Intakes of Fruits, Vegetables, Vitamins A, C, and E, and Carotenoids and Risk of Renal Cell Cancer

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Abstract

Background: **Fruits and vegetables rich in antioxidants have been proposed to reduce the risk of renal cell cancer. However, few prospective studies have examined the intakes of fruits, vegetables, and antioxidant vitamins in relation to the risk of renal cell cancer.**

Methods: **We prospectively examined the associations between the intakes of fruits, vegetables, vitamins A, C, and E, and carotenoids and risk of renal cell cancer in women and men. We followed 88,759 women in the Nurses' Health Study from 1980 to 2000, and 47,828 men in the Health Professionals Follow-up Study from 1986 to 2000. We assessed dietary intake every 2 to 4 years using a validated semiquantitative food frequency questionnaire. The Cox proportional hazards model was used to estimate study-specific multivariate relative risks (RR), which were pooled using a random effects model.**

Results: **A total of 248 (132 women and 116 men) incident renal cell cancer cases were ascertained during 2,316,525 person-years of follow-up. The consumption of fruits and vegetables was associated with a decreased risk of renal cell cancer in men (multivariate RR, 0.45; 95% CI, 0.25-0.81, for ≥6 servings of fruit and vegetable intake/d versus <3 servings/d; *P* test for trend = 0.02), but not in women (multivariate RR, 1.17; 95% CI, 0.66-2.07, for the same contrast; *P* test for trend = 0.25; *P* test for between-studies heterogeneity = 0.02). Intakes of vitamins A and C from food and carotenoids were inversely associated with the risk of renal cell cancer in men only, but we cannot exclude the possibility that this was due to other factors in fruit and vegetables. No clear association was observed for vitamin E in women or men.**

Conclusions: **Fruit and vegetable consumption may reduce the risk of renal cell cancer in men.** (Cancer Epidemiol Biomarkers Prev 2006;15(12):2445–52)

Introduction

The incidence rates of kidney cancer, and specifically, renal cell cancer, which accounts for >80% of all kidney cancers, have been increasing globally (1). Obesity and hypertension have contributed to this upward trend (2, 3), but the association of diet with risk of renal cell cancer is unclear.

Although antioxidants and other bioactive compounds in fruits and vegetables have been proposed to prevent cancers, evidence of the effects of fruit, vegetable, and antioxidant consumption on the risk of renal cell cancer is limited, particularly from prospective studies. An international review panel sponsored by the IARC concluded that the evidence for a cancer-preventive effect of fruit and vegetable consumption on kidney cancer was limited (4). Recent prospective studies generally have found no association between fruit and vegetable intakes and risk of renal cell cancer (5-7), although a cohort of Swedish women found a suggestive inverse association (8). For intakes of vitamins A, C, or E, or carotenoids in relation to renal cell cancer risk (5, 9-14), the results have also been inconsistent.

We prospectively examined whether the intake of fruits, vegetables, vitamins A, C, and E, and carotenoids were associated with a lower risk of renal cell cancer in two large cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Materials and Methods

Study Population. The NHS was established in 1976, when 121,700 female registered nurses who were 30 to 55 years of age returned a mailed questionnaire. The HPFS was initiated in 1986 when 51,529 male health professionals, consisting of dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians, aged 40 to 75 years, returned a mailed questionnaire. Participants in these two cohorts provided detailed information about medical history, lifestyle, and various risk factors for chronic diseases; follow-up questionnaires were sent at 2-year intervals. The follow-up rates to questionnaires for both studies exceeded 90% of the potential person-years.

Dietary Assessment. Dietary information was collected from the NHS participants using validated semiquantitative food frequency questionnaires (SFFQ) in 1980, 1984, 1986, and every 4 years thereafter, and from the HPFS participants every 4 years since 1986. In the NHS, the 1980 SFFQ included 61 food items, including 6 questions on fruits, 11 questions on vegetables, and 3 on potatoes. The SFFQ used in 1984 in the NHS was expanded to include 15 questions on fruits, 28 questions on vegetables, and 3 on potatoes. The SFFQs used in 1986, 1990, 1994, and 1998 were similar to the 1984 SFFQ. In the HPFS, SFFQs with 116 food items, including 15 questions on fruits, 30 questions on vegetables, and 3 on potatoes were administered in 1986, and subsequent SFFQs have had a similar number of questions on fruit and vegetable consumption.

