Tofu and Risk of Breast Cancer in Asian-Americans

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Abstract

Breast cancer rates among Asian-Americans are lower than those of US whites but considerably higher than rates prevailing in Asia. It is suspected that migration to the US brings about a change in endocrine function among Asian women, although reasons for this change remain obscure. The high intake of soy in Asia and its reduced intake among Asian-Americans has been suggested to partly explain the increase of breast cancer rates in Asian-Americans.

We conducted a population-based case-control study of breast cancer among Chinese-, Japanese-, and Filipino-American women in Los Angeles County MSA, San Francisco Oakland MSA, and Oahu, Hawaii. Using a common questionnaire which assessed frequency of intake of some 90 food items, 597 Asian-American women (70% of those eligible) diagnosed with incident, primary breast cancer during 1983–1987 and 966 population-based controls (75% of those eligible) were interviewed. Controls were matched to cases on age, ethnicity, and area of residence. This analysis compares usual adult intake of soy (estimated primarily from tofu intake) among breast cancer cases and control women. After adjustment for age, ethnicity and study area, intake of tofu was more than twice as high among Asian-American women born in Asia (62 times per year) compared to those born in the US (30 times per year). Among migrants, intake of tofu decreased with years of residence in the US. Risk of breast cancer decreased with increasing frequency of intake of tofu after adjustment for age, study area, ethnicity, and migration history; the adjusted OR associated with each additional serving per week was 0.85 (95% CI = 0.74–0.99). The protective effect of high tofu intake was observed in pre- and postmenopausal women. This association remained after adjustment for selected dietary factors and menstrual and reproductive factors. However, this study was not designed specifically to investigate the role of soy intake and our assessment of soy intake may be incomplete. We cannot discount the possibility that soy intake is a marker of other protective aspects of Asian diet and/or Asian lifestyle.

Introduction

The search for a role of fat in the etiology of breast cancer has been the subject of numerous epidemiological studies (1–3). Because most of the analytic studies show either no association or a weak association between dietary fat and risk of breast cancer, the focus on diet has shifted to the investigation of other dietary factors, such as soy, which may protect against breast cancer and may be part of the explanation of international differences in breast cancer rates (4, 5). The intake of soy products may be particularly relevant in studies of Asian-Americans because the traditional Asian diet is rich in soy (6), and high intake of soy has been associated with a reduced risk of breast cancer in one case-control study (7, 8). Soy may protect against the risk of breast cancer through its influence on sex hormone metabolism, its purported antiestrogenic effect, or its inhibitory effects on cancer cell growth (5, 6, 9–11).

In a recent collaborative breast cancer case-control study of Asian-Americans we conducted, there was a 6-fold gradient in breast cancer risk by migration history between recent Asian migrants to the United States and American-born Asian-Americans with at least three grandparents also born in the West. An increase in risk was observed, even in the migrating generation. The risk of breast cancer for migrant women who had lived in the United States for 7 years or less was clearly lower than the risk for migrants who had lived in the United States for longer periods of time or for American-born Asian-Americans (12). At present, we can only speculate which lifestyle factors may explain the gradient in breast cancer risk noted in these Asian-American women. We report here our findings on the possible role of soy, based primarily on the intake of tofu, in the etiology of breast cancer.

Subjects and Methods

Study methods of this population-based case-control study conducted among Chinese-, Japanese-, and Filipino-American women in Los Angeles County MSA,[2] San-Francisco-Oakland MSA, and Oahu, Hawaii have been described in detail previously (12–14). Briefly, this study included all women of these Asian ethnicities who were diagnosed with histologically confirmed, first primary breast cancer at ages 20–55 years during

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[2] The abbreviations used are: MSA, metropolitan statistical area; OR, odds ratio; CI, confidence interval.

