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Intake of flavonoids and risk of cancer in Finnish men: The Kuopio Ischaemic Heart Disease Risk Factor Study

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Limited amount of evidence suggests that high intake of flavonoids could be associated with decreased risk of lung and colorectal cancer, but more studies are needed. In this prospective cohort study, we assessed the relation between the intakes of 26 flavonoids from 5 subclasses; flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins, and the risk of lung, prostate and colorectal cancer. The study population consisted of 2,590 middle-aged eastern Finnish men of the prospective population-based Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. The mean intake of flavonoids was 131.0 ± 214.7 mg/day. During the mean follow-up time of 16.2 years, 62 lung, 138 prostate, and 55 colorectal cancers occurred. All lung cancer cases occurred among either current smokers ($n = 50$) or previous smokers ($n = 12$). After adjustment for age, examination years, body mass index, smoking status, pack-years of smoking, physical activity and intakes of alcohol, total fat, saturated fat, fiber, vitamin C and E, relative risk (RR) for lung cancer was 0.27 (95% CI: 0.11–0.66) for the highest quarter of total flavonoid intake as compared with the lowest quarter. Out of 5 flavonoid subclasses, flavonols and flavan-3-ols were associated with lung cancer, for the highest quarter of intake the RR were 0.29 (95% CI: 0.11–0.78) and 0.24 (95% CI: 0.09–0.64), respectively. No association between flavonoid intake and risk of prostate or colorectal cancer were found. We conclude that high intake of flavonoids is associated with decreased risk of lung cancer in middle-aged Finnish smoking men.

Key words: cohort study; cancer; flavonoids; Kuopio Ischaemic Heart Disease Risk Factor Study; lung cancer

Increasing evidence suggests that high consumption of fruit and vegetables decreases the risk of chronic diseases such as cancers.[1] Flavonoids are a large group of polyphenolic compounds (>5,000 identified) abundant in plant kingdom, and are thus one candidate of health promoter in them.[2] To date, only a few epidemiological studies on flavonoid intake and the risk of cancer have been published. Flavonoid intake has been associated with the decreased risk of lung[3–5] and colorectal[6–8] cancer in some, but not in all studies. For the other types of cancer, such as, stomach, urinary tract or prostate cancer no such association has been detected.[3–6]

Out of 10 subclasses of flavonoids, 5 subclasses (anthocyanidins, flavonols, flavones, flavan-3-ols and flavanones) have been estimated to contribute significantly for the daily intake, and thus being potential to have effects on health.[9,10] Previous epidemiological studies have concentrated mainly on 2 subclasses; flavonols and flavones, while the role of other subclasses, such as flavan-3-ols, has been only evaluated in a few studies. Studying the role of those flavonoid subclasses, which are considered to be relevant to the daily intake, has been difficult because of incomplete databases. Efforts to update databases are constantly made, *e.g.*, in 2003 United States Department of Agriculture (USDA) published a new food composition data which contained 5 subclasses; flavones, flavonols, flavan-3-ols, flavanones and anthocyanidins, a total of 26 flavonoids.[11]

Our aim was to assess whether the intakes of the most commonly consumed flavonoids are related with the risk of lung, prostate and colorectal cancer in Finnish men in a population-based cohort study.

Material and methods

Study population

The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study is an ongoing population-based study designed to investigate risk factors for cardiovascular diseases (CVD), atherosclerosis and related outcomes in middle-aged men from Eastern Finland.[12] The study was approved by the Research Ethics Committee, Hospital District of Northern Savo. A total of 2,682 participants (82.9% of those eligible), aged 42, 48, 54 or 60 years, were enrolled in the study between March 1984 and December 1989. All study subjects gave their written informed consent. Complete data for the present analysis were available for 2,590 men with no cancer at the study baseline.

