Soy intake and risk of breast cancer in Asians and Asian Americans[1,2]

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ABSTRACT Evidence from case-control studies suggests, although not entirely consistently, that soy intake may protect against breast cancer. The designs and findings of studies conducted in Asian women living in Japan, Singapore, China, and the United States are reviewed. Because of the considerably higher intake of soy by native Asians than by Asian Americans living in California and Hawaii, these studies investigated different segments of the dose-response relation between soy intake and breast cancer risk. Data are not sufficient to determine the amount or frequency of soy intake effective in protecting against breast cancer. Of concern is that soy intake may be homogeneously high in Asia, making it difficult to identify differences in breast cancer risk between high and moderate daily consumers. In studies conducted in Asian Americans, it is difficult to be certain that soy intake is not a marker of other factors related to Western lifestyle that are causally associated with risk of breast cancer. Additional studies assessing the role of soy and breast cancer are needed. These studies should assess intake of all food sources of soy, considering portion size as well as other dietary and nondietary factors that may confound the soy–breast cancer association. A better understanding of the mechanisms whereby soy intake may influence the risk of breast cancer is also needed. Dietary intervention studies with soy will provide information on the acute effects of soy on endogenous hormone concentrations. Cross-sectional and longitudinal studies are necessary to investigate the longer-term relations between hormone concentrations and soy intake in women. *Am J Clin Nutr* 1998;68(suppl):1437S–43S.

KEY WORDS Diet, soy, breast cancer, Asians, Asian Americans, hormones, women

INTRODUCTION

The risk of breast cancer varies substantially throughout the world. Rates tend to be highest among whites in the United States and Western Europe, whereas native Japanese and Chinese (and other Asian populations in their homelands) have the lowest rates. Historically, there has been a ≈6-fold difference in breast cancer risk between these population groups (1). This extraordinary variation in risk is not due to underlying genetic differences, because the rates of breast cancer in Asian American women shift substantially toward those of white US women within a few generations after migration. In a study of breast cancer in Asian Americans that we completed, Asian women who were born in the United States or in the West had estimated incidence rates of breast cancer similar to the rates of white women residing in the same study areas (2).

In a series of studies conducted by MacMahon et al (3, 4) and Trichopoulos et al (5), urinary estrone and estradiol excretion during the follicular and luteal phases of the menstrual cycle were consistently lower in Asian women than in white women. Similarly, almost all studies that compared serum estradiol concentrations in Asian and white women found lower serum concentrations in Asian women, both pre- and postmenopausally (6, 7). The lower estradiol concentrations in Asian women compared with white women are observed even after adjusting for differences in body size (8, 9). Reasons for the differences in endogenous estrogen concentrations between white and Asian women have not been identified.

Steep increases in breast cancer incidence and mortality rates have been reported in Japan, Singapore, and urban areas of China (10, 11). Concurrent with these increases has been an extraordinary change in the dietary habits of women in urban areas of Asia. In particular, there has been a huge increase in the proportion of total energy consumed derived from fat. For example, in the early 1950s fat composed only ≈8% of the typical Japanese diet; by the late 1980s fat consumption was 32% of energy, approaching the typical US proportion of ≈35% (12, 13). These secular and international data correlating per capita fat consumption and breast cancer incidence and mortality rates, combined with some evidence that decreases in dietary fat to ≈20% of energy can decrease circulating estrogen concentrations (14–16), have led to the hypothesis that dietary fat consumption may be a risk factor for breast cancer and that differences in dietary fat consumption may help explain international variations in breast cancer rates. However, results from analytic epidemiologic studies do not support a strong positive association between dietary fat intake and the risk of breast cancer (17).

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There are alternative dietary hypotheses that may explain the traditionally low rates of breast cancer in Asia, the rapid secular changes in breast cancer incidence in Asia, and the effects of migration on breast cancer risk. One hypothesis focuses on the traditional soy-rich Asian diet and the decrease in consumption of soy products as the Asian diet has become more westernized. Soybeans are a rich source of isoflavones, a main type of plant estrogens (phytoestrogens) (18). It has been suggested that these plant-derived, estrogen-like substances might partly suppress or inhibit normal estrogen secretion or normal estrogen activity in estrogen-responsive tissues such as breast (possibly by competing with endogenous estrogens for receptor sites in breast tissue), while themselves being less estrogenic to breast tissue, thereby reducing breast cancer risk (19–21).