Table 1 Mean tofu intake (times/year) of controls by birthplace and by Asian ethnicity, all study areas combined, and by study area

	All controls	By birthplace		By ethnicity		
		East	West	Chinese	Japanese	Filipino
All study areas						
No. of subjects	961	597	364	287	394	280
No. of times/yr	54.7[a]	62.0[b]	29.5[b]	61.6[c]	79.1[c]	26.1[c]
By study area						
San Francisco						
No. of subjects	310	257	53	146	58	106
No. of times/yr[d]	64.2	69.3	39.5	74.9	82.5	39.4
Los Angeles County						
No. of subjects	273	224	49	85	82	106
No. of times/yr[d]	56.8	61.1	37.5	77.6	70.9	29.4
Hawaii						
No. of subjects	378	116	262	56	254	68
No. of times/yr[d]	45.3	46.8	44.6	29.3	53.9	25.9

[a] Adjusted for ethnicity (Chinese, Japanese, and Filipino), age (≤25, 26–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55+), study area (Hawaii, Los Angeles, and San Francisco-Oakland MSA), and migration status (born in the West, urban East 1–7 yrs in West, urban East 8+ yrs in West, rural East 1–7 yrs in West, rural East 8+ yrs in West, and other migrants) using General Linear Models procedure.
[b] Migration status was excluded from the model described in footnote *a*.
[c] Ethnicity was excluded from the model described in footnote *a*.
[d] Crude mean intake per year.

the period April 1, 1983 to June 30, 1987. Using a common study design and questionnaire in the three study areas, we conducted in-person interviews with 597 Asian-American women diagnosed with incident, primary breast cancer during 1983–1987 (70% of those eligible) and 966 population-based controls (75% of those eligible). Controls were matched to cases on age, ethnicity, and area of residence. In-person interviews were conducted with the subjects using a structured questionnaire in the language they preferred (English, Chinese, or Japanese). Of the subjects interviewed, approximately one-third were of each of the three Asian ethnic groups, and approximately one-third of the interviews were conducted in each of the three study centers (12).

Our in-person interview elicited information on each subject's migration history (12), menstrual and reproductive histories (13), body size measures (14), previous medical and family history, and smoking and alcohol use. In addition, the subject's dietary patterns during adult life were obtained by asking the usual frequency of intake of approximately 60 food items/groups. About 50 food items were asked of all subjects, and in addition, women in each separate ethnic group were asked about 10 food items that were specific to their ethnic group. Frequencies of intake were in times per day, week, month, or year, whichever time frame was most relevant for respondents. Portion size of intake was not assessed. All subjects were asked their average intake of "a tofu (bean curd) dish of any type." Japanese-American women were also asked the frequency of intake of miso (soybean paste) soup and natto (fermented soybean), two other common sources of soy in the Japanese diet. For Japanese-Americans only, total soy intake was calculated by summing the frequency of intake of tofu, miso soup, and natto, weighting miso soup and natto at about ¼ and 1/12, respectively, of the soy content of a tofu dish (15, 16).

ORs (relative risk estimates) and their corresponding 95% CIs and two-sided statistical significance levels (*P* values) were calculated. Unconditional logistic regression methods were used with single variables as well as for multivariate analysis (17). Based on the intake of tofu among control women, ORs were computed by defining the lowest quartile of intake as the referent category. Tests for trend were performed. Three models are presented in the tables. The first model includes the matching variables used in the study design [ethnicity (Chinese, Filipino, and Japanese), study area (Hawaii, Los Angeles County, and San Francisco Bay Area), and age (in 5-year age groups) (adjusted OR; see Table 1, footnote *a*)]. The second model was in addition adjusted for migration history. The second set of ORs (adjusted OR; see Table 1, footnote *b*) allows us to investigate the effect of tofu with adjustment for migration history, which we reported previously to strongly determine the risk of breast cancer (12). The migration variables were birthplace of the subject, in the West or the East, and for subjects born in the East, this was further categorized by whether the subject always lived in urban or rural communities in the East and by years of residence in the West (≤7 *versus* 8+ years). Women who had more than one move between the East and the West or who had not always lived in either urban or rural communities in the East were classified as "other migrants" (see below). To examine the role of potential confounder factors, we also added to the first model age at menarche, menopausal status, parity, and age at first livebirth in the multivariate model (adjusted OR[c]).