Measurements

Subjects were instructed to abstain from ingesting alcohol for 3 days, from smoking and eating for 12 hr. Blood samples were drawn between 8 and 10 A.M. after the subject had rested in the supine position for 30 min. Blood was drawn with Terumo Venoject (Leuven, Belgium) vacuum tubes without tourniquet and LDL cholesterol and HDL cholesterol (Kone Instruments, Espoo, Finland), and triacylglycerols (Boehringer Mannheim, Mannheim, Germany) were determined from fresh serum samples using combined ultracentrifugation and precipitation. Maximal oxygen uptake was measured as previously described.[13] Body weight was measured using digital scale. Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m^2). Resting systolic blood pressure was measured by 2 trained nurses with a random-zero mercury sphygmomanometer (Hawksley, United Kingdom). The measuring protocol included, after supine rest of 5 min, 3 measurements in supine, 1 on standing and 2 in sitting position with 5-min intervals. The mean of all 6 measurements was used as the systolic blood pressure. The number of cigarettes, cigars and pipefuls of tobacco currently smoked daily, duration of regular smoking in years, alcohol consumption and medication were recorded with a self-administered questionnaire, which was checked by an interviewer. A subject was defined a smoker if he had ever smoked cigarettes, cigars, or a pipe on a regular basis.

Classification of cancers

Since 1953, cancers diagnosed in Finland have been reported to the Finnish Cancer Registry. Coverage of the national cancer registry is virtually complete with no losses to follow-up.[14] Our cohort study was record-linked with the Cancer Registry data by using the Finnish personal identification code (social security number) given to all residents of Finland since 1967. All cancer diagnoses that occurred between the study entry (March 1984–December 1989) and December 31, 2005 were included. Deaths were ascertained by linkage to the national causes of death register using the personal identifiers. In 2003, 93% of cancer cases diagnosed in Finland were microscopically verified.[15]

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TABLE I – CHARACTERISTICS OF THE 2,590 STUDY SUBJECTS ACCORDING TO THE QUARTERS OF ENERGY-ADJUSTED FLAVONOID INTAKE[1]

	Quarters of flavonoid intake (mg/day)				p^2
	1 (Lowest)	2	3	4 (Highest)	
Mean flavonoid intake, not energy adjusted (mg/day)	9.1 ± 10.1	16.3 ± 15.8	82.7 ± 46.8	416.3 ± 265.0	
Mean flavonoid intake, energy adjusted (mg/day)	0.0 ± 16.8	25.6 ± 8.3	90.2 ± 37.6	415.8 ± 260.6	
Age (yr)	52.6 ± 5.2	53.6 ± 5.0	53.2 ± 5.0	52.7 ± 5.3	0.001
Body mass index (kg/m^2)	26.7 ± 3.6	27.1 ± 3.6	27.0 ± 3.6	26.7 ± 3.6	0.092
Systolic blood pressure (mmHg)	134 ± 17	135 ± 17	134 ± 17	134 ± 17	0.261
Serum total cholesterol (mmol/L)	5.93 ± 1.04	6.00 ± 1.15	5.84 ± 1.08	5.86 ± 1.01	0.034
Serum LDL cholesterol (mmol/L)	4.08 ± 1.00	4.11 ± 1.07	3.96 ± 1.03	4.02 ± 0.92	0.039
Serum HDL cholesterol (mmol/L)	1.32 ± 0.30	1.28 ± 0.31	1.30 ± 0.31	1.28 ± 0.29	0.072
Serum triacylglycerols (mmol/L)	1.24 ± 0.71	1.37 ± 0.79	1.34 ± 0.83	1.30 ± 0.91	0.034
Maximal oxygen uptake (mL/(kg min))	30.8 ± 7.4	29.6 ± 7.5	30.4 ± 7.6	30.9 ± 7.8	0.006
Smokers (%)	39.4	35.8	30.7	21.5	<0.001
Alcohol intake (g/week)	80.7 ± 128.1	76.8 ± 120.7	74.6 ± 155.1	66.2 ± 133.2	0.263
Fat intake (% of total energy)	40.5 ± 6.5	38.9 ± 6.6	37.7 ± 6.3	38.1 ± 5.8	<0.001
Saturated fatty acid intake (% of total energy)	19.5 ± 4.5	18.0 ± 4.4	17.1 ± 4.2	17.5 ± 3.9	<0.001
Carbohydrate intake (% of total energy)	41.6 ± 6.7	42.7 ± 7.0	43.9 ± 6.8	44.1 ± 6.3	<0.001
Fiber intake (g/d)[3]	23.8 ± 8.3	24.6 ± 6.4	25.9 ± 7.0	26.0 ± 7.0	<0.001
Folate intake (μg/d)[3]	235.6 ± 53.4	246.6 ± 49.3	261.6 ± 58.7	272.6 ± 59.2	<0.001
Vitamin C intake (mg/d)[3]	55.8 ± 39.7	68.8 ± 44.2	85.3 ± 56.8	78.4 ± 52.0	<0.001
Vitamin E intake (mg/d)[3]	8.5 ± 2.7	8.7 ± 2.2	9.2 ± 2.4	9.2 ± 2.5	<0.001
Events, number (%)					
Lung cancer	28 (4.3%)	17 (2.6%)	10 (1.5%)	7 (1.1%)	0.001
Prostate cancer	31 (4.8%)	31 (4.8%)	36 (5.6%)	40 (6.2%)	0.625
Colorectal cancer	15 (2.3%)	12 (1.9%)	9 (1.4%)	19 (2.9%)	0.252

