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Fruit and Vegetable Intakes Are Associated with Lower Risk of Bladder Cancer among Women in the Multiethnic Cohort Study[1,2]

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Abstract

Fruits and vegetables have been examined for their possible effects on the risk of bladder cancer, as they contain numerous nutrients, phytochemicals, and antioxidants with potentially anticarcinogenic properties. In a prospective analysis of 185,885 older adults participating in the Multiethnic Cohort Study, we examined whether the consumption of fruits and vegetables, or of nutrients concentrated in fruits and vegetables, was associated with bladder cancer risk. Cox proportional hazards models were used to calculate HRs and 95% CIs for bladder cancer in relation to dietary intakes. A total of 581 invasive bladder cancer cases (429 men and 152 women) were diagnosed over a mean follow-up period of 12.5 y. In women, total fruits and vegetables [HR = 0.35 (95% CI: 0.22, 0.56); highest vs. lowest quartile], total vegetables [HR = 0.49 (95% CI: 0.29, 0.83)], yellow-orange vegetables [HR = 0.48 (95% CI: 0.30, 0.77)], total fruits [HR = 0.54 (95% CI: 0.34, 0.85)], and citrus fruits [HR = 0.56 (95% CI: 0.34, 0.90)] were inversely associated with the risk of invasive bladder cancer in risk factor-adjusted models. In addition, women with the highest intakes of vitamins A, C, and E; the carotenoids α-carotene, β-carotene, and β-cryptoxanthin; and folate had a lower risk of bladder cancer. For men, no associations for fruits, vegetables, or nutrients were found overall, although inverse associations were observed for vegetable intake among current smokers, and in ethnic-specific analyses, for fruit and vegetable intake among Latinos specifically. Our findings suggest that greater consumption of fruits and vegetables may lower the risk of invasive bladder cancer among women and highlight the need for specific subgroup analyses in future studies. J. Nutr. 143: 1283–1292, 2013.

Introduction

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, with an estimated 73,510 new cases and 14,880 deaths occurring annually (1). Tobacco smoking is the most established risk factor for bladder cancer (2), with ~50% of newly diagnosed cases estimated to be attributable to the effects of smoking (3). Although occupational exposures and, in areas with endemic rates of infection, schistosomiasis have been consistently associated with bladder cancer risk (4,5), the evidence with respect to other environmental exposures in the etiology of this disease is less consistent.

Dietary factors have been examined in several previous epidemiological studies (6,7), because they provide an abundant source of nutrients and phytochemicals with potentially anticarcinogenic properties. However, in a recent consensus report, the World Cancer Research Fund (WCRF)[8]/American Institute of Cancer Research (AICR) concluded that the evidence was limited with respect to a role of fruits and vegetables in the development of bladder cancer (8). Since the 2007 WCRF/AICR report, several case-control studies have reported inverse associations for fruits and/or vegetables with the risk of bladder cancer (9–13); however, RRs have generally failed to depart from unity in prospective cohort studies (14,15).

Because previous prospective studies have been conducted primarily in ethnically homogeneous populations of European ancestry, the Multiethnic Cohort (MEC) Study provides an opportunity to expand research on the diet-bladder cancer relationship. Therefore, the aim of our study was to examine prospectively whether greater consumption of fruits and vegetables, or of nutrients concentrated in fruits and vegetables, was associated with the risk of bladder cancer in a population of older adults from diverse ethnic backgrounds.

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[8] Abbreviations: AIRC, American Institute of Cancer Research; MEC, Multiethnic Cohort; QFFQ, quantitative FFQ; WCRF, World Cancer Research Fund.

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Participants and Methods

Study population. The MEC Study is a longitudinal study designed to investigate the associations of dietary, lifestyle, and genetic factors with the incidence of cancer and was previously described in detail (16). Briefly, the cohort was established from 1993 to 1996 by mailing a self-administered, 26-page questionnaire to men and women aged 45–75 y who were residing in Hawaii and California. More than 215,000 adults comprised of 5 main ethnic groups (African Americans, Japanese Americans, Latinos, Native Hawaiians, and whites) voluntarily completed the baseline questionnaire indicating their consent to participate in the study. The study protocol was approved by the institutional review boards of the University of Hawaii and the University of Southern California. For the present study, data were available for 185,885 participants after excluding those who: *1*) were not in 1 of the 5 main ethnic groups recruited into the study (n = 13,989); *2*) reported implausible dietary values based on total energy intake or its components (n = 8263) (17); *3*) were identified through either the questionnaire or tumor registry linkage to have had a diagnosis of cancer of the bladder prior to cohort entry (n = 292); or *4*) had missing data on any of the following key covariates: smoking status, duration and intensity of cigarette smoking, or occupational history (n = 7353).

Cohort follow-up and case identification. Follow-up began on the date of questionnaire completion and accrued until a diagnosis of bladder cancer, death, or the last follow-up date for this analysis (December 31, 2007). Routine linkages to the Surveillance, Epidemiology, and End Results cancer registries for California and Hawaii were conducted to identify incident cases diagnosed over the follow-up period. Routine linkages to the California and Hawaii death certificate files as well as to the National Death Index were conducted to identify deaths during the follow-up period. For the entire cohort, the average out-migration rate for members was only 3.7% after 7 y and 7.6% after 15 y of follow-up, with California as the primary relocation destination for Hawaiian participants. Thus, case ascertainment is thought to be close to complete. The primary outcome for this analysis, invasive bladder cancer, was classified using the International Classification of Diseases for Oncology, Third Edition codes C67.0-C67.9 and was restricted to invasive malignancies. A total of 581 incident invasive bladder cancer cases were diagnosed over a mean follow-up period of 12.5 y. In a secondary outcome analysis, we expanded the case status to include incident in situ cases (n = 1137 total; n = 556 in situ).

