Challenges in Design and Interpretation of Observational Research on Health Behaviors and Cancer Survival

Rachel Ballard-Barbash; Marian L. Neuhouser

JAMA. 2009;302(22):2483-2484 (doi:10.1001/jama.2009.1807)

http://jama.ama-assn.org/cgi/content/full/302/22/2483

Challenges in Design and Interpretation of Observational Research on Health Behaviors and Cancer Survival

Rachel Ballard-Barbash, MD, MPH

Marian L. Neuhouser, PhD

As of 2006, an estimated 11 400 000 adults and children were living with cancer in the United States, and that number is estimated to increase to nearly 17 000 000 by 2020.[1] This increase in the number of persons living with cancer as a chronic condition has also stimulated interest in understanding whether health habits such as diet, physical activity, or weight control may result in beneficial effects on cancer survival.

In this issue of *JAMA*, the report by Shu et al[2] examines whether soy food intake is associated with overall mortality and breast cancer–specific disease-free mortality in a population-based cohort of 5042 breast cancer patients participating in the Shanghai Breast Cancer Survival Study. The authors report that soy food consumption was significantly associated with decreased risk of death and breast cancer recurrence, with adjusted 4-year mortality rates of 10.3% and 7.4% and 4-year recurrence rates of 11.2% and 8.0%, respectively, for women in the lowest and highest quartiles of soy protein intake. This well-designed study has a number of strengths, including detailed data on treatment, clinical characteristics, recurrence, vital status, and lifestyle habits, including diet.

Only 1 prior study examining the association between soy food intake and breast cancer survival has been reported. Within a northern California–based cohort of 1954 breast cancer patients with diagnoses from 1997 through 2000, Guha et al[3] found an inverse association between postdiagnosis soy isoflavone intake and breast cancer recurrence. However, unlike the current study, the inverse association was not observed among women not taking tamoxifen. Prior observational and intervention studies have examined the influence of soy foods and soy isoflavones on breast cancer risk[4,5] as well as on the purported biological mechanisms, including effects of soy on endogenous estrogens,[6,7] mammographic breast density[8,9] and estrogen-independent mechanisms such as inhibition of tyrosine protein kinase,[10] but results have been inconsistent.

See also p 2437.

The limited research on the association of soy food intake with overall mortality and breast cancer–specific mortality limits the ability to make clinical recommendations but provides an opportunity to highlight the challenges in this field of research. Many of these challenges were well addressed in the study by Shu et al[2] and include methodological issues relevant to examining associations with soy foods, overall issues of observational studies of cancer mortality, and the ability to make inferences to US populations of breast cancer survivors from studies of breast cancer survivors in China.

One reason that results have been inconsistent from previous observational studies of soy food intake and cancer risk in US-based cohorts is that soy food intake in the United States is quite low. In contrast, the average daily Chinese soy intake represents 10% or more of daily protein intake.[11] In the report by Shu et al,[2] the average isoflavone intake in their study population was 47 mg/d, compared with 1 to 6 mg/d in the United States. Furthermore, the range of soy intake across the Chinese population is large enough to yield an exposure variable with sufficient heterogeneity across the quartiles of intake. In addition to the overall greater consumption of soy foods in China compared with the United States, the types of soy foods consumed in China may provide greater exposure to isoflavones. For example, Asian populations tend to consume traditional, whole soy foods such as cooked soybeans, edamame, tofu, miso, and soy milk. In contrast, soy supplements, meat analogs made with soy, and various processed foods with isoflavones are consumed in the United States, but these foods may have lower levels of isoflavones.[12,13] Clinicians should be aware of these dietary differences in the quantity and quality of soy foods when advising patients.

Shu et al[2] have designed and presented their analysis to address a number of methodological issues that are critical to observational studies of health behaviors and cancer mortality among cancer patients that are distinct from stud-

Author Affiliations: Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland (Dr Ballard-Barbash); and Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington (Dr Neuhouser).

Corresponding Author: Rachel Ballard-Barbash, MD, MPH, Applied Research Program, National Cancer Institute, EPN 4005, 6130 Executive Blvd, Bethesda, MD 20892-7344 (barbashr@mail.nih.gov).

ies of cancer etiology. Outcome assessment is complex and includes breast cancer recurrence/metastasis, breast cancer–specific death, and total mortality. In the United States, most observational studies of breast cancer mortality have relied on cancer registry ascertainment of disease, which assigns the most advanced disease stage based on the entire initial process of cancer diagnosis. This process is phased and the final stage and characteristics of the initially diagnosed cancer may change as updated clinical data are obtained. In the current study, 20 women who had a disease-free survival time of 0 were excluded from the breast cancer–specific disease-free survival analysis. The authors do not describe the initial diagnosis and treatment process in China and it is possible that differences in that process compared with US practices may result in some differences in survival time estimates.