Participants were asked how frequently, on average, during the past year they consumed one standard serving of a specific

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food item in nine categories (<1/mo, 1-3/mo, 1/wk, 2-4/wk, 5-6/wk, 1/d, 2-3/d, 4-5/d, or ≥6/d). Responses on the frequencies of a specified serving size for each food item were converted to average daily intake. We then calculated the intakes of total fruits and vegetables as well as specific fruit and vegetable groups by summing the average daily intake for each food item in each group. The specific groups examined included total fruits, citrus fruits, total vegetables, green leafy vegetables, cruciferous vegetables, vitamin C–rich fruits, and vegetables (i.e., fruits and vegetables that contain ≥30 mg of vitamin C per serving), legumes, and potatoes. We grouped fruits and vegetables based on the criteria used by Smith et al. (15), and modified it to correspond with our questionnaires (16). Fruit and vegetable juice in relation to risk of renal cell cancer has been examined elsewhere and no association was observed in these two cohorts (17). We excluded beans and potatoes from the total fruit and vegetable group and total vegetable group because of their high protein and starch contents, respectively (18). We calculated the intakes of vitamins and β-carotene from food (dietary intake) and from both food and vitamin supplements (total intake). The quantities of vitamins and carotenoids from foods were calculated by multiplying the reported frequency of each food by the nutrient content of one serving of that food (19). We took into account the participants' current use and dose of vitamin supplements, and the brand and type of multivitamins were asked every 2 years to calculate the supplemental intake.

The average correlation coefficients between intakes of specific fruit and vegetable items from the SFFQs and those from multiple 1-week diet records were 0.79 (range, 0.74-0.84) for fruits and 0.53 (range, 0.30-0.73) for vegetables in women (20), and 0.75 (range, 0.38-0.95) for fruits and 0.46 (range, 0.19-0.80) for vegetables in men (21), following correction for attenuation due to random error in diet records (22). For vitamins, correlation coefficients between intakes from the SFFQs and the average of two to four 1-week diet records were 0.49 for total vitamin A and 0.75 for total vitamin C in women (23), and 0.61, 0.92, and 0.92 for total vitamins A, C, and E, respectively, in men (24). The correlations of the average of the two SFFQs with plasma concentration of α-carotene, β-carotene, β-cryptoxanthin, lutein, and lycopene were 0.21 to 0.48 in male and female nonsmokers (25).

Assessment of Renal Cell Cancer. We obtained self-reported information on the occurrence of kidney cancer on each questionnaire, and asked participants (or next-of-kin for those who died) who reported a diagnosis of kidney cancer for permission to access medical records related to the diagnosis. The deaths in the cohort were ascertained by reports of family members in response to the follow-up questionnaires. In addition, the National Death Index (26) was used to identify fatalities. Physicians blinded to the participants' risk factor status reviewed medical records. We included only those with renal cell cancer as cases because transitional cell cancer, which arises from the renal pelvis, may have a different etiology. After a review of medical records, we included clear cell carcinoma (n = 148), papillary carcinoma (n = 25), chromophobe carcinoma (n = 3), and renal cell carcinoma not otherwise classified (n = 72), based on the classification developed by the workshop held by the WHO (27). A total of 132 cases in the NHS and 116 cases in the HPFS were included after applying exclusion criteria.

Statistical Analyses. We excluded participants who did not return the baseline SFFQ, had been previously diagnosed with cancer (except non–melanoma skin cancer prior to baseline), left extensive items blank on the baseline SFFQs for each analysis (>10 in 1980, >11 in 1984, and ≥70 in 1986), or reported implausible energy intake at baseline (<500 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men). As a result, 88,759 women in the NHS and 47,828 men in the HPFS were included for the analyses, for which follow-up started in 1980 and 1986, respectively. Person-years of follow-up were estimated from the date that the baseline questionnaire was returned to the date of renal cell cancer diagnosis, date of death, or end of follow-up (May 31, 2000, for women, and January 31, 2000, for men), whichever came first.