EARLY EPIDEMIOLOGIC STUDIES IN BREAST CANCER AND SOY INTAKE

Although there is supportive evidence from in vitro and animal studies that soy intake may influence the risk of breast cancer (21–24), there have been few studies on this association in humans (25). Two of 3 epidemiologic studies published before the 1990s provided suggestive or indirect evidence that intake of soy may protect against breast cancer. In a study of dietary habits of the husbands of Japanese American women in Hawaii, Nomura et al (26) found that intake of tofu and soybean paste (miso) soup was less frequent among spouses of women with breast cancer than among those of control women. In a cohort study conducted in Japan, Hirayama (27) reported an approximate halving of risk of breast cancer mortality in daily miso soup consumers compared with nonconsumers, although this finding did not adjust for intake of green-yellow vegetables or other dietary factors that may have influenced the finding on soy and breast cancer. However, breast cancer case and control subjects in Fukuoka, Japan, did not differ in their intake of soy products, but this analysis was based on intake of fat from soy products (28).

MORE RECENT EPIDEMIOLOGIC STUDIES IN BREAST CANCER AND SOY INTAKE

Since 1990, 4 case-control studies of breast cancer have evaluated the association between self-reported soy intake and breast cancer. These studies were conducted in Chinese in Singapore (29, 30), Chinese in Shanghai and Tianjin, China (31), Japanese in Nagoya, Japan (32), and Asian Americans (Chinese, Japanese, and Filipino Americans) residing in the San Francisco–Oakland metropolitan statistical area, Los Angeles County, and Oahu, Hawaii (2, 33).

The study designs of these 4 case-control studies are summarized in **Table 1**. The studies conducted in China and in Asian Americans were population based whereas the studies conducted in Japan and Singapore were hospital based. The sample size was largest in Japan, intermediate in China and the United States, and smallest in Singapore. The study in Asian Americans included only women up to age 55 whereas the studies in Asia included women in their 80s. The possibility of selection bias may be least likely in the study conducted in China because this study was population based and had high participation rates. On the other hand, selection bias is a potential problem in the study conducted in Japan; little information was provided to establish the suitability of the control group, and the study was not designed specifically to investigate risk factors of breast cancer. In this study, subjects routinely completed a self-administered questionnaire upon admission to the Aichi Cancer Center Hospital that included questions on intake of 2 soyfoods (miso and bean curd) and other foods (32). In the other 3 studies, both in-person interviews food-frequency questionnaires were used to assess usual dietary intake. However, the number of food items and the specific soy products included in the interviews and questionnaires also differed among these 3 studies. The specific soyfoods in the Singapore questionnaire were not presented. Intake of soymilk, tofu (bought in government stores and private markets), and vegetarian chicken (a soybean product) was recorded in Shanghai, whereas intake of tofu, smelly (fermented) soybean curd, and soymilk was recorded in Tianjin. In our study (33), all Asian American subjects were asked about their usual intake of any tofu dish. In addition, Japanese Americans were asked about intake of miso soup and fermented soybeans (natto). Portion sizes were not included in our study in the United States (33) or in Japan (32), but were estimated in the studies conducted in Singapore (29, 30) and China (31).

The intake patterns of soy products for control subjects in 3 of the 4 study areas are shown in **Table 2**. Because of insufficient data presented on the total intake of soy in the Japanese study (32), we did not attempt to quantify the consumption pattern in that study population. The median and the lower and upper tertiles of intake are presented for Singapore. Quartiles of total soy intake are shown for Shanghai and Tianjin combined. On the basis of the quartile distribution of soy-protein intake (31), we calculated total soy intake by assuming that 1.4 g soy protein is equivalent to ≈20 g soy product [soymilk contains ≈3% soy protein whereas tofu (bean curd) contains ≈6% soy protein (34)]. Quartiles of soy intake are presented for all Asian Americans combined and separately by migration status and Asian ethnicity. Migration status is defined by birthplace (Western- or Eastern-born) and by years of residence in the West for migrants born in the East. We converted the respondents' frequency of intake of a tofu dish/y to g soy intake/d by assuming that 28 g soy (≈1 ounce) was consumed each time tofu was consumed. Thus, based on a single question on intake of soy in Asian Americans, the median intake of soy was 10–15 times higher by Chinese subjects in Asia than by Asian subjects currently residing in California and Hawaii. Even the median intake of soy by recent migrants (ie, migrants who had lived in the United States for 1–7 y) was substantially lower than the intake in Asia. The soy intake among Chinese and Japanese Americans was similar but was considerably higher than that of Filipino Americans. Two estimates of intake are presented for Japanese Americans: one is based on intake of tofu and the other is based on intake of tofu, natto, and miso soup combined. These results show that for Japanese Americans in this study, >80% of the soy intake was derived from tofu.