[1]$\bar{x}$ ± SD.–[2]p-value from the ANOVA (continuous variables) or p value from χ-square test (discrete variables).–[3]Adjusted for energy intake.

Assessment of nutrient intake

The consumption of foods was assessed at the study baseline with an instructed 4-day food recording by household measures. The instructions were given and the completed food records were checked by a nutritionist. The intakes of nutrients were estimated using the NUTRICA® version 2.5 software. The intakes of nutrients were energy-adjusted by the residual method.[16] Energy adjustment is based on the notion that a larger, more physically active person requires a higher caloric intake, which is associated with a higher absolute intake of all nutrients. Therefore, energy adjustment takes into account differences in the energy requirements among individuals. The residuals were standardized by the mean nutrient intake of a subject consuming 10 MJ/day, the approximate average total energy intake in this study population. The measurement of total, subclass and individual flavonoid intake was mainly based on USDA flavonoid database.[11] Database includes total of 26 flavonoids from 5 subclasses; flavonols (quercetin, kaempferol, myricetin, isorhamnetin), flavones (luteolin, apigenin), flavanones (hesperitin, naringenin, eriodictyol), flavan-3-ols [(+)-catechin, (+)-gallocatechin, (−)-epicatechin, (−)-epigallocatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin-3-gallate, theaflavin, theaflavin-3-gallate, theaflavin-3′-gallate, theaflavin-3,3′-digallate, thearubigins] and anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin). The USDA database is incomplete for anthocyanidin-rich berries, which are commonly consumed in Finland. Therefore, additional anthocyanidin data for those Finnish berries were derived from the work conducted by Kähkönen *et al.*[17]

Statistical analysis

The data are expressed as mean ± SD. The heterogeneity of the means of baseline variables between the quarters of total flavonoid intake was tested by using the analysis of variance (ANOVA) and frequency distribution of the categorical variables between quarters of the total flavonoid intake was compared by the χ^2 test. Subjects were classified into quartiles according to their energy-adjusted flavonoid intake, and the relationship of flavonoid intake with the relative risk (RR) of cancer incidence was analyzed using Cox proportional hazards models. Model 1 was adjusted for age and examination years, and Model 2 in addition to BMI, smoking status, pack-years of smoking, physical activity, intake of alcohol, total fat (percent of energy, *E%*), saturated fat (percent of energy, *E%*) and energy-adjusted intake of fiber and vitamins C and E. RRs were estimated as antilogarithms of coefficients for independent variables. The confidence intervals (CI) were estimated based on the assumption of asymptotic normality of estimates. All the statistical tests were 2-tailed. Data were analyzed using SPSS for Windows version 14.0 statistical software (SPSS, Chicago, IL).

Results

The mean intake of flavonoids was 131.0 ± 214.7 mg/day, and flavonoid subclasses contributed to the total intake as follows: flavan-3-ols 86% (112.3 mg/day); flavonols 7% (9.5 mg/day); anthocyanidins 5% (5.9 mg/day); flavanones 2% (2.9 mg/day) and flavones less than 1% (0.3 mg/day). Men who had high intake of flavonoids were less likely to be a smoker, had lower intakes of alcohol, total fat and saturated fatty acids (SAFA), but had higher intakes of polyunsaturated fatty acids (PUFA), carbohydrates, folate, fiber and vitamins C and E (Table I).