Results

Birthplace and Asian ethnicity are two important determinants of intake of tofu in this population. Table 1 shows the mean intake of tofu by birthplace and by Asian ethnicity for all study areas combined and separately by individual study area. Intake of tofu (in times per year) was more than double among Asian-Americans who were migrants (62.0) compared to those who were born in the West (29.5) after adjustment for ethnicity, age, and study area. This difference in intake between Asians born in the West compared to those born in the East was less apparent in Hawaii. This may be explained by a preponderance of Filipinos among the control women in Hawaii who were born in the East and their lower intake of tofu compared to Chinese and Japanese women. A gradient in the intake of tofu was observed among subjects born in the West classified by their parents' birthplace (data not shown). In subjects born in the West, after adjustment for ethnicity, age, and study area, intake of tofu per year was 39.7 if both parents were born in the East, 28.5 if one parent was born in the East and 22.6 if neither

Table 2 ORs for breast cancer and usual intake of tofu, for all study areas and ethnic groups combined, and separately by study area and by ethnicity

	Cases	Controls	Adj. OR[a]	Adj. OR[b]	Adj. OR[c]
Tofu (times per year)					
≤12	209	289	1.00	1.00	1.00
13–42	135	199	0.95	0.95	0.97
43–54	138	232	0.80	0.84	0.84
55+	114	238	0.62	0.70	0.67
OR per 1 category change			0.86	0.89	0.88
95% CI			0.78–0.95	0.81–0.99	0.79–0.97
P			0.002	0.03	0.01
OR per 1 time/week			0.81	0.85	0.83
95% CI			0.70–0.93	0.74–0.99	0.72–0.95
P			0.002	0.03	0.008
OR per 1 category change and 95% CI[d]					
By study area[d]					
San Francisco			0.77	0.80	0.81
			0.64–0.93	0.66–0.96	0.66–0.98
Los Angeles County			0.88	0.88	0.88
			0.73–1.05	0.73–1.06	0.74–1.06
Hawaii			0.97	1.00	1.00
			0.82–1.24	0.84–1.19	0.84–1.19
By ethnicity[e]					
Chinese			0.86	0.91	0.88
			0.71–1.04	0.75–1.11	0.72–1.07
Japanese			0.90	0.94	0.91
			0.77–1.05	0.80–1.11	0.78–1.07
Filipino			0.83	0.82	0.82
			0.69–1.01	0.68–1.00	0.67–1.00

[a] Adjusting for age (≤25, 26–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55+), study area (Hawaii, Los Angeles, and San Francisco-Oakland MSA), and ethnicity (Chinese, Japanese, and Filipino).
[b] Adjusting for age, study area, ethnicity, and migration status (born in the West, urban East 1–7 yrs in West, urban East 8+ yrs in West, rural East 1–7 yrs in West, rural East 8+ years in West, and other migrants).
[c] Adjusting for age, study area, ethnicity, menopausal status, age at menarche, ever pregnant, number of livebirths, and age at first livebirth.
[d] Study area was excluded from the models described in footnotes *a*, *b*, and *c*.
[e] Ethnicity was excluded from the models described in footnotes *a*, *b*, and *c*.

parents were born in the East. Among migrants, the number of years they had lived in the West also influenced the frequency of tofu intake (data not shown). Intake of tofu was higher among migrants who have lived in the West for 7 years or less (74.4; presumably because they were less acculturated and had a diet more typical of their diet in Asia) compared with migrants who have lived in the West for 8 years or more (57.8). A second determinant of intake of tofu is the specific Asian ethnicity. The higher intake of tofu among Chinese and Japanese-Americans compared to Filipino-Americans was observed in each study area. After adjustment for age, study area, and migration status, intake of tofu was highest in Japanese (79.1), followed by intake in Chinese (61.6), and was substantially lower in Filipino women (26.1).