The results from these 4 case-control studies are compared in **Table 3**. In all 4 studies, adjustment was made for some relevant dietary factors and menstrual and reproductive factors in the analysis on soy and breast cancer, but adjustment for total energy was made in only the study in China (29). In China, there was no association between intake of soy and risk of breast cancer. This lack of an association was seen in both pre- and postmenopausal women (31). In Singapore, high intake of soy was associated with a reduced risk in premenopausal women but not in postmenopausal women. In premenopausal women, high daily con-

TABLE 1
Case-control studies on breast cancer risk and soy intake[1]

Study characteristic	Lee et al (29, 30)	Yuan et al (31)	Hirose et al (32)	Wu et al (33)
Study area	Singapore	Shanghai and Tianjin, China	Aichi Cancer Center Hospital in Nagoya, Japan	SF, LA, and Oahu, HI USA
Asian groups included	Chinese	Chinese	Japanese	Americans of Chinese, Japanese, and Filipino descent
Time period of study	1986–1988	1984–1986	1988–1992	1983–1987
Sources of case subjects	Consecutive admissions to 2 hospitals	Population-based cancer registries of the 2 study areas	Outpatients who were diagnosed with a first breast cancer	Population-based cancer registries of the 3 study areas
Sources of control subjects	Hospital patients admitted to general surgery, eye, and orthopedic wards of the same hospital as case subjects	Community control subjects individually matched to case subjects by sex and age	Noncancer outpatients who were ≤20 y of age at the time of hospital admission	Population-based control subjects selected by random digit dialing in SF and LA and with the Health Surveillance Program in Hawaii
Age range of case subjects	28–83 y	20–69 y	≥20 y of age; upper age limit was not specified	30–55 y
Number of case subjects	200	834 (534 in Shanghai, 300 in Tianjin)	1186 (607 premenopausal 445 postmenopausal)	597 (169 in SF, 215 in LA, and 213 in Hawaii)
Number of control subjects	420	834 (534 in Shanghai, 300 in Tianjin)	21295 (15084 premenopausal 6215 postmenopausal)	966 (310 in SF, 273 LA, and 378 in Hawaii)
Percentage participation	93% for case subjects 94% for control subjects	83% for case subjects, 99% for control subjects	Not available	70% for case subjects 75% for control subjects
Diet assessment	Food-frequency questionnaire, diet 1 y before interview	Food-frequency questionnaire; usual adult diet	Food-frequency questionnaire; diet period not specified	Food-frequency questionnaire; usual adult diet
Number of food items on food-frequency questionnaire	90	64 in Shanghai, 68 in Tianjin	Number of foods asked was not specified but data on 16 foods were presented	About 50 items common to all 3 Asian ethnic groups; ≈10 items unique to each group
Portion size	5 categories: 0.5, 0.75, 1.0, 1.5, and 2.0 times a standard portion	Market weights of a standard portion	Not asked	Not asked
Individual soyfoods	Not specified	Tofu, soy milk, smelly soybean, and vegetarian chicken (a soybean product)	Bean curd, miso	A tofu dish that includes fresh, dried, or deep-fried tofu product: natto, and miso (fermented soybeans) among Japanese only

[1] SF, San Francisco–Oakland metropolitan statistical area; LA, Los Angeles.