In addition, because of the marked differences in mortality between in situ and invasive breast cancer, studies of disease-specific mortality usually do not combine these 2 groups. This is particularly important for breast cancer because survival rates in the United States for ductal carcinoma in situ (TNM stage 0) have been documented to be better than the population average.[14] This is likely because ductal carcinoma in situ in the United States is predominantly a screen-detected disease, and US women who participate in screening are generally very health conscious.

In their analysis of the association of soy intake with outcomes according to disease stage (eTable 3), Shu et al[2] have combined women with stages 0 and 1. However, because only 156 women in this sample had stage 0 disease, it is unlikely that this small number of women would have altered results, as has been noted by the authors. In the United States and other countries where breast cancer screening is common, the proportion of stage 0 disease is close to 20% and, therefore, is likely to represent a much larger number of cases in a population-based study of breast cancer survivors. In addition, given differences in mortality rates by stage of disease at diagnosis, it is important when possible to examine mortality rates by stage at diagnosis. However, Shu et al[2] report that the association between soy intake and all-cause mortality did not vary by cancer stage. In addition, rather than using time from baseline diagnosis as the time metric, Shu et al have correctly used age as the time metric to enable comparison of women of similar age for survival. An additional strength of the study and analysis is the presentation of results by clinically relevant characteristics, including estrogen receptor status and use of tamoxifen.

Several caveats should be noted that highlight the need for further replication of these results reported by Shu et al in other cohorts of breast cancer patients. First, the median follow-up time for this cohort is relatively short at 4 years. Second, it is likely that there are differences in screening rates in China compared with the United States and in the completeness of medical record abstraction for initial diagnosis and treatment that may make it difficult to compare stage- and treatment-specific results in China with outcomes in the United States. Third, the authors correctly note that the study has limited power to address subgroups by estrogen receptor status or tamoxifen use, highlighting the need for larger studies to examine clinically relevant groups of women.

Even though the findings by Shu et al suggest that consumption of soy foods among breast cancer patients is probably safe, studies in larger cohorts are required to understand the effects of these foods among diverse clinical subgroups of breast cancer patients and survivors. In the meantime, clinicians can advise their patients with breast cancer that soy foods are safe to eat and that these foods may offer some protective benefit for long-term health. Moreover, the potential benefits are confined to soy foods, and inferences should not be made about the risks or benefits of soy-containing dietary supplements. Patients with breast cancer can be assured that enjoying a soy latte or indulging in pad thai with tofu causes no harm and, when consumed in plentiful amounts, may reduce risk of disease recurrence.

Financial Disclosures: None reported.

REFERENCES

1. Horner MJ, Ries LAG, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2006.* Bethesda, MD: National Cancer Institute; 2009. http://seer.cancer.gov/csr/1975_2006/. Accessed November 10, 2009.
2. Shu XO, Zheng Y, Cai H, et al. Soy food intake and breast cancer survival. *JAMA*. 2009;302(22):2437-2443.
3. Guha N, Kwan ML, Quesenberry CP, et al. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat*. 2009;118(2):395-405.
4. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. *Br J Cancer*. 2008;98(1):9-14.
5. Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst*. 2006;98(7):459-471.
6. Maskarinec G, Franke AA, Williams AE, et al. Effects of a 2-year randomized soy intervention on sex hormone levels in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2004;13(11 Pt 1):1736-1744.
7. Kurzer MS. Hormonal effects of soy in premenopausal women and men. *J Nutr*. 2002;132(3):570S-573S.
8. Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A 2-year soy intervention in premenopausal women does not change mammographic densities. *J Nutr*. 2004;134(11):3089-3094.
9. Maskarinec G, Verheus M, Steinberg FM, et al. Various doses of soy isoflavones do not modify mammographic density in postmenopausal women. *J Nutr*. 2009;139(5):981-986.
10. Akiyama T, Ishida J, Nakagawa S, et al. Genistein, specific inhibitor of tyrosine-specific protein kinases. *J Biol Chem*. 1987;262(12):5592-5595.
11. Zhang X, Shu XO, Gao YT, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. *J Nutr*. 2003;133(9):2874-2878.
12. Erdman JW Jr, Badger TM, Lampe JW, Setchell KD, Messina M. Not all soy products are created equal: caution needed in interpretation of research results. *J Nutr*. 2004;134(5):1229S-1233S.
13. Frankenfeld CL, Patterson RE, Horner NK, et al. Validation of a soy food-frequency questionnaire and evaluation of correlates of plasma isoflavone concentrations in postmenopausal women. *Am J Clin Nutr*. 2003;77(3):674-680.
14. Ernster V, Barclay J, Kerlikowske K, et al. Mortality among women with ductal carcinoma in situ of the breast in the population-based Surveillance, Epidemiology and End Results program. *Arch Intern Med*. 2000;160(7):953-958.

