

# Dietary Fat, Fat Subtypes, and Breast Cancer Risk: Lack of an Association among Postmenopausal Women with No History of Benign Breast Disease<sup>1</sup>

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## Abstract

**A recent study among 13,707 postmenopausal women without benign breast disease (BBD) from the Breast Cancer Detection Demonstration Project (BCDDP) cohort found breast cancer risk associated with greater total fat, unsaturated fat, and oleic acid intake. We assessed the associations between cumulative averaged dietary intake from 1980, 1984, 1986, and 1990 with breast cancer risk through 1994 among 44,697 postmenopausal participants without BBD in the Nurses' Health Study (NHS).**

**Multivariate Cox proportional hazard models, with age as the time variable, provided the estimated rate ratios (RRs) with 95% confidence intervals (CIs) from the 14 years of follow-up and the 1,071 breast cancer cases. In the Nurses' Health Study, breast cancer rates over the time period from 1980 to 1994 did not increase significantly with greater total fat [quintile (Q) 5 versus Q1 RR, 0.94; 95% CI, 0.77–1.15], saturated fat (RR<sub>Q5 to Q1</sub>, 0.88; 95% CI, 0.70–1.12), unsaturated fat (RR<sub>Q5 to Q1</sub>, 1.16; 95% CI, 0.92–1.46), oleic acid (RR<sub>Q5 to Q1</sub>, 1.13; 95% CI, 0.81–1.57), linoleic acid (RR<sub>Q5 to Q1</sub>, 0.93; 95% CI, 0.74–1.16), trans fatty acid (RR<sub>Q5 to Q1</sub>, 0.9184; 95% CI, 0.73–1.13), or energy intake (RR<sub>Q5 to Q1</sub>, 0.81; 95% CI, 0.67–0.99). A parallel analysis restricted to the same time period as the BCDDP study did not differ substantially. We found no increase in the rate of breast cancer with greater intake of dietary fat and fat subtypes among postmenopausal women without a history of BBD.**

## Introduction

Velie *et al.* (1) reported a positive association of total fat, unsaturated fat, and oleic acid intake with breast cancer rates from the 255 cases of breast cancer among 13,707 postmenopausal women with no prior report of BBD<sup>3</sup> from the BCDDP cohort. These authors suggested that diet may play an important

role in breast cancer etiology among women without BBD but may not be involved in the disease pathway that includes BBD. They also proposed that women with BBD may have changed their diets toward lower fat intake or recalled their diet less accurately because of their increased risk of breast cancer. Thus, for women with a history of BBD, a recent dietary assessment may not reflect relevant long-term dietary exposures. Because their report was the first of such an association, the BCDDP authors suggested that this issue be investigated in other studies. In contrast to the BCDDP findings, pooled data from five prospective studies found breast cancer risk increased with greater fat intake only among women with a history of BBD (2). However, the definitions of BBD varied substantially among each of the five studies in the pooled analysis, and these analyses were not restricted to postmenopausal women (2).

We previously reported findings from the NHS cohort that the association between total fat and breast cancer was not significantly modified by a history of BBD (3). However, unlike the analysis by Velie *et al.* (1) the previous NHS analysis was not restricted to postmenopausal women, and the effect modification by BBD history was not investigated for fat subtypes. Despite the fact that many women may have BBD without ever being diagnosed, the risk of breast cancer is about 50–100% greater for women who have reported a history of BBD. However, it is not known whether their breast cancer develops through different pathways. In this analysis, we evaluate the association between subtypes of fat and breast cancer rates among participants in the NHS who were postmenopausal and had not reported a diagnosis of BBD, and we compare our findings with those from the BCDDP cohort.

## Materials and Methods

The NHS cohort was started in 1976, when 121,700 female registered nurses (35–55 years of age) from 11 states in the United States responded to a mailed questionnaire about their risk factors for disease. Since that time, biennial questionnaires have been mailed to participants to update exposure histories and ascertain changes in medical and health status. To assess dietary intake, a 61-item food frequency questionnaire was included in 1980. Dietary intake was assessed again in 1984, 1986, and 1990 with an expanded (131-item) food frequency questionnaire. All returned questionnaires with implausible scores for total energy (<500 kcal/day or >3500 kcal/day; ~2% of those returned) were excluded from analyses.