Dietary assessment. Dietary intake was measured at baseline by using a quantitative FFQ (QFFQ) that assessed the frequency and quantity of food items consumed during the preceding year (16). Grams of food consumed were calculated from single food items and mixed dishes. Mixed dishes were first disaggregated to the ingredient level using a customized recipe database. Nutrient intakes were computed using the food composition tables developed and maintained by the University of Hawaii Cancer Center. Foods and food groups included in this analysis were: total fruits and vegetables, total vegetables, light green vegetables, dark green vegetables, yellow-orange vegetables, cruciferous vegetables, total fruits, fruit juice, citrus fruits, and yellow-orange fruits. Nutrients

TABLE 1 Baseline characteristics of the study sample by bladder cancer status[1]

	Men		Women	
	Invasive bladder cancer	Entire cohort	Invasive bladder cancer	Entire cohort
Participants, *n*	429	83,694	152	102,191
Age at cohort entry, *y*	65.3 ± 7.1	60.2 ± 8.9	64.4 ± 8.2	59.7 ± 8.9
Ethnicity, *%*				
African American	12.4	13.7	36.2	19.7
Native Hawaiian	3.5	7.0	7.9	7.5
Japanese American	31.5	30.2	18.4	27.7
Latino	18.2	23.6	14.5	20.7
White	34.5	25.5	23.0	24.4
Education, *y*	12.8 ± 3.3	13.3 ± 3.3	12.9 ± 3.0	13.1 ± 3.2
BMI, *kg/m²*	25.9 ± 3.6	26.6 ± 4.2	26.9 ± 6.0	26.5 ± 5.8
Smoking status, *%*				
Never	20.5	30.8	36.8	56.7
Former	55.7	51.1	36.2	29.0
Current	23.8	18.2	27.0	14.3
Pack-years of cigarette smoking[2]	27.5 ± 17.3	20.6 ± 16.6	20.9 ± 14.3	15.5 ± 14.3
High-risk industry,[3] *%*	2.1	1.7	0.7	1.0
Family history of bladder cancer, *%*	0.9	0.5	2.0	0.8
Alcohol, *g/d*	16.0 ± 32.1	14.6 ± 32.4	6.4 ± 14.0	4.3 ± 14.9
Total energy, *kcal/d*	2260 ± 1100	2380 ± 1100	1990 ± 1060	1940 ± 940
Food intake, *g/(1000 kcal · d)*				
Fruits and vegetables	290 ± 141	292 ± 144	325 ± 163	373 ± 174
Total vegetables	142 ± 67.4	147 ± 71.6	151 ± 65.6	177 ± 87.6
Light green vegetables	31.9 ± 22.5	31.8 ± 22.3	36.2 ± 22.0	41.5 ± 29
Dark green vegetables	18.2 ± 16.5	19.4 ± 18.1	22.7 ± 17.4	27.1 ± 24.5
Yellow-orange vegetables	11.9 ± 12.0	12.3 ± 13.1	13.9 ± 14.8	17.8 ± 18.1
Cruciferous vegetables	19.0 ± 16.7	20.3 ± 19.6	23.4 ± 19.1	27.9 ± 25.7
Total fruits	149 ± 110	145 ± 113	174 ± 133	196 ± 139
Fruit juice	34.6 ± 42.6	37.4 ± 49.2	37.7 ± 47.7	45.1 ± 57.5
Citrus fruits	57.9 ± 63.0	57.2 ± 67.4	59.3 ± 67.0	73.2 ± 81.5
Yellow-orange fruits	23.0 ± 29.4	20.8 ± 28.0	30.9 ± 37.4	32.5 ± 38.7

[1] Values are percentages or means ± SDs.
[2] For current and former smokers only.
[3] Employed ≥10 y in rubber or tire manufacturing, plastic production or processing, or pesticide production.

TABLE 2 HRs and 95% CIs for invasive bladder cancer according to dietary pattern and food intake