Table 2 shows the association between risk of breast cancer and intake of tofu for all study areas combined and separately by study area and by Asian ethnicity. After adjusting for age, study area, and ethnicity, the risk of breast cancer decreased significantly with increasing quartile level of tofu intake (Table 2, Adj. OR[a] for per quartile was 0.86, *P* for trend = 0.002); the OR associated with each serving of tofu intake per week was 0.81 ($P = 0.002$) (Table 2, Adj. OR[a]). When tofu intake was in addition adjusted for migration status, these ORs were slightly weakened (toward the null) to 0.89 and 0.85, respectively, and the significance level decreased to 0.03 (Table 2, Adj. OR[b]). This finding was unchanged after adjustment for age at menarche, menopausal status, parity, and age at first livebirth (Table 2, Adj. OR[c]). The association between tofu intake and risk of breast cancer was found primarily in the California study areas, although the results were not significantly different by study areas (Table 2). The inverse association between intake of tofu and risk of breast cancer was observed in each of the three Asian ethnic groups included in the study, but the sample sizes for the subgroup analysis were substantially reduced (Table 2). For Japanese-Americans, the risk of breast cancer associated with intake of soy per week (*i.e.*, tofu, natto, and miso soup combined; adjusted OR, 0.91; 95% CI, 0.79–1.05) was similar to that associated with the intake of tofu per week (adjusted OR, 0.90; 95% CI, 0.72–1.13; Chinese- and Filipino-Americans were not asked about intake of natto and miso soup because these foods were judged to be consumed primarily by Japanese).

Table 3 shows the association between intake of tofu and risk of breast cancer by menopausal status. The protective effect of tofu was observed in both premenopausal and postmenopausal women and was of similar magnitude. The result was statistically significant only in premenopausal women. This appears to be solely an effect of the larger number of premenopausal than postmenopausal women since the magnitudes of the effects are very similar.

Analysis to fully examine the role of dietary factors in this study population is in progress. However, to consider dietary factors that may potentially confound the association between soy intake and risk of breast cancer, we selected food items we consider to be indicators of high fat foods in Western diet (*e.g.*, beef) and indicators of low fat foods in Eastern diet (*e.g.*, beans

Table 3 ORs for breast cancer and usual intake of tofu in adult life by menopausal status

	Cases	Controls	Adj OR[a] (95% CI)	Adj. OR[b] (95% CI)
Premenopausal women				
Tofu (times per year)				
≤12	157	215	1.00	1.00
13–42	93	135	0.99	0.96
43–54	95	144	0.87	0.91
55+	76	162	0.61	0.67
OR per 1 category change			0.86 (0.76–0.96)	0.89 (0.79–1.01)
P			0.01	0.06
OR per 1 time/week			0.79 (0.67–0.93)	0.84 (0.70–0.99)
P			0.005	0.04
Postmenopausal women				
Tofu (times per year)				
≤12	50	72	1.00	1.00
13–42	39	63	0.82	0.85
43–54	43	85	0.62	0.67
55+	38	75	0.60	0.70
OR per 1 category change			0.83 (0.69–1.00)	0.88 (0.72–1.07)
P			0.05	0.19
OR per 1 time/week			0.80 (0.63–1.03)	0.86 (0.66–1.13)
P			0.09	0.28

[a] Adjusting for age (≤25, 26–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55+), study area (Hawaii, Los Angeles, and San Francisco-Oakland MSA), and ethnicity (Chinese, Japanese, and Filipino).
[b] Adjusting for age, study area, ethnicity, and migration status (born in the West, urban East 1–7 yrs in West, urban East 8+ yrs in West, rural East 1–7 yrs in West, rural East 8+ years in West, and other migrants).

Table 4 ORs for breast cancer in association with migration status

Migration status	Adj. OR[a] (95% CI)	Adj. OR[b] (95% CI)
Born in the West	1.00	1.00
Urban East, 8+ yrs in West	0.70 (0.51–0.97)	0.76 (0.55–1.05)
Rural East, 8+ years in West	0.63 (0.40–1.00)	0.67 (0.42–1.06)
Urban East, 1–7 yrs in West	0.43 (0.27–0.67)	0.48 (0.30–0.77)
Rural East, 1–7 yrs in West	0.28 (0.14–0.59)	0.30 (0.15–0.64)
Other migrants	0.65 (0.46–0.92)	0.70 (0.49–0.99)

[a] Adjusting for age (≤25, 26–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55+), study area (Hawaii, Los Angeles, and San Francisco-Oakland MSA), and ethnicity (Chinese, Japanese, and Filipino).
[b] Adjusting for age, study area, ethnicity, and tofu intake.

and other legumes). When we added intake of beef, beans, and other legumes to the adjustment model (first model in Table 2), the OR associated with each serving of tofu intake per week was 0.85 (95% CI, 0.74–0.99; compared to OR, 0.81; 95% CI, 0.70–0.93; Table 2, Adj. OR[a]).