sumers (≥55.0 g soy product) showed a 60% (95% CI: 0.2, 0.9) reduced risk compared with low daily consumers (<20.3 g) (29, 30). Similarly, in Japan, compared with low intake (≤3 times/mo), high intake (≥3 times/wk) of bean curd was associated with a statistically nonsignificant reduced risk of breast cancer in premenopausal women but not in postmenopausal women. However, in both groups of women, there was no association between intake of miso soup, which was categorized in the food-frequency questionnaire as daily or occasional-to-never, and breast cancer risk (32). Among Asian Americans, intake of tofu was associated with a lower risk of breast cancer both overall and separately in pre- and postmenopausal women. Similar results were obtained after adjustment for relevant menstrual and reproductive factors and selective dietary factors (33). Asian American women in the highest intake group (>120 times/y) showed a 30% reduced risk (95% CI: 0.4, 1.0) compared with women in the lowest intake group (<12 times/y) (Table 3). Analysis by migration status showed a significant protective effect in migrants but not in Western-born Asian Americans (Table 3). However, the results in migrants and Western-born Asian Americans were not statistically different.

DISCUSSION

The 4 case-control studies reviewed here show some suggestive evidence for an association between soy intake and risk of

TABLE 2
Estimated distribution of intake of soy products among control subjects in Singapore, China, and the United States

Subject characteristics (reference)	Soy intake Low	Median	Upper
		g/d	
Chinese in Singapore, *n* = 420 (29, 30)[1]	20	36	55
Chinese in Shanghai and Tianjin, China, *n* = 834 (31)[2,3]	27	45	141
Asian Americans	0.9	2.8	4.1
In San Francisco–Oakland, Los Angeles and Oahu, HI, *n* = 961 (33)[2,4]			
By place of birth and years of residence in the US[5]			
US- or Western-born, *n* = 364	0.9	1.9	4.0
Non-US- or Western-born			
≥8 y in US/West, *n* = 303	0.9	2.1	8.0
1–7 y in in US/West, *n* = 140	0.9	4.0	8.0
Other, *n* = 154[6]	1.8	4.0	8.0
By ethnicity			
Chinese Americans, *n* = 287	1.8	4.0	8.0
Japanese Americans (tofu only), *n* = 394	1.8	4.0	7.0
Japanese Americans (tofu, natto, and miso), *n* = 394	2.2	4.9	10.0
Filipino Americans, *n* = 280	0.1	0.9	4.0

[1] Lower and upper tertiles of intake of soy products are shown.
[2] Lower and upper quartiles of intake are shown.
[3] Obtained by converting intakes of soy protein in Shanghai and Tianjin combined (Table 2, 31) and assuming that 1.4 g soy protein is equivalent to 20 g soy product (34).
[4] We assume that 28 g tofu was consumed per time a tofu dish was eaten. Frequency of intake/y was converted to g intake/d.
[5] US/West includes the United States, Guam, Midway Island, and other US Pacific territories, Canada, western Europe, central Europe, the former Soviet Union, Australia, and New Zealand.
[6] Non-US/Western-born migrants who had multiple moves between the US or West and Asia.

breast cancer, but the results are inconclusive. There are no obvious reasons for the differences in findings in these studies, but the adjustment for dietary factors was not identical in the studies. There are some methodologic issues of concern that are inherent in all case-control studies of diet and cancer as well as other issues that may be more relevant to studies in transitional populations.

One concern common to all studies of diet and cancer is the ability to characterize accurately the dietary exposure of interest (ie, soy intake). None of the 4 studies were designed to investigate specifically the role of soy and none of the dietary instruments were formally validated. The assessment of soy intake was crude in the study in Asian Americans. Because there are few primary soyfoods (foods with soy ingredients excluded) consumed by Asian Americans, even a relatively crude dietary instrument may be able to classify individuals as high, medium, and low consumers of soy for the purpose of epidemiologic studies. In Japanese Americans for whom we have information on intake of 3 common soyfoods, >80% of the total soy intake was derived from tofu. However, improvement of the dietary instruments with which total intake of soy (ie, fresh, fermented, dried, and fried tofu and other soy products) can be assessed as well as the compilation of the isoflavone content of soyfoods is clearly needed. Moreover, because of the diverse manner in which soy is used in Asian cuisine, portion sizes may be particularly important. The relevant period of exposure is also not known. Usual adult intake of soy was the primary focus of these studies.

Soy may have long-lasting effects on the sensitivity of estrogen-responsive target organs to estrogen exposures in adult life, particularly if the exposure to soy is initiated during neonatal and prenatal periods (35). In rats, genistein administered during the neonatal period protected against chemically induced mammary tumors (36). Intake of soy during early childhood and premenarche years may be important, but at this time there is no reliable way to obtain this information from self-reporting data in case-control studies. Other dietary and nondietary variables may potentially confound the soy and breast cancer association. In particular, intake of vegetables and legumes that are rich in fiber or lignans may be associated with intake of soy and may need to be considered.

