Dietary Phytoestrogens and Breast Cancer Risk: Potential Protective Effect Against Non-Receptor Mediated Subtypes

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Introduction

- Breast Cancer (BC) remains one of the most prevalent malignancies and is the leading cause of cancer-related mortality worldwide [1]. 60-65% of cases are estrogen receptor positive (ER+), making them highly responsive to anti-estrogenic therapies such as tamoxifen and raloxifene.
- HER2-positive and hormone receptor-negative (ER-/PR-) BCs are more aggressive, more difficult to treat, and associated with higher recurrence and lower survival rates [2].
- Phytoestrogens (PEs) are plant-derived compounds with structural similarities to endogenous estrogens and can bind to estrogen receptors throughout the body [3]. The two major classes of PEs include isoflavones (genistein, daidzein, formononetin, biochanin A) and coumestans [3].
- Women in Asian countries consume an average of 15-50 mg of isoflavones daily and exhibit significantly lower incidence rates of BC [1,4].
- Prior studies have suggested that hormone receptor-positive BC subtypes are linked to hormone-related risk factors, and some findings indicate that higher dietary intake of PEs may be associated with reduced risk of HER2-positive and ER−/PR− subtypes [5-7].
- While compounds such as coumestrol, genistein, and daidzein have demonstrated protective potential against more aggressive BC subtypes, additional research is needed to update dietary guidelines and clarify the role of PEs in prevention of HER2-positive and HR- breast cancers [6-7].
- **Objective:** To evaluate the association between intake of total and individual phytoestrogens and the risk of aggressive breast cancer subtypes among women enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Methods

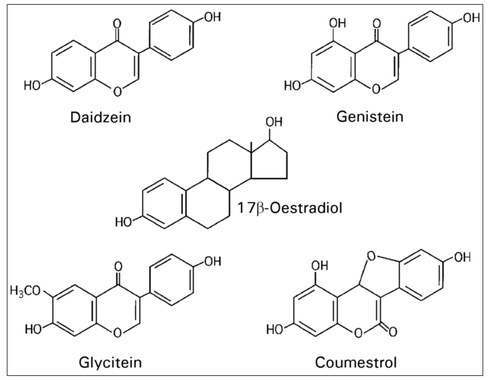
- Approximately 155,000 men and women were enrolled to the PLCO from 10 screening centers across the U.S. between November 1993 and July 2001.
- Women with a positive diagnosis of BC were included in the analysis. After exclusions for incomplete questionnaires, previous history of breast cancer before enrollment, and outliers for total isoflavone intake, 2,055 positive breast cancer cases were identified during a median follow-up time of 11.8 years.
- Demographic, anthropometric, and lifestyle characteristics of subjects were compared by hormone receptor status using Chi-square tests for categorical variables and independent sample t-tests for continuous variables.
- Cox proportional hazards regression analysis was conducted to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for hormone receptor status BC risk in relation to dietary intake of total and individual phytoestrogens.
- Variables included in the final model: age when first became pregnant, age at hysterectomy, race, cigarette smoking status, family history of female breast cancer

Results

Characteristic	HR-	HR+	p-value
Race (%)			
Non-Hispanic White	90.6%	93.1%	0.002
Non-Hispanic Black	5.9%	2.3%	
Other Race – Including Multiracial	3.5%	4.6%	
BMI at Age 50 [mean (SD)]	25.32 (4.73)	25.12 (4.42)	0.501
Cigarette Smoking Status (%)			
Never Smoker	52.4%	56.7%	0.181
Former or Current Smoker	47.6%	43.3%	
Age Stopped Smoking [mean (SD)]	41.77 (12.25)	42.15 (12.48)	0.768
Family History of Breast Cancer (%)			0.602
No	79.8%	81.1%	
Yes	20.2%	18.9%	
Age First Became Pregnant (%)			0.915
Under 30 years old	93.7%	93.5%	
At or over 30 years old	6.3%	6.5%	
Age at Hysterectomy (%)			0.402
Under 50 years old	80.6%	76.8%	
At or over 50 years old	19.4%	23.2%	
Food Energy from Diet (kcal/day) [mean (SD)]	1469.46 (515.56)	1510.84 (553.65)	0.213
Total Fat from Diet (g/day) [mean (SD)]	52.49 (24.60)	53.93 (26.79)	0.364
Meat (g/day) [mean (SD)]	97.80 (55.23)	97.61 (63.84)	0.959
Iron from Diet (mg/day) [mean (SD)]	12.35 (4.70)	12.95 (5.13)	0.048
Vitamin B-6 from Diet (mcg/day) [mean (SD)]	1.70 (0.66)	1.74 (0.72)	0.284
Vitamin B-12 from Diet (mcg/day) [mean (SD)]	3.82 (1.86)	3.92 (2.26)	0.399