	Men (n = 83,694)			Women (n = 102,191)			
	Cases	HR (95% CI)[1]	HR (95% CI)[2]	Cases	HR (95% CI)[1]	HR (95% CI)[2]	P-interaction[3]
Dietary pattern (factor score)							
Vegetables pattern							
Quartile 1	128	1.00	1.00	44	1.00	1.00	
Quartile 2	118	0.98 (0.76, 1.26)	1.06 (0.82, 1.37)	37	0.69 (0.44, 1.08)	0.73 (0.47, 1.14)	
Quartile 3	102	0.86 (0.65, 1.13)	0.98 (0.74, 1.30)	47	0.78 (0.50, 1.20)	0.86 (0.55, 1.33)	
Quartile 4	81	0.70 (0.51, 0.96)	0.85 (0.62, 1.17)	24	0.34 (0.20, 0.59)	0.40 (0.23, 0.69)	
P-trend[4]		0.02	0.33		<0.001	0.004	0.14
Fruit and milk pattern							
Quartile 1	111	1.00	1.00	38	1.00	1.00	
Quartile 2	110	0.96 (0.73, 1.25)	1.09 (0.83, 1.42)	35	0.69 (0.43, 1.10)	0.78 (0.49, 1.25)	
Quartile 3	108	0.93 (0.71, 1.24)	1.13 (0.85, 1.50)	38	0.63 (0.39, 1.01)	0.76 (0.47, 1.22)	
Quartile 4	100	0.95 (0.70, 1.29)	1.26 (0.92, 1.72)	41	0.57 (0.34, 0.94)	0.75 (0.45, 1.25)	
P-trend[4]		0.67	0.17		0.03	0.30	0.18
Foods [g/(1000 kcal · d)]							
Fruits and vegetables							
<216	145	1.00 (ref)	1.00 (ref)	45	1.00 (ref)	1.00 (ref)	
216–308	116	0.80 (0.63, 1.03)	0.92 (0.72, 1.18)	40	0.63 (0.41, 0.96)	0.69 (0.45, 1.06)	
309–425	104	0.81 (0.62, 1.04)	0.98 (0.76, 1.28)	35	0.41 (0.26, 0.64)	0.48 (0.31, 0.76)	
≥426	64	0.67 (0.50, 0.90)	0.87 (0.64, 1.17)	32	0.28 (0.18, 0.45)	0.35 (0.22, 0.56)	
P-trend[4]		0.01	0.48		<0.001	<0.001	<0.001
Total vegetables							
<107	135	1.00	1.00	33	1.00	1.00	
107–147	126	1.02 (0.80, 1.29)	1.08 (0.85, 1.38)	53	1.38 (0.89, 2.13)	1.43 (0.92, 2.21)	
148–200	101	0.92 (0.71, 1.19)	1.01 (0.78, 1.31)	42	0.92 (0.58, 1.46)	0.99 (0.62, 1.56)	
≥201	67	0.77 (0.57, 1.03)	0.89 (0.66, 1.19)	24	0.44 (0.26, 0.75)	0.49 (0.29, 0.83)	
P-trend[4]		0.06	0.39		<0.001	<0.001	0.004
Light green vegetables							
<19.3	134	1.00	1.00	31	1.00	1.00	
19.3–30.4	121	0.95 (0.74, 1.22)	1.03 (0.80, 1.32)	44	1.18 (0.75, 1.88)	1.23 (0.78, 1.96)	
30.5–47.1	107	0.90 (0.69, 1.16)	1.01 (0.78, 1.31)	39	0.88 (0.55, 1.42)	0.95 (0.59, 1.54)	
≥47.2	67	0.68 (0.51, 0.92)	0.80 (0.59, 1.08)	38	0.70 (0.43, 1.14)	0.78 (0.48, 1.27)	
P-trend[4]		0.01	0.14		0.04	0.11	0.23
Dark green vegetables							
<10.0	143	1.00	1.00	24	1.00	1.00	
10.0–17.0	118	0.94 (0.73, 1.20)	1.00 (0.79, 1.28)	47	1.63 (0.99, 2.66)	1.66 (1.01, 2.72)	
17.1–29.4	104	0.93 (0.72, 1.20)	1.02 (0.79, 1.32)	44	1.21 (0.73, 1.99)	1.26 (0.76, 2.09)	
≥29.5	64	0.70 (0.52, 0.94)	0.80 (0.60, 1.09)	37	0.80 (0.47, 1.34)	0.87 (0.52, 1.46)	
P-trend[4]		0.02	0.17		0.03	0.07	0.48
Yellow-orange vegetables							
<5.6	144	1.00	1.00	44	1.00	1.00	
5.6–10.4	121	0.87 (0.68, 1.11)	0.94 (0.74, 1.20)	34	0.64 (0.41, 1.01)	0.69 (0.44, 1.09)	
10.5–19.4	93	0.75 (0.58, 0.97)	0.86 (0.66, 1.12)	42	0.65 (0.42, 0.99)	0.73 (0.48, 1.13)	
≥19.5	71	0.70 (0.52, 0.93)	0.84 (0.63, 1.12)	32	0.40 (0.25, 0.63)	0.48 (0.30, 0.77)	
P-trend[4]		0.01	0.21		<0.001	0.005	0.03
Cruciferous vegetables							
<10.1	135	1.00	1.00	30	1.00	1.00	
10.1–17.9	122	0.98 (0.76, 1.26)	1.05 (0.82, 1.35)	46	1.21 (0.76, 1.93)	1.27 (0.79, 2.02)	
18.0–30.8	105	0.92 (0.71, 1.00)	1.02 (0.78, 1.33)	39	0.84 (0.51, 1.37)	0.90 (0.55, 1.47)	
≥30.9	67	0.70 (0.52, 0.95)	0.81 (0.60, 1.10)	37	0.63 (0.38, 1.03)	0.70 (0.42, 1.15)	
P-trend[4]		0.02	0.16		0.007	0.02	0.27
Total fruits							
<77.4	135	1.00	1.00	42	1.00	1.00	
77.4–144	102	0.71 (0.55, 0.92)	0.81 (0.62, 1.05)	35	0.61 (0.39, 0.96)	0.69 (0.44, 1.09)	
145–238	118	0.88 (0.68, 1.13)	1.07 (0.83, 1.38)	34	0.45 (0.29, 0.72)	0.55 (0.35, 0.88)	
≥239	74	0.69 (0.52, 0.92)	0.89 (0.66, 1.19)	41	0.42 (0.27, 0.65)	0.54 (0.34, 0.85)	
P-trend[4]		0.05	0.82		<0.001	0.01	0.02

(Continued)

TABLE 2 *Continued*

	Men (*n* = 83,694)			Women (*n* = 102,191)			
	Cases	HR (95% CI)[1]	HR (95% CI)[2]	Cases	HR (95% CI)[1]	HR (95% CI)[2]	*P*-interaction[3]
Fruit juice							
<4.7	120	1.00	1.00	37	1.00	1.00	
4.7–20.2	108	0.94 (0.72, 1.22)	1.01 (0.78, 1.31)	42	1.18 (0.76, 1.84)	1.28 (0.82, 2.00)	
20.3–59.6	111	0.98 (0.76, 1.27)	1.10 (0.85, 1.42)	38	0.89 (0.56, 1.41)	1.01 (0.64, 1.60)	
≥59.7	90	0.81 (0.62, 1.07)	0.94 (0.72, 1.24)	35	0.71 (0.45, 1.13)	0.81 (0.51, 1.30)	
P-trend[4]		0.16	0.67		0.05	0.14	0.34
Citrus fruits							
<13.4	122	1.00	1.00	39	1.00	1.00	
13.4–40.6	107	0.88 (0.68, 1.14)	0.98 (0.76, 1.28)	39	0.91 (0.58, 1.41)	0.99 (0.64, 1.55)	
40.7–93.9	108	0.86 (0.66, 1.12)	1.00 (0.77, 1.31)	43	0.81 (0.52, 1.25)	0.95 (0.61, 1.47)	
≥94.0	92	0.80 (0.61, 1.06)	0.97 (0.74, 1.28)	31	0.46 (0.29, 0.74)	0.56 (0.34, 0.90)	
P-trend[4]		0.17	0.89		<0.001	0.007	0.03
Yellow-orange fruits							
<6.0	136	1.00	1.00	29	1.00	1.00	
6.0–14.7	116	0.88 (0.69, 1.13)	0.94 (0.73, 1.20)	45	1.20 (0.75, 1.92)	1.30 (0.81, 2.08)	
14.8–35.1	90	0.76 (0.58, 0.99)	0.84 (0.64, 1.10)	33	0.72 (0.44, 1.19)	0.82 (0.50, 1.36)	
≥35.2	87	0.77 (0.58, 1.02)	0.90 (0.68, 1.19)	45	0.83 (0.51, 1.34)	0.98 (0.60, 1.60)	
P-trend[4]		0.10	0.53		0.19	0.49	0.27