On every biennial questionnaire, participants were asked to report whether they had a diagnosis of fibrocystic disease or other BBD, and information on menopausal status was updated. Women were asked whether their menstrual periods had ceased permanently and if so for what reason. This information, along with age and smoking status, determined whether participants were postmenopausal. Women were considered postmeno-

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<sup>3</sup> The abbreviations used are: BBD, benign breast disease; BCDDP, Breast Cancer Detection Demonstration Project; NHS, Nurses' Health Study; RR, rate ratio; CI, confidence interval.

pausal if they reported that their menstrual periods had ceased because of natural menopause, radiation-induced menopause, or bilateral oophorectomy. Women who had undergone hysterectomy but retained one or more ovaries were considered postmenopausal at age 54 if they smoked and at age 56 if they did not smoke; these are the ages at which 90% of participants in NHS who had a natural menopause became postmenopausal. Medical records were sought for all reported diagnoses of breast cancer, which were identified either through self-report or through a vital-records search during the follow-up period. The diagnosis was confirmed in 99% of reported cases. Only invasive breast cancers were counted in analyses.

We conducted two different analyses to evaluate the association between dietary fat subtypes and rates of breast cancer among postmenopausal women without a history of BBD. The primary analysis used Cox proportional hazard models with age as the time variable. We included postmenopausal women who answered the 1980 diet questionnaire, had plausible scores for total energy, did not have a diagnosis of cancer prior to the return of their 1980 questionnaire, and had not previously reported a diagnosis of fibrocystic or other BBD. Person-time was accumulated from the date of the return of the 1980 questionnaire or from the return of the questionnaire when a woman was considered postmenopausal, whichever occurred later. Follow-up ended when a woman reported the diagnosis of BBD or cancer, died, or June 1, 1994, whichever occurred first. Covariates that have previously been reported to be associated with breast cancer with the NHS were included in these models: age (4), height (5), age at menarche (5), use of postmenopausal hormones (6,7), duration of use of postmenopausal hormones (6,7), parity (5), age at first birth (5), body mass index at age 18 (8), weight gain since age 18 (8), physical activity (9), and intake of total energy (3), alcohol (10), and vitamin A (11).

The cumulative average intake of fat from all preceding questionnaires determined the exposure categories in the analysis, providing a more stable estimate of dietary intake. The nutrient density for total fat and types of fat was calculated at the time of each dietary assessment. The information was cumulatively averaged over time, categorized into quintiles, and updated at each new dietary assessment. Intake of other dietary components, such as total energy, carbohydrates, protein, and vitamin A, were calculated in the same manner. The semiquantitative food-frequency questionnaire and the cumulative averaging of diet information has been described in detail (3). For tests of linear trend, the continuous measures of each dietary component were considered.

We also evaluated the subtypes of fat as continuous factors in sequential models to separate the risk of each component. In addition to the other covariates, model 1 included total fat; model 2 included saturated fat and unsaturated fat; model 3 included saturated fat, oleic acid, linoleic acid, and other unsaturated fat; and model 4 included saturated fat, *trans* fatty acids, and other unsaturated fat. The unit for each subtype of fat was the equivalent of a 5% change in energy, except *trans* fatty acid, for which each unit represented a 1% change in energy.

A secondary analysis was designed to parallel that of Velie *et al.* (1), who had evaluated the association within the BCDDP cohort between dietary assessments in 1987–1989 and breast cancer outcomes through 1995 with an average follow-up period of 5.3 years (1). We analyzed the associations between dietary fat assessment in 1986 and breast cancer rates through 1992 among NHS participants with no previous diagnosis of cancer, a plausible dietary intake in 1986, were postmenopausal, and no previous report of BBD. Person-time accumulated from the later of the return of the 1986 questionnaire or a

Table 1 Covariate distribution among 31,673 postmenopausal women with no history of BBD in 1986