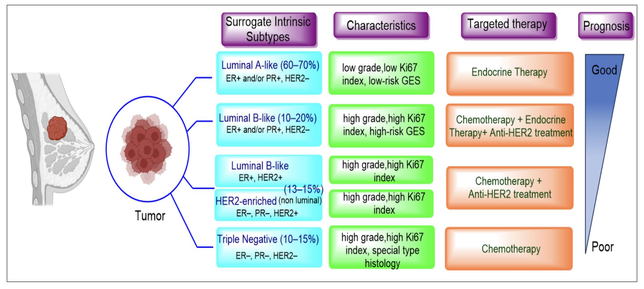
Table 1: Baseline Characteristics of women diagnosed with HR- and HR+ breast cancer.

Figure 1: Structural similarities between 17β-estradiol and select phytoestrogens



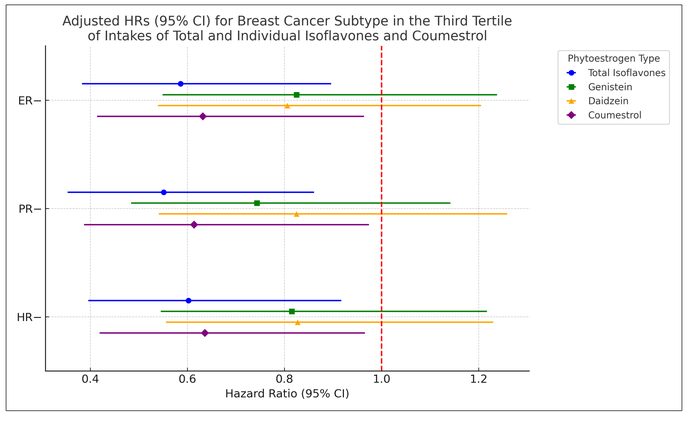
Source: Anderson, J.J.B., Anthony, M., Messina, M., & Garner, S.C. (1999). "Effects of phyto-oestrogens on tissues." *Nutrition Research Reviews* 12: 75-116.

Figure 2: Comparisons of different types of Breast Cancer (estrogen/progesterone receptor-negative, HER2 Status) by survival rates and treatment options.



Source: Di Leo, A., Malomi, L., & Malomi, W. (2024) "Therapies for the Treatment of Advanced/Metastatic Estrogen Receptor-Positive Breast Cancer: Current Situation and Future Directions."*Cancers* 16, no. 3: 552

Figure 3: HR (95% CI) for select breast cancer subtypes in the third tertile of intake of total isoflavones and coumestrol in the PLCO Screening Trial



*Adjusted for age when first became pregnant, age at hysterectomy, race, smoking status, family history of female breast cancer

Results

- HR+ breast cancer cases consumed a significantly higher amount of total isoflavones, daidzein, genistein, and coumestrol compared to HR- breast cancer cases

Phytoestrogen [mean (SD)]	HR-	HR+	p-value
Total Isoflavones	0.54 (0.84)	0.67 (1.12)	0.024
Daidzein	0.26 (0.23)	0.31 (0.46)	0.023
Genistein	0.27 (0.49)	0.35 (0.66)	0.016
Coumestrol	0.12 (0.14)	0.14 (0.16)	0.030
Formononetin	0.04 (0.06)	0.04 (0.06)	0.895
Biochanin A	0.03 (0.03)	0.03 (0.03)	0.733

Table 2: Mean and standard deviation of total and individual phytoestrogen intake by hormone receptor breast cancer subtype

Discussion

- Higher dietary intake of total isoflavones and coumestrol was significantly associated with a decreased risk of HR-breast cancer, including ER- and PR- subtypes, in the PLCO Trial.
- In vitro studies have demonstrated that phytoestrogens inhibit proliferation and induce apoptosis in ER- breast cancer subtypes [8].
- Populations with high habitual intake of soy-based foods, such as Japan and China, have lower incidence of ER- and triple-negative breast cancer compared to Western populations [9].
- A dose-response relationship has been observed in previous studies, where higher quartiles of phytoestrogen intake corresponded to progressively lower risks of HR- breast cancer [9].