[1] Adjusted for age at cohort entry, ethnicity, and total energy intake (log transformed).
[2] Additionally adjusted for first-degree family history of bladder cancer, employment in a high-risk industry, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time-dependent), number of years since quitting (time-dependent), interactions of ethnicity with smoking status, average number of cigarettes, and squared average number of cigarettes.
[3] Based on the Wald statistic for cross-product terms of dietary variables and sex in the risk factor-adjusted models.
[4] Based on the Wald statistic for a trend variable assigned the sex- and ethnic-specific medians within the appropriate quartiles.

included in this analysis were those known to be concentrated in fruits and vegetables. Two dietary patterns previously identified by exploratory factor analysis and validated by confirmatory factor analysis in the entire MEC Study population (17) were included in this study. The "vegetables" dietary pattern was characterized by high loadings on vegetable groups and the "fruit and milk" dietary pattern was characterized by high loadings on milk/yogurt and fruit groups. In a calibration study (18), using energy-adjusted intakes [g/(1000 kcal · d)] measured from the QFFQ and multiple 24-h recalls, Pearson correlation coefficients were 0.43 and 0.36 for vegetables and 0.60 and 0.60 for fruits among men and women, respectively.

Statistical analysis. Cox proportional hazards models with age as the time metric were used to calculate HRs and 95% CIs for invasive bladder cancer. Foods and nutrients were examined as energy densities (per 1000 kcal) in all models, as correlations between dietary estimates from the QFFQ and 24-h recalls were found to improve after energy adjustment in the calibration study mentioned above (18). Dietary exposures were modeled as quartiles and based on the exposure distribution of all cohort members. The lowest intake group served as the referent in all models. Linear trends were tested by entering sex- and ethnic-specific medians within the appropriate quartile as continuous variables into the models. Estimates are presented separately for men and women, as results were found to differ by sex. Basic models were adjusted for age at cohort entry, ethnicity, and total energy (log-transformed kcal/d) in the log-linear model component. Multivariable models were further adjusted for family history of bladder cancer (yes/no), occupation in a high-risk industry (yes/no; employed ≥10 y in rubber or tire manufacturing, plastic production or processing, or pesticide production), and cigarette smoking using a comprehensive base model developed for the study of lung cancer in the MEC Study (19). The smoking model included smoking status; average number of cigarettes smoked per day; average number of cigarettes smoked per day squared; number of years smoked (time-dependent); number of years since quitting (time-dependent); and interactions of ethnicity with smoking status, average number of cigarettes, and average number of cigarettes squared. Covariates were selected a priori based on their association with bladder cancer risk (20). The assumption of proportional hazards was found to be satisfied in all models by examining the relationship of scaled Schoenfeld residuals with time. We also examined a possible nonlinear relation between fruit and vegetable consumption and bladder cancer risk with restricted cubic splines (21).

We ran the models stratified by smoking status and ethnicity. Tests for interactions were based on the Wald test of the cross-product terms of the dietary variables and the subgroup membership indicators. Lag analyses excluding participants diagnosed with bladder cancer within 2 y of questionnaire completion (*n* = 75) and sensitivity analyses restricting the cases to those with transitional cell carcinomas (*n* = 533) were also conducted. Associations with risk were also examined for calibration-corrected nutrient density values. All statistical tests were 2-sided and $P < 0.05$ was considered significant. All data analyses were performed using SAS 9.2 statistical software (SAS Institute).

Results

Baseline characteristics of the study population are presented in **Table 1**. For both men and women, participants with incident bladder cancer were older than same-sex cohort members. Compared with all MEC Study participants, the proportions of white men and African American women, current/former smokers, and the mean values for pack-years of cigarette smoking and alcohol consumption were higher among the incident cases. Fruit and vegetable intakes were lower in bladder cancer cases, particularly for women.

The HRs for bladder cancer according to quartiles of fruit and vegetable intakes are provided in **Table 2**. A dietary pattern characterized by the high consumption of vegetables was associated with a decreased risk of bladder cancer among women in both basic and risk factor-adjusted [highest vs. lowest quartile, HR = 0.40 (95% CI: 0.23, 0.69); *P*-trend = 0.004] models. In women, a dietary pattern characterized by the high intakes of fruit and milk was inversely associated with bladder cancer risk in the basic model [HR = 0.57 (95% CI: 0.34, 0.94); *P*-trend = 0.03]; however, the risk estimates were attenuated and not

TABLE 3 HRs and 95% CIs for invasive bladder cancer according to nutrient intake from foods