A concern in case-control studies is the possibility of differential recall of past events between case and control subjects. The extent of recall bias in case-control studies of dietary factors is controversial (37–39). The degree to which an odds ratio is reduced or exaggerated in relation to the true risk estimate is also influenced by the size of the true association, the direction and the probabilities of misclassification, and the prevalence of the exposure in the study population (40); each of these factors may have differed in the case-control studies examined in this discussion (29–33). Confirmation of the role of soy in cohort studies in which diet is assessed before the diagnosis of breast cancer will strengthen the evidence for this relation. Both the multiethnic cohort study being conducted in Hawaii and Los Angeles and the cohort study of Chinese in Singapore conducted by colleagues at the University of Hawaii and the University of Southern California will be able to evaluate the role of soy and breast cancer in the near future.

Differences in soy intakes may have influenced our ability to detect an association in these studies. Although there was a 3–4-fold difference in soy intake between women in the lower and upper tertiles of intake in these studies (Table 2), these studies investigated different levels of the dose-response relation between soy intake and breast cancer risk. Only about one-quarter of Asian American control subjects reported intake of any

TABLE 3
Intake of soy products and risk of breast cancer in Asia and among Asian women in the United States[1]

Reference, location, and intake	Risk
	OR (95% CI)
Lee et al (29, 30), Singapore	
Intake of total soy products (g/d)	
Premenopausal women[2]	
< 20.3	1.0
20.3–54.9	0.6 (0.3, 1.2)
≥ 55.0	0.4 (0.2, 0.9)
Postmenopausal women[3]	
< 20.3	1.0
20.3–54.9	0.9 (0.4, 1.9)
≥ 55.0	1.1 (0.5, 2.3)
Yuan et al (31), China	
Per 18 g soy protein/d[4]	
Shanghai	0.9 (0.6, 1.3)
Tianjin	1.4 (0.7, 3.0)
Shanghai and Tianjin combined	1.0 (0.7, 1.4)
Hirose et al (32), Japan	
Premenopausal women	
Bean curd ≤ 3 times/mo	1.0
Bean curd 1–2 times/wk	0.9 (0.7, 1.2)
Bean curd ≥ 3 times/wk	0.8 (0.6, 1.0)
Miso soup occasionally to never	1.0
Miso soup daily	1.2 (1.0, 1.4)
Postmenopausal women	
Bean curd ≤ 3 times/mo	1.0
Bean curd 1–2 times/wk	0.9 (0.6, 1.2)
Bean curd ≥ 3 times/wk	1.0 (0.7, 1.3)
Miso soup occasionally to never	1.0
Miso soup daily	1.0 (0.8, 1.2)
Wu et al (33), intake of soy products in times/y[5]	
US-born Asian women	
< 13	1.0
13–42	1.2 (0.7, 1.8)
43–54	0.9 (0.6, 1.4)
55–119	1.0 (0.5, 1.8)
≥ 120	0.8 (0.4, 1.8)
OR per 1 time intake per week	0.93 (0.73, 1.18)
Non-US-born Asian women	
< 13	1.0
13–42	0.7 (0.5, 1.1)
43–54	0.8 (0.5, 1.1)
55–119	0.6 (0.4, 1.0)
≥ 120	0.5 (0.3, 0.8)
OR per 1-time intake per week	0.79 (0.66, 0.94)
Combined[6]	
< 13	1.0
13–42	0.9 (0.7, 1.3)
43–54	0.9 (0.6, 1.2)
55–119	0.8 (0.5, 1.1)
≥ 120	0.7 (0.4, 1.0)
OR per 1 time intake per week	0.85 (0.74, 0.99)

[1] OR, odds ratio; US/West, United States and its Pacific territories, Canada, Western Europe, central Europe, the former Soviet Union, Australia, and New Zealand.

[2] OR was adjusted for age and age at first birth; $P = 0.01$ for trend.

[3] OR was adjusted for age, nulliparity, height, education, and family history of breast cancer; $P = 0.05$ for trend.

[4] 18 g soy protein/d represents the range between the 5th and 95th percentile among controls. OR was adjusted for energy intake and relevant menstrual and reproductive factors.