During the mean follow-up time of 16.2 years, 62 lung, 138 prostate and 55 colorectal cancers occurred. In a Cox proportional hazards model adjusted for age and examination years (Model 1), the RR for the lung cancer in the highest quarter of total flavonoid intake was 0.24 (95% CI: 0.11–0.55) when compared with the lowest quarter. Out of flavonoids subclasses, the intakes of flavonols (RR 0.20 [95% CI: 0.09–0.50]) and flavan-3-ols (RR 0.24 [95% CI: 0.10–0.60]) were significantly associated with the decreased risk of lung cancer.

After further adjustment for smoking, BMI, physical activity, intake of alcohol, total fat, saturated fat, fiber and vitamins C and E, the RR for the lung cancer in the highest quarter of total flavonoid intake was 0.27 (95% CI: 0.11, 0.66) when compared with the lowest quarter (Table II). The RR for the flavonol and flavan-3-ol intakes were 0.29 (95% CI: 0.11–0.78) and 0.24 (95% CI: 0.09–0.64), respectively. The intakes of other subclasses, anthocyanidins, flavanones or flavones, were not associated with the risk of lung cancer (Table II).

All the lung cancer cases occurred among either current smokers (n = 50) or previous smokers (n = 12), and therefore, we repeated the analyses among current or previous smokers (n = 1,910). In comparison between smokers *versus* never smokers, smokers had lower intake of flavonoids (120.5 ± 201.4 *vs.* 160.4 ± 242.6 mg, $p < 0.001$). In addition, smokers had higher intakes of alcohol (139.3 ± 77.6 *vs.* 87.2 ± 148 g/week, $p < 0.001$), total

TABLE II – RELATIVE RISKS AND 95% CONFIDENCE INTERVALS OF LUNG, PROSTATE AND COLORECTAL CANCERS ACCORDING TO THE QUARTERS OF ENERGY-ADJUSTED FLAVONOID INTAKE[1]

	Quarters of flavonoid intake (mg/day)				
	1 (Lowest)	2	3	4 (Highest)	*p* for trend
Lung cancer					
Flavonols	1	0.58 (0.30–1.13)	0.59 (0.29–1.21)	0.29 (0.11–0.78)	0.055
Flavones	1	1.68 (0.78–3.63)	1.19 (0.53–2.63)	1.36 (0.62–3.01)	0.876
Flavanones	1	1.28 (0.62–2.64)	1.24 (0.59–2.60)	1.16 (0.51–2.65)	0.774
Flavan-3-ols	1	0.84 (0.46–1.54)	0.46 (0.21–0.99)	0.24 (0.09–0.64)	0.003
Anthocyanidins	1	0.99 (0.49–1.96)	1.03 (0.51–2.10)	0.80 (0.36–1.78)	0.514
Total sum of flavonoids	1	0.62 (0.33–1.17)	0.44 (0.20–0.95)	0.27 (0.11–0.66)	0.003
Prostate cancer					
Flavonols	1	0.86 (0.52–1.40)	0.78 (0.47–1.29)	0.99 (0.61–1.62)	0.661
Flavones	1	1.10 (0.69–1.76)	0.97 (0.60–1.57)	0.73 (0.44–1.22)	0.183
Flavanones	1	1.14 (0.69–1.89)	1.36 (0.83–2.23)	1.10 (0.64–1.89)	0.587
Flavan-3-ols	1	0.96 (0.58–1.58)	0.92 (0.56–1.52)	1.13 (0.70–1.82)	0.941
Anthocyanidins	1	1.14 (0.67–1.91)	1.30 (0.77–2.17)	1.41 (0.85–2.33)	0.178
Total sum of flavonoids	1	0.90 (0.54–1.50)	0.99 (0.60–1.62)	1.14 (0.70–1.84)	0.970
Colorectal cancer					
Flavonols	1	0.68 (0.30–1.58)	0.86 (0.38–1.97)	1.53 (0.72–3.23)	0.585
Flavones	1	1.26 (0.59–2.68)	1.16 (0.54–2.50)	0.71 (0.30–1.65)	0.561
Flavanones	1	0.84 (0.36–1.98)	1.80 (0.85–3.85)	0.90 (0.37–2.20)	0.518
Flavan-3-ols	1	1.04 (0.48–2.28)	0.80 (0.34–1.86)	1.37 (0.65–2.89)	0.820
Anthocyanidins	1	0.69 (0.30–1.60)	1.62 (0.80–3.31)	0.59 (0.24–1.41)	0.974
Total sum of flavonoids	1	0.74 (0.34–1.60)	0.52 (0.22–1.23)	1.16 (0.58–2.34)	0.831