Covariate	Mean (SD) or percentage
Age (mean years)	56.8 (5.5)
BMI (mean kg/m <sup>2</sup> )	25.8 (4.9)
Menarche before age 13 (%)	47%
Parous (%)	91.6%
Parity <sup>a</sup> (mean number of children)	3.4 (1.6)
Age at first birth <sup>b</sup> (mean age)	25.2 (3.5)
Family history of breast cancer (%)	8%
Alcohol intake (mean g/day)	6.3 (11.2)
Mean percentage of energy from	
Total fat	32.3 (5.7)
Saturated fat	11.5 (2.6)
Unsaturated fat	20.8 (3.8)
Oleic acid	10.8 (2.3)
Linoleic acid	5.2 (1.5)
<i>Trans</i> fatty acid	1.4 (0.5)
Protein	18.7 (3.4)
Carbohydrates	48.6 (7.9)
Total energy (mean kcal)	1751 (519)
Physical activity (mean MET/wk)	13.7 (17.9)
Currently using postmenopausal hormones (%)	20.6%

<sup>a</sup> BMI, body mass index.

<sup>b</sup> Among parous women only.

questionnaire when a woman was considered postmenopausal. Follow-up ended when a woman reported BBD, had cancer, died, or June 1, 1992, whichever occurred first. We used the multivariate nutrient-density method to adjust our analyses of dietary fat intake for total energy intake. In this analysis, quintiles of each dietary component were based on the distribution of the entire cohort in 1986. The covariates used in the BCDDP model were included in analyses: age (continuous), total energy (continuous), total energy quadratic, body mass index (continuous), body mass index quadratic, height (continuous), family history of breast cancer (yes/no), parity (continuous), parous (yes/no), age at first birth (continuous), alcohol use (yes/no and continuous), and age at menarche (continuous). The analysis of each fat subtype was mutually adjusted for the other fat subtypes.

## Results

Table 1 presents the covariate distribution of the 31,673 postmenopausal women without a history of BBD in 1986. The percent of energy from total fat was highly correlated ( $P = 0.0001$ ) with that from saturated fat [Pearson's correlation coefficient ( $r$ ) = 0.84], unsaturated fat ( $r = 0.93$ ), oleic acid ( $r = 0.94$ ), linoleic acid ( $r = 0.57$ ), and *trans* fatty acid ( $r = 0.55$ ). The fat subtypes were also highly correlated; the percentage of energy from saturated fat was correlated with that from unsaturated fat ( $r = 0.57$ ), linoleic acid ( $r = 0.10$ ), oleic acid ( $r = 0.70$ ), and *trans* fatty acid ( $r = 0.41$ ).

Table 2 presents the analysis that incorporates updated dietary information from the 1980, 1984, 1986, and 1990 questionnaires. There were 1,071 cases of breast cancer among 44,697 postmenopausal women without BBD diagnosed during the 1980–1994 follow-up. Compared with women in the lowest quintile of intake for each nutrient (Q1), those in the highest quintile (Q5) had no indication of increased breast cancer rates with total fat (RR<sub>Q5 to Q1</sub>, 0.94; 95% CI, 0.77–1.15), saturated fat (RR<sub>Q5 to Q1</sub>, 0.88; 95% CI, 0.70–1.12), unsaturated fat (RR<sub>Q5 to Q1</sub>, 1.16; 95% CI, 0.92–1.46), oleic acid (RR<sub>Q5 to Q1</sub>, 1.13; 95% CI, 0.81–1.57), linoleic acid (RR<sub>Q5 to Q1</sub>, 0.93; 95%

Table 2 Adjusted RR of breast cancer by quintiles of cumulatively averaged and updated intake from fat, fat subtypes, and of total energy intake among 44,697 postmenopausal women with no reported history of benign breast disease in the Nurses' Health Study, 1980–1994