[5] All ORs were adjusted for age, location, ethnicity, and menopausal status.

[6] OR adjusted for migration status (US/Western born, residence in urban east and 1–7 y in US/West, residence in urban east and ≥ 8 y in US/West, residence in rural East and 1–7 y in US/West, residence in rural east and ≥ 8 y in US/West, and other migrants.

tofu dish ≥ 1 time/wk (33), and we estimate that the median soy intake of Asian Americans is one-tenth that of Chinese women in Singapore and China (Table 2). However, in the study in Singapore and China, women in the lowest quartile of intake were still daily or at least weekly soy consumers. Although the total intake of soy could not be determined in the study in Japan because results were not presented for miso and bean curd combined, intake of soy can be presumed to be reasonably high even among the lower-soy consumers. It may be easier to detect an association in groups in which the intake of soy is not uniformly high. It is intriguing that in one animal study, incremental dietary increases in soy protein in the diet were not associated with a proportionate increase in tumor inhibition (23). Rats fed diets with 10% and 20% soybean protein isolate showed a 40% reduction in tumor growth. If these results can be extended to humans, they suggest that risk reduction by soy may exhibit an upper limit rather than a continuously increasing dose-response effect. Further studies are needed to establish whether intake of soyfoods protects against breast cancer and the nature of the dose-response relation.

Alternatively, soy intake may be a marker of other factors associated with migration or with degree of westernization that are causally associated with risk of breast cancer. This may explain the more apparent association between soy intake and breast cancer risk in premenopausal than in postmenopausal women in Singapore and Japan and in Asian American migrants than in Western-born Asians. The evidence for a causal role of soy in breast cancer development will be substantially weakened if the association is present only in Asian migrants and not in Western-born Asians, because this suggests that the association may be due to our inability to fully adjust for other effects of migration. In our study in Asian Americans, the protective effect associated with soy intake was substantially weaker among US-born Asian Americans than in non-US-born Asian Americans (Table 3).

Finally, the mechanisms by which intake of soy may influence risk of breast cancer must be identified. A predominant hypothesis focuses on the potential effects of soy on hormone production and metabolism. However, there is currently only circumstantial evidence in support of this hypothesis. On the basis of in vitro studies showing that isoflavonoids may increase the synthesis of hepatic sex hormone binding globulin, it was suggested that soy may lower the risk of estrogen-related cancers by decreasing the amount of free and bioavailable endogenous estrogens (41). A recent, small cross-sectional study in premenopausal women in Japan suggests an association between soy intake and estrogen concentrations (46). There are some data on the effects of soy on estrogen concentrations from dietary intervention studies (42–45). Results from studies in postmenopausal women do not show any significant effect of soy on serum concentrations of estradiol, progesterone, sex hormone binding globulin, luteinizing hormone, or follicle-stimulating hormone (44, 45). Results from studies in premenopausal women are conflicting. In a 12-mo study (6 mo of soy protein isolate supplementation in 14 premenopausal women, nonsignificant increases in serum estradiol concentrations and reductions in progesterone and sex hormone binding globulin concentrations were found during soy supplementation compared with concentrations before and after supplementation (45). However, blood samples were collected at variable times during each of the menstrual cycles in this study (45). In 2 other studies, each in 6 premenopausal women who added soy to their diet for 1 mo and have provided blood specimens during the follicular and luteal phases of the menstrual cycle, serum estradiol concentrations decreased significantly with daily supplementation with soymilk (44), whereas no reductions in serum estradiol were observed in another study in which soy protein was added to the daily diet (42). No change was noted in concentrations of sex hormone binding globulin in one study (42) and it was not measured in the other (44). However, in both studies, the concentrations of serum progesterone decreased and the duration of menstrual cycles increased. Larger and longer-term soy intervention studies are needed to investigate the acute and chronic effects of soy intake on hormonal function in pre- and postmenopausal women. Collection of biological samples during fixed times of the follicular and luteal phases of the menstrual cycle is also needed in studies in premenopausal women because of the cyclic variation in hormone profiles. In addition, cross-sectional studies that investigate the interrelations of soy intake and other dietary and nondietary factors and endogenous hormone concentrations will help to clarify whether intake of soy explains in part the lower estradiol concentrations in Asians.

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