	Men (n = 83,694)			Women (n = 102,191)			
	Cases	HR (95% CI)[1]	HR (95% CI)[2]	Cases	HR (95% CI)[1]	HR (95% CI)[2]	P-interaction[3]
Vitamin A [RE/(1000 kcal · d)]							
<458	142	1.00	1.00	34	1.00	1.00	
458–630	122	0.86 (0.68, 1.10)	0.96 (0.75, 1.22)	43	0.83 (0.53, 1.30)	0.90 (0.57, 1.42)	
631–887	98	0.77 (0.59, 1.00)	0.91 (0.70, 1.18)	36	0.52 (0.32, 0.84)	0.59 (0.37, 0.96)	
≥888	67	0.67 (0.50, 0.90)	0.82 (0.61, 1.11)	39	0.44 (0.28, 0.71)	0.54 (0.34, 0.87)	
P-trend[4]		0.006	0.19		<0.001	0.006	0.05
α-Carotene [μg/(1000 kcal · d)]							
<225	142	1.00	1.00	44	1.00	1.00	
225–378	123	0.89 (0.70, 1.13)	0.96 (0.76, 1.23)	33	0.65 (0.41, 1.03)	0.70 (0.45, 1.11)	
379–674	86	0.71 (0.54, 0.92)	0.81 (0.62, 1.06)	43	0.72 (0.47, 1.10)	0.80 (0.52, 1.24)	
≥675	78	0.77 (0.58, 1.01)	0.92 (0.69, 1.22)	32	0.43 (0.27, 0.68)	0.52 (0.32, 0.83)	
P-trend[4]		0.05	0.49		0.001	0.01	0.02
β-Carotene [μg/(1000 kcal · d)]							
<1306	154	1.00	1.00	35	1.00	1.00	
1306–2022	117	0.83 (0.65, 1.06)	0.90 (0.71, 1.15)	47	0.98 (0.63, 1.51)	1.04 (0.67, 1.62)	
2023–3193	93	0.75 (0.58, 0.98)	0.87 (0.67, 1.13)	32	0.51 (0.32, 0.83)	0.57 (0.35, 0.93)	
≥3194	65	0.71 (0.53, 0.95)	0.86 (0.64, 1.16)	38	0.46 (0.29, 0.74)	0.55 (0.35, 0.89)	
P-trend[4]		0.02	0.32		<0.001	0.004	0.03
Lycopene [μg/(1000 kcal · d)]							
<860	113	1.00	1.00	39	1.00	1.00	
860–1287	115	1.12 (0.86, 1.45)	1.17 (0.90, 1.52)	35	0.91 (0.57, 1.43)	0.94 (0.60, 1.49)	
1288–1920	113	1.16 (0.89, 1.51)	1.22 (0.94, 1.59)	34	0.85 (0.53, 1.35)	0.89 (0.56, 1.41)	
≥1921	88	0.97 (0.73, 1.28)	1.03 (0.77, 1.37)	44	0.95 (0.61, 1.47)	0.98 (0.63, 1.53)	
P-trend[4]		0.77	0.90		0.87	0.96	0.85
β-Cryptoxanthin [μg/(1000 kcal · d)]							
<33.0	126	1.00	1.00	44	1.00	1.00	
33.0–83.8	107	0.84 (0.65, 1.08)	0.93 (0.72, 1.20)	46	0.89 (0.59, 1.35)	0.99 (0.65, 1.50)	
83.9–195	99	0.79 (0.61, 1.03)	0.93 (0.71, 1.21)	35	0.56 (0.36, 0.88)	0.66 (0.42, 1.03)	
≥196	97	0.81 (0.62, 1.07)	0.98 (0.74, 1.30)	27	0.38 (0.23, 0.62)	0.47 (0.28, 0.77)	
P-trend[4]		0.33	0.85		<0.001	0.002	< 0.001
Lutein [μg/(1000 kcal · d)]							
<755	144	1.00	1.00	30	1.00	1.00	
755–1156	112	0.87 (0.68, 1.12)	0.92 (0.72, 1.19)	46	1.14 (0.71, 1.81)	1.18 (0.74, 1.88)	
1157–1773	94	0.84 (0.65, 1.10)	0.92 (0.70, 1.20)	37	0.72 (0.44, 1.17)	0.77 (0.47, 1.26)	
≥1774	79	0.89 (0.67, 1.19)	1.01 (0.76, 1.34)	39	0.57 (0.35, 0.94)	0.63 (0.39, 1.04)	
P-trend[4]		0.53	0.87		0.004	0.01	0.18
Vitamin C [mg/(1000 kcal · d)]							
<50.0	144	1.00	1.00	39	1.00	1.00	
50.0–76.8	103	0.71 (0.55, 0.92)	0.81 (0.62, 1.04)	43	0.77 (0.50, 1.18)	0.85 (0.55, 1.32)	
76.9–113	111	0.81 (0.63, 1.04)	0.98 (0.76, 1.27)	35	0.48 (0.30, 0.76)	0.56 (0.35, 0.89)	
≥114	71	0.65 (0.49, 0.87)	0.83 (0.62, 1.11)	35	0.37 (0.23, 0.58)	0.46 (0.28, 0.73)	
P-trend[4]		0.01	0.43		<0.001	<0.001	0.002
Vitamin E [α-TE/(1000 kcal · d)]							
<4.2	136	1.00	1.00	37	1.00	1.00	
4.2–4.9	119	1.02 (0.79, 1.30)	1.09 (0.85, 1.40)	45	0.91 (0.59, 1.40)	0.97 (0.63, 1.50)	
5.0–5.8	84	0.80 (0.61, 1.05)	0.89 (0.67, 1.17)	42	0.74 (0.48, 1.16)	0.81 (0.52, 1.27)	
≥5.9	90	0.85 (0.65, 1.11)	0.97 (0.74, 1.27)	28	0.43 (0.26, 0.70)	0.48 (0.29, 0.78)	
P-trend[4]		0.13	0.60		<0.001	0.001	0.03
Folate [μg/(1000 kcal · d)]							
<125	124	1.00	1.00	35	1.00	1.00	
125–164	127	0.95 (0.74, 1.23)	1.08 (0.84, 1.38)	51	0.98 (0.63, 1.51)	1.06 (0.69, 1.64)	
165–215	89	0.70 (0.53, 0.92)	0.84 (0.63, 1.12)	30	0.45 (0.27, 0.74)	0.52 (0.31, 0.85)	
≥216	89	0.74 (0.56, 0.98)	0.93 (0.70, 1.25)	36	0.46 (0.29, 0.74)	0.56 (0.35, 0.91)	
P-trend[4]		0.01	0.39		<0.001	0.003	0.01

(Continued)

TABLE 3 *Continued*

	Men (n = 83,694)			Women (n = 102,191)			
	Cases	HR (95% CI)[1]	HR (95% CI)[2]	Cases	HR (95% CI)[1]	HR (95% CI)[2]	P-interaction[3]
Dietary fiber [g/(1000 kcal · d)]							
<14.9	114	1.00	1.00	48	1.00	1.00	
14.9–21.9	105	0.76 (0.58, 1.01)	0.89 (0.67, 1.18)	37	0.59 (0.37, 0.93)	0.68 (0.43, 1.07)	
22.0–32.0	116	0.76 (0.57, 1.03)	0.98 (0.72, 1.33)	32	0.42 (0.25, 0.70)	0.53 (0.31, 0.89)	
≥32.1	94	0.61 (0.42, 0.88)	0.89 (0.61, 1.30)	35	0.35 (0.19, 0.67)	0.50 (0.26, 0.97)	
P-trend[4]		0.01	0.58		0.004	0.07	0.99

[1] Adjusted for age at cohort entry, ethnicity, and total energy intake (log transformed). RE, retinol equivalents (μg); α-TE, α-tocopherol equivalents (mg).
[2] Additionally adjusted for first-degree family history of bladder cancer, employment in a high-risk industry, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), interactions of ethnicity with smoking status, average number of cigarettes, and squared average number of cigarettes.
[3] Based on the Wald statistic for cross-product terms of dietary variables and sex in the risk factor-adjusted models.
[4] Based on the Wald statistic for a trend variable assigned the sex- and ethnic-specific medians within the appropriate quartiles.

significant in the risk factor-adjusted model [HR = 0.75 (95% CI: 0.45, 1.25); P-trend = 0.30]. Similarly, among women, higher intakes of total fruits and vegetables [HR = 0.35 (95% CI: 0.22, 0.56); P-trend < 0.001], total vegetables, yellow-orange vegetables, total fruits, and citrus fruits were inversely associated with the risk of bladder cancer in risk factor-adjusted models. For men, a significant inverse association was found for the "vegetables" dietary pattern, fruits and vegetables, all vegetable subgroups, and total fruits in the basic models. However, the associations did not depart from unity in the risk factor-adjusted models, with the attenuation in risk largely attributable to adjustment for smoking variables. Restricted cubic spline analyses adjusted for covariates also showed a linear reduction in risk with higher intake of fruits and vegetables among women but no significant association among men (data not shown).