[1]Adjusted for age and examination years, BMI, smoking status, pack-years of smoking, physical activity, intakes of alcohol, total fat (percent of energy, *E*%) and saturated fat (percent of energy, *E*%), and energy adjusted intake of fiber, vitamin C and E.

fat (39.1 ± 6.6 *vs.*37.8 ± 5.6 *E*%, $p < 0.001$), and had lower maximal oxygen uptake (29.7 ± 7.3 *vs.* 32.6 ± 8.0 ml/(kg min), $p < 0.001$), lower intakes of fiber (24.6 ± 7.2 *vs.* 26.4 ± 7.3 g/day, $p < 0.001$) and vitamin C (69.5 ± 48.8 *vs.* 79.3 ± 51.9 mg/day, $p < 0.001$). Among smokers, the multivariate-adjusted RR for the highest quarter intake of total flavonoids, flavonols and flavan-3-ols were 0.32 (95% CI: 0.13–0.78), 0.34 (95% CI: 0.13–0.92) and 0.29 (95% CI: 0.11–0.76) when compared with the lowest quarter.

Flavonoid intake was not associated with the risk of prostate or colorectal cancer. The RR for the total flavonoid intake and prostate and colorectal cancers were 1.14 (95% CI: 0.70–1.84) and 1.16 (95% CI: 0.58–2.34), respectively.

Discussion

The aim of our study was to assess the role of flavonoids with regard to the risk of lung, prostate and colorectal cancer in the middle-aged Finnish men in a population-based prospective cohort study. The main finding of our study was that the high intake of flavonoids, a sum of 26 compounds, was associated with a decreased risk of lung cancer in smokers (current or former). In the further analysis, out of 5 flavonoid subclasses, significant inverse association was found for flavan-3-ols and flavonols. The associations were strong, linear and not attenuated by extensive adjustment for risk factors of cancer. For the other subclasses (flavones, flavanones and anthocyanidins), no associations were found. The lack of association is likely explained by the fact that altogether the intake of these subclasses was less than 10% of the total intake, and thus the association could be too weak to be detected. On the other hand, flavonoids differ in their chemical structure and properties, and thus in theory, different compounds could have different effects on human health.[2] Neither the total flavonoid intake nor intakes of subclasses were associated with the risk of either prostate or colorectal cancer.

A strength of our study was that due to the complete follow-up system of cancer cases in the Finnish population with no losses to follow-up.[14] We also assessed the role of a total of 26 flavonoids from 5 subclasses instead of 1–2 subclasses evaluated in most of the previous studies. Nutrient intake was assessed with 4-day food recording, which has some limitations. The intake of flavonoids may vary between different seasons, being highest in summer and autumn, when vegetables are consumed in high amounts. Seasonal variation may have caused some misclassification of subjects and therefore underestimation in the relation between flavonoid intake and the risk of cancer. The main limitation of our study was relatively small number of cases (a total of 62 lung cancer cases of which 50 occurred among smokers and 12 among ex-smokers). Although the number of prostate and colorectal cases was similar to lung cancers, the statistical association of flavonoids with lung cancer was very strong, and power to detect a smaller, but still important effect for the other cases was limited.