Conclusion

- Total isoflavones and coumestrol consistently demonstrated a statistically significant inverse association across hormone receptor negative subtypes of breast cancer, suggesting a potential protective effect.
- These results highlight the potential role of diet in preventing more aggressive and less treatable subtypes of breast cancer.
- Individual isoflavones such as genistein and daidzein did not show statistically significant associations with a decreased HR- BC risk, indicating that overall increased consumption, not individual, may be key to the protective effect at low levels of dietary intake.
- Although these results highlight the potential role of diet, particularly phytoestrogen intake, in the prevention of more aggressive and less treatable forms of breast cancer, further investigation is needed to confirm these results in a population with higher and more variable intake to determine the specific dose-response relationship, dietary guidelines, and population-specific recommendations..

References

1. Torre, L.A., Islami, F., Siegel, R.L., Ward, E.M., & Jemel, A. (2017). "Global Cancer in Women: Burden and Trends." *Cancer Epidemiology, Biomarkers & Prevention* 26 (4): 444–457. doi:10.1158/1055-9965.EPI-16-0858.
2. Dunnwald, L.K., Rossing, M.A., & Li, C.I. (2007). Hormone Receptor Status, Tumor Characteristics, and Prognosis: A Prospective Cohort of Breast Cancer Patients." *Breast Cancer Research* 9 (1): R6. doi:10.1186/bcr1639.
3. Kuhnle, G.G.C., Dell'Aquila, C., Low, Y-L., Kussmaul, M., & Bingham, S.A. (2007). "Extraction and Quantification of Phytoestrogens in Foods using Automated Solid-Phase Extraction and LC/MS/MS." *Analytical Chemistry* 79 (23): 9234–9239. doi:10.1021/ac701732r.
4. Bacciottini, L., Falchetti, A., Pampaloni, B., Bartolini, E., Carossino, A.M., & Brandi, M.L. (2007). "Phytoestrogens: Food Or Drug?" *Clinical Cases in Mineral and Bone Metabolism* 4 (2): 123–130.
5. Yang, J., Ju, J., Guo, L., Ji, B., Shi, S., Yang, Z., Gao, S., et al. (2021). "Prediction of HER2-Positive Breast Cancer Recurrence and Metastasis Risk from Histopathological Images and Clinical Information Via Multimodal Deep Learning." *Computational and Structural Biotechnology Journal* 20: 333–342. doi:10.1016/j.csbj.2021.12.028.
6. Hedelin, M., Löf, M., Olsson, M., Adlercreutz, H., Sandin, S., & Weiderpass, E. (2008). "Dietary Phytoestrogens are Not Associated with Risk of overall Breast Cancer but Diets Rich in Coumestrol are Inversely Associated with Risk of Estrogen Receptor and Progesterone Receptor Negative Breast Tumors in Swedish Women." *The Journal of Nutrition* 138 (5): 938–945. doi:10.1093/jn/138.5.938.
7. Touillaud, M.S., Pillow, P.C., Jakovljevic, J., Bondy, M.L., Singletary, S.E., Li, D., & Chang, S. (2005). "Effect of Dietary Intake of Phytoestrogens on Estrogen Receptor Status in Premenopausal Women With Breast Cancer." *Nutrition and Cancer* 51 (2): 162–69.
8. Seo, H.S., Choi, H.S., Choi, H.S., Choi, Y.K., Um, J-Y., Choi, I., Shin, Y.C., & Ko, S-G. (2011). "Phytoestrogens Induce Apoptosis via Extrinsic Pathway, Inhibiting Nuclear Factor-κB Signaling in HER2-overexpressing Breast Cancer Cells." *Anticancer Research* 31, no. 10: 3301–3313.
9. Wu, A.A., Koh, W-P., Wang, R., Lee, H-P., & Yu, M.C. (2008). "Sot intake and breast cancer risk in Singapore Chinese Health Study." *British Journal of Cancer* 99 (1): 196-200.