The HRs for bladder cancer according to quartiles of selected nutrients and carotenoids concentrated in fruits and vegetables are presented in **Table 3**. For women, higher intakes of vitamins A, C, and E; the carotenoids α-carotene, β-carotene, and β-cryptoxanthin; and folate were associated with a reduced risk of bladder cancer in risk factor-adjusted models. For men, no significant associations were observed in risk factor-adjusted models for any nutrient or phytochemical examined. Similar results for food groups and nutrients were obtained when excluding cases diagnosed within the first 2 y of follow-up or when restricting case status to include only transitional cell carcinomas (data not shown). Also, in secondary outcome analyses that included in situ cases, the results were generally similar to those presented in Tables 2 and 3, although modestly attenuated. For example, the HRs for fruit and vegetable consumption were 1.03 (95% CI: 0.84, 1.27; P-trend = 0.61) for men and 0.51 (95% CI: 0.36, 0.73; P-trend < 0.001) for women (P-interaction between sexes < 0.001) (data not shown). When examining noninvasive cases only, no significant association was found in either men or women; for fruit and vegetable intake, HR = 1.24 (95% CI: 0.93, 1.64; P-trend = 0.11) in men and HR = 0.91 (95% CI: 0.51, 1.61; P-trend = 0.72) in women, and the P-interaction between sexes = 0.37 (data not shown). In addition, for the nutrients examined, the risk estimates for bladder cancer were similar when modeling calibration-corrected nutrient densities (data not shown).

We examined these relationships in selected subgroups among men to see whether some of the strong inverse associations in women might become apparent in men also. In analyses stratified by smoking status at baseline (**Table 4**), we did find significant inverse trends for a dietary pattern characterized by the high consumption of vegetables and for total vegetable intake, but only among current male smokers [HR = 0.40 (95% CI: 0.18, 0.90); P-trend = 0.02, P-interaction across smoking status = 0.04; and HR = 0.43 (95% CI: 0.18, 1.02); P-trend = 0.03, P-interaction = 0.08, respectively]. In ethnic-specific analyses among men (**Table 5**) conducted for the 3 largest ethnicities in the study (Japanese Americans, Latinos, and whites), there was considerable heterogeneity among the groups. The only significant findings were in the Latinos, among whom a lower risk of bladder cancer was seen for the highest level of consumption of fruits and vegetables [HR = 0.36 (95% CI: 0.17, 0.76); P-trend = 0.006, P-interaction between Latinos and the other 2 groups = 0.006] and of total fruits [HR = 0.40 (95% CI: 0.19, 0.84); P-trend = 0.02, P-interaction = 0.002]. Inverse associations confined to Latino men were also found for lycopene, vitamin C, and folate (P-interaction < 0.05, data not shown). Subgroup analyses among women indicated that the associations did not vary across smoking status and between the 2 ethnic groups with more cases [African Americans (n = 55) and whites (n = 35)], although the number of cases in all subgroups of women was limited (data not shown). We also examined the associations separately for Hawaii and California, because differences in unmeasured environmental exposures (e.g., drinking water and air pollution) between the 2 study areas might modify the diet-bladder cancer relationship; however, there was no indication that the associations varied for any dietary exposure examined between the 2 study areas (data not shown).

Discussion

In this large, multiethnic cohort of older adults, we found a lower risk of bladder cancer among women with a dietary pattern characterized by the high intake of vegetables as well as for those consuming the greatest amounts of total fruits and vegetables, total vegetables, yellow-orange vegetables, total fruits, and citrus fruits. Among women, higher intakes of several nutrients and carotenoids concentrated in fruits and vegetables, including vitamins A, C, and E; the carotenoids α-carotene, β-carotene, and β-cryptoxanthin; and folate, were also associated with a lower risk of bladder cancer. Among men, the inverse associations in basic models were attenuated upon adjustment for smoking variables. In subgroup analyses based on a limited number of cases, vegetable intake remained inversely associated with bladder cancer risk only among current smokers at baseline. In ethnic-specific analyses among men, Latinos with the greatest consumption of fruits and vegetables, fruits, and citrus fruits were at lower risk for bladder cancer.

TABLE 4 HRs and 95% CIs for invasive bladder cancer according to fruit and vegetable intakes by smoking status at baseline among men