Nutrient	Quintile (Q) of intake					P test for trend <sup>a</sup>
	Q1	Q2	Q3	Q4	Q5	
<b>Fat<sup>b</sup></b>						
No. of cases	258	214	201	216	182	
RR	1.0	.94	.94	1.07	.94	0.57
95% CI		(0.78–1.13)	(0.78–1.14)	(0.89–1.30)	(0.77–1.15)	
<b>Saturated fat<sup>b,c</sup></b>						
No. of cases	259	234	198	187	193	
RR	1.0	1.00	0.87	0.86	0.88	0.05
95% CI		(0.83–1.21)	(0.71–1.07)	(0.69–1.07)	(0.70–1.12)	
<b>Unsaturated fat<sup>b,c</sup></b>						
No. of cases	233	225	211	207	195	
RR	1.0	1.11	1.14	1.20	1.16	0.30
95% CI		(0.92–1.35)	(0.92–1.40)	(0.96–1.49)	(0.92–1.46)	
<b>Oleic acid<sup>b,c</sup></b>						
No. of cases	250	232	187	211	191	
RR	1.0	1.09	0.96	1.22	1.13	0.67
95% CI		(0.88–1.34)	(0.75–1.24)	(0.92–1.61)	(0.81–1.57)	
<b>Linoleic acid<sup>b,c</sup></b>						
No. of cases	284	208	193	189	197	
RR	1.0	0.83	0.84	0.83	0.93	0.75
95% CI		(0.69–0.99)	(0.69–1.02)	(0.67–1.02)	(0.74–1.16)	
<b>Trans fatty acids<sup>b,c</sup></b>						
No. of cases	256	220	221	186	188	
RR	1.0	0.95	1.01	0.89	0.91	0.33
95% CI		(0.78–1.15)	(0.83–1.23)	(0.72–1.10)	(0.73–1.13)	
<b>Protein<sup>b</sup></b>						
No. of cases	215	187	207	222	240	
RR	1.0	0.89	0.98	1.01	1.02	0.62
95% CI		(0.73–1.08)	(0.80–1.19)	(0.83–1.23)	(0.84–1.25)	
<b>Carbohydrates<sup>b</sup></b>						
No. of cases	232	207	220	199	213	
RR	1.0	0.94	1.00	0.90	0.88	0.53
95% CI		(0.78–1.15)	(0.82–1.22)	(0.73–1.11)	(0.72–1.09)	
<b>Energy, kcals<sup>b</sup></b>						
No. of cases	238	210	222	207	194	
RR	1.0	0.91	0.95	0.89	0.81	0.03
95% CI		(0.76–1.10)	(0.79–1.14)	(0.73–1.08)	(0.67–0.99)	

<sup>a</sup> P (Wald test) for continuous linear term.

<sup>b</sup> Adjusted for: age in months (underlying time variable); height (<63, 63–63.9, 64–65.9, ≥66 inches); age at menarche (<13, 13, ≥14, missing); combined age at menopause (45, 45–52, 53+) and use of postmenopausal hormones (never, past user, current <5 years, current ≥5 years); combined parity (nulliparous, 1–2, 3–4, 5+) and age at first birth (<25, 25–29, 30+); body mass index at age 18 (<19, 19–20.9, 21–22.9, ≥23, missing); weight change since age 18 (lost 2 kg or more, –2 to +2 kg, +2.1 to 5 kg, +5.1 to 10 kg, +10.1 to 20 kg, +20.1 to 25 kg, >25.1 + kg, missing); intake of total energy (quintiles); alcohol intake (none, <5 g/day, 5–14.9 g/day, 15+ g/day); family history of breast cancer (no, yes); and vitamin A (quintiles).

<sup>c</sup> Mutually adjusted for other fat subtypes.

CI, 0.74–1.16), and *trans* fatty acid (RR<sub>Q5 to Q1</sub>, 0.91; 95% CI, 0.73–1.13). This analysis showed a significant test for linear trend for decreased breast cancer rates with increased intake of saturated fat ( $P = 0.05$ ) and total energy ( $P = 0.03$ ).

Information of physical activity was available beginning in 1986. We performed a subanalysis (not in tables) that also controlled for six levels of physical activity, with follow-up from 1986 to 1994. Increased saturated fat intake was not associated with decreased breast cancer (RR<sub>Q5 to Q1</sub>, 0.98; 95% CI, 0.74–1.30;  $P$  for trend, 0.33). Controlling for physical activity level, those in the upper quintile of total energy still had lower rates (RR<sub>Q5 to Q1</sub>, 0.79; 95% CI, 0.62–1.00), but the linear trend across quintiles was no longer significant ( $P = 0.11$ ).

From 1990 to 1994, there were 23,946 postmenopausal women (193 cases) with no history of BBD who reported

having mammographic breast cancer screening in the previous follow-up interval. Among this subgroup (not in tables), none of the dietary fats were associated with increased rates of breast cancer.