Because the intake of tofu may be a marker of acculturation or other lifestyle habits that are causally associated with the risk of breast cancer, we examined the association stratified by birthplace. The OR for breast cancer associated with each serving of tofu intake per week was 0.93 (95% CI, 0.73–1.18) for Asians born in the West and 0.79 (95% CI, 0.66–0.94) for those born in the East after adjustment for ethnicity, study area, and age. Table 4 shows the ORs for migration variables before and after adjustment for intake of tofu. There was little change in the point estimates associated with the different migration variables; approximately 10% of the effect associated with migration can be explained by intake of tofu.

Discussion

Despite the growing interest in determining the role of soy products in the development of breast cancer since the publication of the first epidemiological study in 1991 (7, 8), there is relatively little epidemiological data available, in part because soyfoods are consumed mainly in Asian populations. This study represents the first study on the risk of breast cancer in relation to intake of soyfoods among Asian-American women.

In interpreting these findings, several limitations of this study should be considered. This study was not designed to assess total tofu intake or total soy intake and our analysis was based on one question on intake of tofu. Portion size of intake was also not included in our dietary assessment and the diet questionnaire has not been formally validated. Despite these limitations, this study represents one of the first studies to examine the role of multiple dietary factors in the three largest Asian populations in the United States. Fresh tofu is the main source of tofu and soy accessible to Asian-Americans, whereas many of the other types of tofu (*e.g.*, dried or fried tofu) and soybean products (*e.g.*, frozen soybeans) were not readily available, even in California and Hawaii, until recent years. We are not aware of published data on soy intake (*i.e.*, sources of soy foods and frequencies or amounts of soy intake) among Asian-Americans to estimate the extent to which we might have underestimated their intake based on this one question. However, data on Japanese-Americans in this study indicated that the risk of breast cancer in association with intake of tofu intake was similar to the association with intake of tofu and other soy products (natto and miso soup). An added complexity in studies of dietary factors in migrant populations, such as the present study, is that subjects may have had multiple and substantial dietary changes over their adult life. We attempted to address the problem of multiple changes by asking subjects to consider all dietary changes in their adult life and to estimate their dietary intake for the period that was most representative (*i.e.*, the longest period) of their adult life. However, intakes of specific foods and nutrients are correlated with each other and it is difficult to sort out the separate effects of specific foods or nutrients. Consistencies in study findings in subgroup analyses

and after adjustment for potential confounders lend credibility to the results. The hypothesis relating soy and breast cancer was not appreciated when this study was conducted; thus, it is unlikely that nondifferential misclassification was operating. However, the possibility of selection bias cannot be ruled out since our response rates were modest (70–75%). The persistence of the migration effects after adjustment for tofu intake (Table 4) suggests that there are other unidentified factors associated with migration that influence the risk of breast cancer. Adjustment for migration reduced the tofu effect by some 20%. It may be that if these unidentified factors could be adjusted for, the tofu effect would be much reduced.

The present results show a statistically significant reduction in breast cancer risk in relation to intake of tofu. Intake of tofu at least once a week was associated with a significant 15% reduction in risk. Subgroup analyses indicate a lower risk associated with tofu intake among Asians born in the West and in the East, among Filipino-, Chinese-, and Japanese-Americans separately, and among pre- and postmenopausal women. Results in this study are supportive of the Singapore study (7, 8) to the extent that high intake of soy was associated with a significant reduction in breast cancer risk in premenopausal women. The intake of soy was not associated with a reduced risk of breast cancer in postmenopausal women in Singapore. On the other hand, the risk of breast cancer was not associated with intake of soy in Shanghai and Tianjin, China (18). This lack of an association was found in analyses conducted for the two study areas separately or combined, for pre- and postmenopausal women separately or combined, and with and without adjustment for other dietary and nondietary risk factors.

At this time, we can only speculate on reasons for the differing results on the role of soy intake and risk of breast cancer in these three case-control studies. The study in Singapore was hospital based, whereas the studies in China and the present study were population based. The sample size of the China study was the largest, followed by the present study, and was smallest in the Singapore study. All three studies asked about the usual frequency of intake of soy but differed in the specific questions on soy products that were asked. None of the studies were designed specifically to investigate the role of soy. The portion size of intake was not assessed in the present study but was asked in the Singapore and China studies. Adjustment for other dietary and nondietary factors was made in all three studies, but because of the complexity of diet, soy may represent other aspects of an Asian diet. Despite these differences in study design, it is not apparent how they can explain the differences in study results.