	Never smokers (n = 25,748)		Former smokers (n = 42,758)		Current smokers (n = 15,188)		
	Cases	HR (95% CI)[1]	Cases	HR (95% CI)[1]	Cases	HR (95% CI)[1]	P-interaction[2]
Dietary patterns (factor score)							
Vegetables pattern							
Quartile 1	26	1.00	54	1.00	48	1.00	
Quartile 2	23	0.94 (0.53, 1.66)	66	1.28 (0.89, 1.85)	29	0.86 (0.53, 1.38)	
Quartile 3	16	0.68 (0.35, 1.31)	69	1.36 (0.93, 1.99)	17	0.65 (0.36, 1.17)	
Quartile 4	23	0.97 (0.51, 1.85)	50	1.06 (0.69, 1.63)	8	0.40 (0.18, 0.90)	
P-trend[3]		0.72		0.69		0.02	0.04
Fruit and milk pattern							
Quartile 1	14	1.00	58	1.00	39	1.00	
Quartile 2	19	1.04 (0.52, 2.10)	64	1.13 (0.78, 1.62)	27	1.08 (0.65, 1.80)	
Quartile 3	29	1.52 (0.78, 2.95)	60	1.12 (0.76, 1.63)	19	0.93 (0.52, 1.67)	
Quartile 4	26	1.41 (0.68, 2.93)	57	1.28 (0.84, 1.94)	17	1.20 (0.63, 2.29)	
P-trend[3]		0.25		0.31		0.76	0.64
Foods [g/(1000 kcal · d)]							
Fruits and vegetables							
<216	18	1.00	69	1.00	58	1.00	
216–308	25	1.02 (0.56, 1.88)	68	1.00 (0.71, 1.40)	23	0.77 (0.48, 1.26)	
309–425	27	1.06 (0.58, 1.92)	61	1.07 (0.75, 1.52)	16	0.83 (0.47, 1.46)	
≥426	18	0.81 (0.42, 1.57)	41	1.03 (0.69, 1.52)	5	0.56 (0.22, 1.40)	
P-trend[3]		0.54		0.78		0.17	0.34
Total vegetables							
<107	27	1.00	62	1.00	46	1.00	
107–147	24	0.86 (0.50, 1.49)	67	1.21 (0.86, 1.71)	35	1.09 (0.70, 1.69)	
148–200	16	0.63 (0.34, 1.17)	70	1.40 (0.99, 1.97)	15	0.66 (0.37, 1.19)	
≥201	21	0.93 (0.53, 1.65)	40	1.05 (0.71, 1.57)	6	0.43 (0.18, 1.02)	0.08
P-trend[3]		0.73		0.63		0.03	
Total fruits							
<77.4	16	1.00	61	1.00	58	1.00	
77.4–144	19	0.83 (0.42, 1.61)	64	1.00 (0.70, 1.42)	19	0.57 (0.34, 0.96)	
145–238	31	1.23 (0.67, 2.26)	72	1.26 (0.89, 1.78)	15	0.69 (0.39, 1.23)	
≥239	22	0.93 (0.48, 1.78)	42	1.00 (0.67, 1.49)	10	0.81 (0.41, 1.60)	
P-trend[3]		0.98		0.75		0.30	0.43

[1] Adjusted for age at cohort entry, ethnicity, total energy intake (log transformed), first-degree family history of bladder cancer, employment in a high-risk industry, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), interactions of ethnicity with average number of cigarettes, and squared average number of cigarettes (for current and former smokers only).
[2] Based on the Wald statistic for cross-product terms of dietary variables and smoking status in the risk factor-adjusted models.
[3] Based on the Wald statistic for a trend variable assigned the sex- and ethnic-specific medians within the appropriate quartiles.

A systematic literature review conducted by the WCRF/AICR in 2007 did not find strong evidence in support of fruits and vegetables in the development of bladder cancer. More recent studies have generally reported findings consistent with the WCRF/AICR summary conclusion. Two recent prospective cohort studies reported no association for fruits and vegetables (14,15), whereas an additional study suggested a protective effect for β-carotene from foods but not from supplements (22). Case-control studies have consistently reported inverse associations for fruits, vegetables, or related micronutrients with bladder cancer risk (9–13,23); however, these studies are limited due to the potential for differential recall between cases and controls to have affected the findings. Contrary to our findings in women, one prior case-control study examined dietary patterns in relation to bladder cancer risk and reported no association for a prudent dietary pattern characterized by the high consumption of fruits and vegetables (24); however, this analysis was conducted in an Uruguayan population comprised primarily of men (~88%). Most previous studies have included noninvasive as well as invasive bladder cancer as end points. In the current study, we found no association for noninvasive tumors in either men or women. Thus, should dietary factors operate to influence the progression of bladder cancer from in situ to malignant disease, the inclusion of noninvasive tumors may weaken the association between diet and bladder cancer risk. Further investigation is needed to confirm our findings that are restricted to invasive bladder cancer.

The present study found an inverse association between fruits, vegetables, and bladder cancer risk that was largely confined to women. The reason for the heterogeneity between sexes is not clear, although it may in part reflect the higher intake of fruits and vegetables among women. However, we found no association in the risk of bladder cancer among men with the highest fruit and vegetable intakes when examined as quartiles of exposure or as continuous variables using restricted cubic splines in regression. Interestingly, although the number of cases in women (n = 152) was smaller than in men (n = 429), the estimated risk reduction in women was large enough to reach significance. Also, the significant inverse associations for women remained in the lag analyses that excluded incident cases diagnosed within 2 y of completing the baseline questionnaire and in several sensitivity analyses that included in situ cases, restricted

TABLE 5 HRs and 95% CIs for invasive bladder cancer according to fruit and vegetable intakes by ethnicity among men

	Japanese Americans (n = 25,250)		Latinos (n = 19,746)		Whites (n = 21,333)		
	Cases	HR (95% CI)[1]	Cases	HR (95% CI)[1]	Cases	HR (95% CI)[1]	*P*-interaction[2]
Dietary patterns (factor score)							
Vegetables pattern							
Quartile 1	19	1.00	40	1.00	46	1.00	
Quartile 2	32	0.83 (0.47, 1.48)	15	0.62 (0.33, 1.15)	54	1.66 (1.12, 2.48)	
Quartile 3	39	0.79 (0.44, 1.39)	14	0.72 (0.36, 1.42)	33	1.23 (0.77, 1.94)	
Quartile 4	45	0.77 (0.43, 1.39)	9	0.68 (0.31, 1.49)	15	0.76 (0.42, 1.40)	
P-trend[3]		0.45		0.22		0.70	0.60
Fruit and milk pattern							
Quartile 1	55	1.00	15	1.00	21	1.00	
Quartile 2	35	1.01 (0.65, 1.56)	20	0.96 (0.48, 1.93)	30	1.04 (0.59, 1.82)	
Quartile 3	26	1.12 (0.68, 1.82)	19	0.79 (0.39, 1.61)	50	1.49 (0.88, 2.51)	
Quartile 4	19	1.76 (1.00, 3.09)	24	0.68 (0.32, 1.45)	47	1.53 (0.88, 2.66)	
P-trend[3]		0.13		0.26		0.06	0.005
Foods [g/(1000 kcal · d)]							
Fruits and vegetables							
<216	41	1.00	34	1.00	49	1.00	
216–308	40	1.17 (0.75, 1.83)	17	0.40 (0.22, 0.74)	41	1.05 (0.69, 1.59)	
309–425	33	1.14 (0.71, 1.84)	18	0.48 (0.26, 0.89)	38	1.19 (0.77, 1.84)	
≥426	21	1.10 (0.64, 1.91)	9	0.36 (0.17, 0.76)	20	0.96 (0.56, 1.65)	
P-trend[3]		0.72		0.006		0.91	0.006
Total vegetables							
<107	48	1.00	23	1.00	42	1.00	
107–147	37	0.87 (0.57, 1.34)	19	0.82 (0.44, 1.55)	51	1.54 (1.02, 2.32)	
148–200	28	0.79 (0.49, 1.26)	20	0.85 (0.45, 1.58)	39	1.39 (0.89, 2.15)	
≥201	22	0.87 (0.52, 1.46)	16	0.71 (0.37, 1.38)	16	0.82 (0.46, 1.46)	
P-trend[3]		0.51		0.35		0.62	0.60
Total fruits							
<77.4	39	1.00	33	1.00	40	1.00	
77.4–144	32	0.87 (0.54, 1.41)	20	0.50 (0.27, 0.91)	34	0.95 (0.60, 1.51)	
145–238	36	1.11 (0.69, 1.77)	16	0.56 (0.30, 1.04)	47	1.51 (0.98, 2.34)	
≥239	28	1.24 (0.74, 2.08)	9	0.40 (0.19, 0.84)	27	1.26 (0.75, 2.10)	
P-trend[3]		0.27		0.02		0.16	0.002

