breast cancer.
- There must be more studies on how soy effects breast cancer on high soy or soy-supplemented diets, testing if soy components can protect against genetic damage and prevent the development of breast cancer, and also if it can enhance the effectiveness of breast cancer treatments or prevent drug resistance

Results

Article	Population	Research Design	Measurements/statistical analyses	Findings
Barnes (1998)	Women (premenopausal and postmenopausal)	Experimental (clinical trials)	An isolated soy protein beverage providing 42 mg genistein and 27 mg daidzein per day was given to women for 6 months to determine the effect on breast cancer risk factors measurable in nipple aspirate fluid (NAF)	<ul style="list-style-type: none"> Premenopausal women had a noticeable increase in NAF volume, which persisted even after coming off the soy beverage, whereas postmenopausal women there was no change Data suggest soy isoflavones are having estrogenic effect with induction of apoptosis and increased differentiation of tumour cells The effect of phytoestrogens on breast cancer risk is incomplete, since phytoestrogens have a large array of potential mechanisms of action
Dong & Qin (2011)	Asian and Western Women	Prospective study (cohort or nested case-control study)	<ul style="list-style-type: none"> Homogeneity of effect size across studies was tested by Q test (P<0.10) and I² for inconsistency across studies dose-response analysis was conducted based on isoflavones intake levels on median dose 	<ul style="list-style-type: none"> Soy isoflavones intake was associated with a significant reduced risk of breast cancer in Asian populations (RR=0.76, 95% CI: 0.65-0.86) but not in Western populations (RR= 0.97, 95% CI: 0.87-1.06) risk of breast cancer decreased by 4% for every 10mg/day increase of soy isoflavones intake (RR=0.96, 95% CI: 0.90-1.02, P=0.176, heterogeneity=0.230)
Mishra et al. (2003)	Premenopausal women	Observational (case control) epidemiological studies	<ul style="list-style-type: none"> Study sample recruited from hospital admits Measured total soy product intake but not intake of individual soy foods 	<ul style="list-style-type: none"> Decreased breast cancer risk in premenopausal women associated with higher intake of soy protein: OR= 0.43, CI= 0.23-0.79; soy products: OR= 0.44, CI= 0.24-0.81; protein from soy sources OR=0.29, CI= 0.15-0.57 Phytoestrogens appear to be ideal for long-term clinical trials and a good potential for preventive medicine
Trock et al. (2006)	Women at high risk of breast cancer or those who survived the disease	Meta-analysis of 18 epidemiological studies	Examined soy exposure and breast cancer risk based on either the original soy exposure measure defined in each study or an estimate of daily soy protein intake	<ul style="list-style-type: none"> In a pooled analysis, among all women high soy intake was modestly associated with reduced breast cancer risk (OR= 0.86, 95% CI= 0.75-0.99) Association was stronger in premenopausal women (OR= 0.70, 95% CI=0.58-0.85) than in postmenopausal (OR=0.77, 95% CI= 0.60-0.98)
Wu et al. (2013)	Women (premenopausal and postmenopausal)	Observational epidemiological studies	<ul style="list-style-type: none"> Odds ratios (OR) and confidence intervals (CI) were used to determine the risk of breast cancer in association with soy intake. Intake of soy in Asian women and women from Western populations were compared to see if a relationship existed between soy consumption and breast cancer risk. 	<ul style="list-style-type: none"> In Asian populations, soy intake of 10-20mg isoflavones/day may be associated with a reduced risk of breast cancer. Further research is needed to assess the relationship between soy and breast cancer risk in non-Asian populations. A significant inverse association was observed between soy isoflavone intake and risk of developing breast cancer in both premenopausal and postmenopausal women in case control studies and prospective studies conducted in Asian populations.
Xie et al. (2013)	Women premenopausal and postmenopausal	Meta-analysis	<ul style="list-style-type: none"> Q test (p<0.05) was used to evaluate heterogeneity. P² value >50% used to indicate significant heterogeneity between trials Random-effects model when the test result for heterogeneity was significant. Otherwise, the fixed-effects model was preferred. Dose-response analysis was performed based on data for categories of isoflavone intake on exposure dose 	<ul style="list-style-type: none"> The risk of breast cancer incidence decreased, on average, by 1% for every 10 mg/day increase of soy isoflavones intake (OR = 0.99, 95% CI: 0.96-1.03, p for heterogeneity=0.018) In Asian populations, 12 trials showed that isoflavone intake was associated with a reduced risk of breast cancer. In Western populations, 10 studies showed no statistically significant association with isoflavone intake and breast cancer, irrespective of menopausal status.
Badger et al. (2005)	Pregnant Sprague-Dawley rats and Women	Epidemiological Animal studies and Meta-analysis	<ul style="list-style-type: none"> Pooled risk estimates from 3 meta-analyses were used to indicate significant reductions in the risk of developing breast cancer among those who consumed foods containing soy protein. Tumour incidence in rats who consumed a casein rich diet were compared to rats who consumed a soy protein isolate diet 	<ul style="list-style-type: none"> Consumption of soy protein isolate intake is associated with lower incidence of breast cancer. Soy protein isolate intake advances mammary gland differentiation to a significant degree and reduces the number of breast cancer target cells.
Lamartiniere (2000)	Rats	Experimental animal study	A control group of rats, whereby they did not receive genistein treatment, was used to compare the outcome of rats who received genistein treatment.	<ul style="list-style-type: none"> Genistein acts directly on the mammary glands of immature rats by up-regulating the expression of EGF receptor. Early genistein action promotes cell differentiation, resulting in a less active EGF-signalling pathway in adulthood that suppresses the development of breast cancer Breast cancer protection in Asian women likely comes from early exposure and ingestion of soybean products containing genistein.

Figure 3. Summary of Literature Review

Conclusion

From this review of the literature, it is clear that women from Asian populations, who consume greater amounts (10-50g/day) of phytoestrogens found in soy products, and who are exposed to soy at an earlier age, have a reduced risk of developing breast cancer compared to American women. Due to the heterogeneity in study design (i.e. study population, menopausal status, duration of study, and inconsistencies in measuring soy agents (product composition and type), amount and intake of soy, however, it is unclear whether phytoestrogens in soy have a preventative or stimulatory effect on the development of breast cancer, particularly in women from the Western sphere of the world.⁸ As a result, more long-term prospective cohort studies are needed to evaluate the relationship between phytoestrogens and breast cancer risk.

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