In sequential models during the complete follow-up period (1980–1994), there was no association for total fat (RR, 0.99; 95% CI, 0.94–1.04), unsaturated fat (RR, 1.09, 95% CI, 0.96–1.14), oleic acid (RR, 0.96; 95% CI, 0.77–1.18), or linoleic acid (RR, 0.96; 95% CI, 0.73–1.25). In an additional model of saturated fat (RR, 0.87; 95% CI, 0.76–1.00), *trans* fatty acid (RR, 0.94, 95% CI, 0.84–1.06) and other unsaturated fat (RR, 1.07; 95% CI, 0.97–1.17), no component was associated with an increased risk of breast cancer.

Analyses using one dietary history that paralleled those of the BCDDP cohort by Velie *et al.* (1) included the 32,005

postmenopausal women with no history of BBD in the NHS between 1986 and 1992 (489 breast cancer cases). Although adding quadratic terms for total energy and body mass index did not improve the model fit within the NHS cohort ( $P = 0.29$ ), for comparison these models controlled for covariates in the same manner as the BCDDP study. Compared with women in the lowest quintile, those in the highest had no indication of increased breast cancer rates with total fat ( $RR_{Q5\ to\ Q1}$ , 1.00; 95% CI, 0.75–1.33), saturated fat ( $RR_{Q5\ to\ Q1}$ , 1.05; 95% CI, 0.76–1.45), unsaturated fat ( $RR_{Q5\ to\ Q1}$ , 0.94; 95% CI, 0.68–1.31), oleic acid ( $RR_{Q5\ to\ Q1}$ , 1.24; 95% CI, 0.79–1.94), linoleic acid ( $RR_{Q5\ to\ Q1}$ , 0.71; 95% CI, 0.50–1.00), and *trans* fatty acid ( $RR_{Q5\ to\ Q1}$ , 0.84; 95% CI, 0.61–1.18).

## Discussion

We did not find that increased intake of dietary fat or fat subtypes was associated with higher incidence of breast cancer among postmenopausal women without BBD in the NHS. However, there were reduced breast cancer rates with increased intake of saturated fat and total energy intake. The decline in rates with increased caloric intake may reflect greater physical activity. After controlling for physical activity, the association with saturated fat intake no longer persisted and the trend of decreased rates with increased energy intake was no longer significant ( $P = 0.11$ ).

Our findings were consistent with the reports from the pooled study of five prospective studies (2). However, all the data in the pooled analysis were based on one dietary assessment. Furthermore, the NHS comprised two (1980–1986 follow-up and 1986–1992 follow-up) of the five studies, and thus the results may not be completely independent for comparison. In contrast, from one baseline dietary assessment, Velie *et al.* (1) reported a nearly 2-fold increased risk with highest intake of oleic acid ( $RR_{Q5\ to\ Q1}$ , 1.82; 95% CI, 0.89–3.71) with a significant linear trend ( $P = 0.03$ ) in the BCDDP.

In many ways, the BCDDP and NHS cohorts are similar. Both study cohorts comprise volunteers, one from a mammographic screening program and the other from a long-term health study. Both study populations are predominately white, and the participants in both studies are generally healthier than the average United States population. In both studies, the dietary intake was assessed by the use of food-frequency questionnaires; additional information on multiple covariates has been collected in a prospective manner, and extensive efforts have gone into assuring minimal loss to follow-up in each cohort. All participants in the BCDDP had the opportunity to have an annual screening mammogram for up to 5 years between 1973 and 1980, whereas the uptake of mammographic screening in the NHS was somewhat later with 34% reporting as having had at least one screening mammogram by 1988 and 85% by 1994.

There were slight differences in how a history of BBD was defined for each cohort. For 13% within the BCDDP cohort, the diagnosis of BBD was based on self-report alone, with the rest having had a breast biopsy during or since the screening program or a recommendation for a biopsy during the screening program. In the NHS, any previous report of a physician's diagnosis of benign or fibrocystic disease was considered as a BBD diagnosis, and these women were excluded from these analyses restricted to women without BBD. The BCDDP study may have excluded more asymptomatic (mammographically detected) cases of BBD. If there are differences in dietary associations between women with and without BBD, and if women in the NHS had underreported their true history of

BBD, then our results may be biased to the null, explaining our lack of association. To address this issue, we performed an analysis restricted to women reporting a mammographic screening exam in the previous follow-up cycle. The results in this restricted analysis (1990–1994) did not differ substantially from the entire follow-up period from 1980 to 1994. These results suggest that women who have been mammographically screened and report no history of BBD do not differ that much from those who report no history of BBD with or without mammographic screening.