[1] Adjusted for age at cohort entry, ethnicity, total energy intake (log-transformed), first-degree family history of bladder cancer, employment in a high-risk industry, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), and number of years since quitting (time dependent).
[2] Interaction was tested between Latinos and the other 2 groups (Japanese Americans and whites combined) based on the Wald statistic for cross-product terms of dietary variables and ethnicity in the risk factor-adjusted models.
[3] Based on the Wald statistic for a trend variable assigned the sex- and ethnic-specific medians within the appropriate quartiles.

case status to transitional cell carcinomas, and examined associations using calibration-corrected nutrient densities. The sex differences in the HRs for incident bladder cancer in the MEC Study contrast with the associations reported in 2 other cohorts, namely, the Health Professionals Follow-up and Nurses' Health Studies: whereas beneficial effects of high cruciferous vegetable consumption were suggested for the men in the Health Professionals Follow-up (25), no associations were seen for the women in Nurses' Health Studies (26). Other prospective studies have reported no sex differences in the associations between fruits or vegetables and bladder cancer risk and, accordingly, combined men and women in the analysis (14,15,27). Parity and early menopause may be related to the incidence of bladder cancer among women, although whether effects are due to female hormones remains uncertain (28). In the current study, however, female reproductive factors were not related to bladder cancer risk and did not change the associations between fruits or vegetables and bladder cancer risk when included in the models.

In men, the beneficial effect of high vegetable intake was confined to current smokers in the risk factor-adjusted models. It is plausible that smokers may benefit the most from the greater consumption of fruits and vegetables high in antioxidants, as they have been shown to have lower antioxidant levels than nonsmokers (29). In addition, fruits and vegetables contain a wide range of bioactive constituents that may operate in the development or progression of bladder cancer, including counteracting nitrosation and influencing bioactive transformations. A cohort study in The Netherlands also found that the inverse association between fruit consumption and bladder cancer was more pronounced in smokers than in those who never smoked (27). However, in a Finnish cohort of male smokers, no association of fruits and vegetables with bladder cancer risk was observed (30). Two other cohort studies have suggested that an inverse association between fruit and/or vegetable intake and the risk of bladder cancer was stronger in (25) or limited to those who never smoked (14), but no significant interaction with smoking status was found in either study. In ethnic-specific analyses, we found that Latino men consuming high amounts of fruit had a lower risk of bladder cancer compared with Japanese American and white men. The mean intake of fruit was slightly higher for Latinos than other ethnic groups and the proportion of current smokers was slightly, but significantly, higher in Latinos (18.3%) than in Japanese Americans (14.9%) and whites (16.2%), possibly contributing to the discrepant findings. However, we were not able to examine whether the inverse association of fruits with bladder cancer risk in Latino men was independent from smoking status due to the limited number of cases.

The current study has several strengths, including the prospective design that allowed for prediagnostic dietary assessment, the ethnic diversity of the study sample, the administration of a validated FFQ with a detailed nutritional database, and the population-based sampling frame utilized by the MEC Study allowing for the generalizability of the study results. There were also potential limitations. Dietary intake was likely measured with error in our study. To minimize errors in dietary assessment associated with the use of a FFQ, we used a detailed and validated instrument that included a comprehensive list of food items. We also examined food and nutrient densities in relation to disease risk, potentially reducing measurement error, because nutrient densities, when compared with absolute values, were more highly correlated with multiple 24-h recalls in our prior calibration study (18). In addition, we examined associations for calibration-adjusted nutrients intakes. Also, a single FFQ may not well represent long-term dietary intake and cannot capture possible changes in diet or other health behaviors occurring during the follow-up period. In future analyses, we will be able to study the impact of repeated dietary measurements and changes in dietary intake and smoking status in relation to bladder cancer risk. Due to the smaller number of bladder cancers diagnosed in women during the follow-up period for this analysis, the statistical power for sex-specific associations for bladder cancer by smoking status or ethnicity was too limited. With additional follow-up time and the accrual of more cases, we will be able to better examine associations for specific subgroups of women. In addition, we cannot rule out the possibility that subgroup findings in men may reflect chance findings due to the small number of cases. Although measured and unmeasured confounding factors may have influenced associations of fruits and vegetables with bladder cancer risk, we were able to examine and control for a wide range of potential confounders. In particular, we rigorously adjusted for cigarette smoking using a comprehensive model developed for a previous lung cancer study, which accounted for changes in smoking status over time using time-dependent variables (19).

In conclusion, our findings suggest that higher consumption of fruits and vegetables may lower the risk of invasive bladder cancer among women. Although no overall association was found for men, subgroup analyses suggest that the association between fruits or vegetables and bladder cancer risk varies by smoking status and ethnicity. Further follow-up is required to confirm these findings with a greater number of cases and to examine associations with risk for specific subgroups of women.

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