

Soy Product intake and the Risk of Breast Cancer

I. Study Purpose and Rationale

The incidence of breast cancer is known to be much lower in Asian than in Western populations. The incidence of breast cancer in China, for instance, was 5.3 times lower than the incidence of breast cancer in North Americaⁱ. Soy-containing diets have been known to be characteristic of certain ethnic groups that have a diet that is relatively high in soy, and this has fueled interest in the connection that soy may play in breast cancer risk. Many epidemiologic studies have been published that have evaluated the association between soy or isoflavone intake and breast cancer risk. Several of these studies, most of which have been conducted in Asia, have shown a protective effect of soyⁱ.

Soy foods are rich in phytoestrogens, mainly in the form of isoflavones, which possess estrogen-like and antiestrogen properties. Some studies have postulated that, due to their estrogen-like properties, phytoestrogens may block endogenous estrogen from binding to the estrogen receptor. Findings have shown that isoflavonoids preferentially bind ER-beta rather than ER alpha receptors, and have led to the idea that isoflavones are more appropriately termed selective estrogen receptor modulators rather than simply phytoestrogensⁱⁱ. Soy constituents have also been shown to inhibit DNA topoisomerases 1 and II, proteases, tyrosine kinases, inositol phosphate, angiogenesis, and may also fortify immune response and possess antioxidant propertiesⁱⁱⁱ.

Although soy consumption has been inversely related to breast cancer development in many epidemiologic studies, concern has been raised over whether soy isoflavones may exert their estrogenic effects, thereby promoting cancer recurrence, in women treated for breast cancer who have a low level of endogenous estrogen. Some have postulated that soy consumption may be of different physiological significance in post-menopausal women due to their naturally low estrogen state than in their pre-menopausal counterparts. Genistein, a major form of isoflavone, has been shown to enhance the proliferation of breast cancer cells *in vitro* and to promote estrogen-dependent mammary tumor growth in ovariectomized ratsⁱⁱ. One study in rats also found that *in utero*, exposure to genistein increased mammary tumorigenesis^{iv}.

The purpose of this study is to evaluate the association between soy product consumption and the risk for the development of breast cancer.

II. Study Design and Statistical Procedures

- a. Hypothesis: Soy consumption is associated with a decrease in the incidence of breast cancer.
- b. Study Design: The study will be a case-control study comparing the daily soy protein consumption of women with primary histologically confirmed breast cancer compared to that of women with no history of breast cancer. Based on the hypothesis, we should be able to show that women without a history of breast cancer have, on average, a higher consumption of soy products as compared to women with breast cancer.
- c. Statistical Procedures: The study will be powered to 80% to detect a 10% difference in the two groups, assuming a p-value of 0.05. The study will include approximately 526 patients in each arm, validated by the Soy Intake and Breast Cancer Survival trial, using Chi-squared test to approximate the size of each arm.
- d. Study Procedures: We will use a validated food frequency questionnaire that was designed to measure consumption of soy foods, including tofu, soy milk, fresh soy beans, and other products. Soy protein will be measured in grams per day, and daily protein consumption will be divided into 4 quartiles. The groups will be compared according to the categorical variables of high versus low soy consumption, as represented by the lowest and highest quartiles.

III. Study Drugs and Devices: N/A

IV. Study Questionnaires

We will use a validated food frequency questionnaire that was designed to measure consumption of soy foods, including tofu, soy milk, fresh soy beans, and other products. One such questionnaire was developed that consisted of a 40-item, semiquantitative soy food frequency, that accounted for genistein and daidzein intake^v. Other data that will be collected during the study are demographic characteristics, reproductive history, medication use, certain lifestyle factors, use of alternative medicines, disease history. Clinical information on cancer stage, tumor ER and PR status, prior treatments (surgery/mastectomy, XRT, chemotherapy, immunotherapy, hormonal therapy, etc.) will also be collected.

V. Study Subjects

Potential case subjects will be women identified via population-based cancer registry based in NYC, and study subjects will be contacted via telephone

Inclusion Criteria:

- a. Female subjects 20 to 75 years old
- b. Must have been living in USA for at least 5 years

Exclusion Criteria:

- a. Inability to consent to study

VI. Recruitment

A research assistant will screen patients for meeting inclusion/exclusion criteria, and will consent patients as well as administer the questionnaire. A second assistant will hand out questionnaires in various settings throughout the city.

VII. Confidentiality of Study Data

All patient data will be kept on a password-protected computer database.

VIII. Potential Risks

None

IX. Potential Benefits

The potential benefits include adding to the fund of knowledge about how the environment plays a role in the development of breast cancer, and possibly adding to the development of treatment strategies to prevent breast cancer.

X. Alternatives

None

References

ⁱ Zhang, Caixia. Soy product and isoflavone intake and breast cancer risk defined by hormone receptor status. Japanese Cancer Association 2009: 1-7

ⁱⁱ Ou Shu, Xiao. Soy Food Intake and Breast Cancer Survival. Journal of American Medical Association 2009: 2437-2443

ⁱⁱⁱ Messina, Mark. Perspectives on the Soy-Breast Cancer relation. *American Journal of Clinical Nutrition* 2009. 1673S-1679S.

^{iv} Bouker, Kerrie B. Genistein: Does it Prevent or Promote Breast Cancer? *Environmental Health Perspectives*. Volume 108. August 2008: 701-708

^v Kirk, Phyllis. Development of a Soy Food Frequency Questionnaire to Estimate Isoflavone Consumption in US Adults. *Journal of the American Dietetic Association*. Volume 99, Issue 5, May 1999: 558-563