Several epidemiological studies have evaluated the role of flavonoids in cancer. Studies have suggested that high intake of flavonoids could be associated with a decreased risk of lung[3–5] and colorectal cancer,[6–8] while for other types of cancer association have mainly not been found. Epidemiological evidence about the protective effects against lung cancer has been provided mainly by the Finnish studies. Knekt *et al.* found in the Finnish Mobile Clinic Health Examination Survey that the flavonoid intake was associated with 44% decreased risk of lung cancer in men and women.[3] Later, in the same cohort they found similar association for quercetin.[5] In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, Hirvonen *et al.* found the intakes of flavonols and flavones to be associated with the decreased lung cancer risk among male smokers.[4] On the other hand, no significant association were found in the Iowa Women's Health study, a large cohort consisting of total of 34,651 postmenopausal women,[6] Zutphen Elderly Study,[18] cross-sectional analysis of Seven Country Study[19] or case–control studies conducted in Hawaii,[20] Greece[21] or Spain.[22] Inconsistency in the findings on cancer may be partly explained by the differences in the study design or population studied, *e.g.*, age and gender.

The intake of apples, which are rich in flavonols and flavan-3-ols, has been linked with the decreased risk of lung cancer.[3,18,20] In the Finnish Mobile Clinic Health Examination Survey, of food sources of flavonoids, the association was strongest for apples.[3] Arts *et al.* did not found association for catechins and lung cancer in the Zutphen Elderly Study, but they found inverse trend for other dietary sources of catechins than tea. Inverse association was also found for apples and onions in a case–control study conducted in Hawaii.[20] Limitation of our study was that we were not able to study further whether particular food sources of flavonoids, such as apples, would be associated with the lung cancer risk.

In addition to lung cancer, limited evidence suggests that flavonoid intake could be associated with a decreased risk of colorectal cancer.[6–8] However, majority of the studies,[3–5,23] including large epidemiological cohorts ATBC, Finnish Mobile Clinic Health Examination Survey and Nurses Health study, as well as our study, have not provided evidence about the protective effects of flavonoids against colorectal cancer.

Flavonoid intake does not seem to be associated with the risk of prostate cancer, as no association has been reported in cohort[3–6] or case–control studies.[24] Similarly, our findings are in line with these studies as we did not detect association between flavonoid intake and risk of prostate cancer.

The etiology of cancers is distinct and may, at least partly, explain why flavonoid intake seems to be related especially with lung cancer. Smoking is the main risk factor for lung cancer, while it has probably much smaller role, if any, in prostate or colorectal cancers. It has been suggested that flavonoids, as well as other antioxidants, could be especially protective when biological system is under high carcinogen exposure.

Flavonoids have several properties that may provide protection against lung cancer. First, flavonoids are powerful antioxidants *in vitro* and thus could prevent the damage of DNA and inhibit tumor promotion.[25] However, the evidence *in vivo* is conflicting and the effects of flavonoids on oxidative stress in humans still remains to be under debate.[26] In addition, flavonoids have been suggested to act through inhibition of cell proliferation, induction of cell apoptosis, and reduction of angiogenesis.[27]

Alternatively, it has been often suggested that the high intake of flavonoids could merely be an overall marker of healthy lifestyle rather than causative factor. In our study, subjects with the high intake were less likely to be a smoker, had lower intakes of total fat, and SAFA and higher intakes fiber, vitamin C and E. Therefore, despite extensive statistical adjustment for risk factors of cancer, we cannot exclude the possibility that the protection is at least partly result of a residual confounding.

In our study, we assessed the role of the most common flavonoids in Western diet, a total of 26 flavonoids from 5 subclasses. Previous studies have concentrated on flavonols and flavones, and only a few have studied the role of monomeric catechins from flavan-3-ol subclass.[6,18] A recent Greek study included also polymeric flavan-3-ols, proanthocyanidins, flavanones and anthocyanidins[21] in the analyses. Further studies are still needed to verify the role of flavonoids in lung cancer, especially in other than Finnish populations. In addition to flavonoids, simple phenolic compounds may also play a role in various types of cancers. It has been estimated that simple phenolic compounds may account as high as 1/3 of the total daily intake of phenolic compounds[28] and therefore, the databases should be updated to include also simple phenolic compounds.

We conclude that the high intake of flavonoids is associated with the decreased risk of lung cancer among smokers in the population-based cohort of middle-aged Finnish men.

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