The different results from the two cohorts (NHS and BCDDP) may be attributable to true dietary differences in the cohorts, differences in the instruments used to assess dietary intake (12–17), residual confounding, different distributions of unknown effect modifiers, or the differing results may be within the range of expected variation based on the ability of such epidemiologic studies to assess dietary impact on disease. The correlations between saturated fat and linoleic acid (0.30 in the BCDDP and 0.10 in the NHS) or oleic acid (0.82 in the BCDDP and 0.70 in the NHS) were not substantially different in the two cohorts.

As part of the NHS, an extensive effort was made to assess dietary fat intake to allow the assessment of fat subtypes including the *trans* fatty acids. The Block FFQ used in the BCDDP had fewer separate questions for dietary sources of fat but did ascertain specific portion size information that was not obtained in the NHS FFQ (16). There seems to be a slight difference between the two cohorts in the foods that contribute to the intake of oleic acid. In the BCDDP, mayonnaise/salad dressing and margarine were the greatest contributors in descending order in each case to linoleic acid intake, whereas margarine and mayonnaise/salad dressing were the greatest contributors to oleic acid. In the NHS, the major contributors to each fat subtype only changed slightly over time. In 1986, the three largest contributors in the NHS to linoleic acid intake were mayonnaise, salad dressing (oil and vinegar), and margarine and to oleic acid intake, beef as a main dish, margarine, and sandwich beef. In 1990, the three largest contributors in the NHS to linoleic acid intake were mayonnaise, margarine, and salad dressing (oil and vinegar) and to oleic acid intake, beef as a main dish, margarine, and sandwich beef.

Velie *et al.* (1) proposed that one possible reason for the increased risk associated with higher intake of oleic acid in their study was that in the United States a major component of margarine is a hydrogenated form of oleic acid. The NHS analysis was able to address the impact of hydrogenated fats, in the evaluation of *trans* fatty acid intake and breast cancer risk. *Trans* fatty acids are the hydrogenated components from oleic acid, linoleic acid, and other fats. The major contributors to *trans* fatty acid intake in the NHS in 1986 were margarine (16.5%), sweet rolls or coffee cake (11.8%), beef (8.7%), french fries (6.7%), and chocolate chip cookies (5.1%). Intake of *trans* fatty acids was correlated with saturated fat intake (Pearson's  $r = 0.41$ ), unsaturated fat (0.53), linoleic acid (0.29), and oleic acid (0.64). There was no indication that a greater intake of hydrogenated fats (*trans* fatty acids) was associated with increased breast cancer risk in our analysis: a 1% change in percentage of energy from *trans* fatty acid was associated with a RR of 0.94 (95% CI, 0.84–1.06). As noted above, many of the fat subtypes are correlated as they often are found in the same food items. This collinearity between fat subtypes makes separation of effects difficult.

Several studies evaluated the relationship between dietary factors and having BBD, with inconsistent results. Some studies found higher fat intake was associated with increased risk of

BBD (18), and particularly atypical hyperplasia (19), but other studies have found no association (20, 21).

In conclusion, the association between greater intake of dietary fat intake, particularly unsaturated fat from oleic acid, and increased risk of breast cancer noted among postmenopausal women without a history of BBD within the BCDDP study was not seen within the NHS cohort. The width of the confidence intervals surrounding the point estimate for oleic acid in the NHS cannot rule out a slight increase in rates, although in this larger study effects of such magnitude seem unlikely. Possible explanations for the differences reported from these two cohorts include a reflection of true differences in the cohorts, which seems somewhat unlikely. There may be measurement differences related to differences in the dietary assessment tools, or there may be no real differences between these studies. Instead, these studies may be reflecting the range of plausible results epidemiological studies are able to detect. If there is a true association between dietary fat intake and breast cancer risk and misclassification of exposures is minimal, the magnitude of such an effect seems as if it would be quite small, given the size of the NHS and the inability to detect any association. The evaluation of this possible association in other populations of women without BBD will be of interest as will the evaluation with further follow-up within the BCDDP itself.

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