On the other hand, the intake level among controls differed substantially between the present study and the studies in Asia. In Singapore and China, almost all subjects consumed soy daily and the risks were calculated for high daily intake *versus* low daily intake (the lowest tertile in Singapore and China was <20 g of soy product and ≤18 g of soy protein per day, respectively). The intake levels were considerably lower in Asian-Americans; about one-third of control women reported tofu intake less than once a month and only one-quarter of control women reported intake at least once per week. Thus, this study investigated the effect of considerably lower levels of soy intake than the studies in Asia.

A protective role of soy against breast cancer is biologically plausible (5, 19). Soybeans are a rich source of isoflavonoids. Genistein, a major isoflavone in soybeans, is an effective inhibitor of cancer cell growth in various breast cancer cell lines (20, 21), probably via the inhibition of tyrosine protein kinases and other enzymes that are associated with signal transduction of cellular growth factors (10, 11). Genistein and daizein (another isoflavone in soybeans) have a diphenolic structure similar to that of 17-β-estradiol. These compounds may have weak estrogenic and antiestrogenic properties, depending on circumstances of use and site of action, competing with endogenous estrogens for receptor sites (5, 6, 22). There is currently only circumstantial evidence that soy may influence hormone profiles (23, 24). Cross-sectional data on the association between soy intake and estrogen levels are not available, and the results on the effects of soy on estrogen levels from short-term dietary intervention studies are inconsistent (25, 26, 28).

Two (25, 26) of the three studies were conducted in premenopausal women, and each included 6 women who added soy to their daily diet for 1 month. In one study, the addition of 60 g of soy protein (45 mg of isoflavones) to the daily diet was associated with an increase in the level of serum estradiol, reductions in midcycle luteinizing hormone and follicle-stimulating hormone, and a lengthening of the follicular phase of the menstrual cycle compared to baseline levels (25). In the second study, intake of three 12-oz. portions of soymilk per day (200 mg of isoflavones; Ref. 26) was associated with reductions in the levels of follicular, midcycle, and luteal phase serum estradiol and luteal phase progesterone and an increase in menstrual cycle length during soy intervention. However, two of the six women in this study (26) had very low luteal progesterone levels during soy intervention, suggesting that they were anovulatory (27).

The only study of soy on hormone levels in postmenopausal women found no clear estrogenic effects of soy (28). Women (n = 66) on the soy diet [38 g of dry texturized vegetable protein and 25 g of soy splits (165 mg isoflavones)] did not differ from control women (n = 25) in their levels of serum estradiol, luteinizing hormone, follicle-stimulating hormone, and serum hormone-binding globulin.

Few conclusions can be drawn from these soy intervention studies at this time. The small sample sizes, the short intervention period, differences in the soyfoods used, and the 4-fold difference in the amount of isoflavones in the soy diet may have contributed to the differences in results. The influence of soy on hormone levels in pre- and postmenopausal women needs to be further investigated in larger and longer term intervention studies. Moreover, it is not known whether the effects on hormone levels are similar for different types soyfoods (*i.e.*, traditional Asian soyfood *versus* soy constituents) that contain comparable amounts of isoflavones.

The endocrine function of Asian and white women has been compared in an attempt to understand the ethnic differences in breast cancer rates. Explanations for the lower urinary and serum estradiol levels in pre- and postmenopausal Asians compared to whites (29–33) have not been identified. The possible effect of soy on serum estrogen levels warrants investigation (34). It will be important in future epidemiological studies to further investigate the association between intake of soy and breast cancer by obtaining a more complete assessment of soy intake by including consumption of fresh soy (such as tofu) and other soybean products (*e.g.*, soybean skins and dried or fermented tofu). With the exception of tofu, which could comprise a complete dish, most of the other soybean products are used in mixed dishes. Because of the diverse ways in which tofu and other soy products could be used in Asian dishes, portion size information should also be included in future studies.

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