Participants were categorized using study-specific absolute cut-points or quartiles on the basis of the distribution of intakes in the study populations. As the main analytic

Table 1. Characteristics of participants by fruit and vegetable consumption in 1986

	Total fruits (servings/d)				Total vegetables (servings/d)			
	<1/d	1-1.9/d	2-2.9/d	≥3/d	<2/d	2-2.9/d	3-3.9/d	≥4/d
NHS women								
Age (y)	51	52	53	54	52	52	53	54
BMI (kg/m^2)	25	25	25	25	25	25	25	25
Physical activity (METS/wk)*	10	12	14	18	9	11	13	17
Alcohol intake (g/d)	14	12	11	9	10	11	12	12
Animal fat (g/d)	37	34	32	30	35	34	33	31
Current smoker (%)	37	24	17	15	31	26	21	18
History of hypertension (%)	24	25	26	27	26	25	26	26
History of diabetes (%)	2.9	3.8	3.8	4.5	3.8	3.7	3.7	4.1
Multivitamin user (%)	36	41	44	47	39	40	42	45
HPFS men								
Age (y)	52	54	55	56	54	54	55	55
BMI (kg/m^2)	26	26	25	25	26	26	26	26
Physical activity (METS/wk)*	15	19	22	27	17	19	21	25
Alcohol intake (g/d)	14	12	11	9	10	11	12	12
Animal fat (g/d)	47	43	40	35	44	42	41	38
Current smoker (%)	18	11	7	5	12	10	9	8
History of hypertension (%)	22	22	22	22	21	22	22	23
History of diabetes (%)	2.4	2.9	3.2	3.8	2.8	2.9	3.3	3.6
Multivitamin user (%)	36	40	44	46	40	40	41	45

NOTE: All values except age were standardized according to the age distribution of cohorts. All values are means except where otherwise noted. Animal fat and dietary fiber values represent the mean energy-adjusted intake.

*METS, metabolic equivalents. One MET is the energy expended by sitting quietly. Each activity was assigned a MET value; e.g., swimming = 7 METS, and running = 12 METS. Total METS per week were calculated by summing all METS per week of each activity.

Table 2. Multivariate RRs for consumption of fruits and vegetables

Food group	Categories (servings)				*P* test for trend	*P* test for between-studies heterogeneity*
Total fruits and vegetables, no. of cases (women; men) †,‡	<3/d (24; 20)	3-4.9/d (41; 37)	5-5.9/d (18; 17)	≥6/d (49; 42)		
RR (95% CI)						
NHS women	1.00	0.73 (0.44-1.23)	0.69 (0.36-1.32)	1.17 (0.66-2.07)	0.25	
HPFS men	1.00	0.61 (0.35-1.07)	0.51 (0.26-1.00)	0.45 (0.25-0.81)	0.02	
Pooled	1.00	0.67 (0.46-0.98)	0.60 (0.38-0.95)	0.73 (0.28-1.87)	0.76	0.02
Total fruits, no. of cases (women; men)	<1/d (23; 19)	1-1.9/d (32; 37)	2-2.9/d (40; 36)	≥3/d (37; 24)		
RR (95% CI)						
NHS women	1.00	0.54 (0.31-0.94)	0.68 (0.39-1.17)	0.78 (0.43-1.40)	0.94	
HPFS men	1.00	0.80 (0.45-1.41)	0.76 (0.42-1.35)	0.47 (0.24-0.91)	0.02	
Pooled	1.00	0.65 (0.44-0.97)	0.71 (0.48-1.06)	0.62 (0.38-1.02)	0.35	0.26
Total vegetables, no. of cases (women; men) ‡	<2/d (33; 31)	2-2.9/d (44; 32)	3-3.9/d (37; 27)	≥4/d (18; 26)		
RR (95% CI)						
NHS women	1.00	1.26 (0.78-2.01)	1.61 (0.94-2.67)	1.17 (0.62-2.20)	0.36	
HPFS men	1.00	0.73 (0.44-1.22)	0.69 (0.40-1.18)	0.44 (0.25-0.77)	0.005	
Pooled	1.00	0.97 (0.57-1.65)	1.06 (0.46-2.44)	0.71 (0.27-1.86)	0.63	0.02
Total citrus fruits, no. of cases (women; men)	<4/wk (44; 47)	4-6.9/wk (29; 18)	1-1.9/d (51; 44)	≥2/d (8; 7)		
RR (95% CI)						
NHS women	1.00	0.84 (0.52-1.34)	1.06 (0.70-1.61)	1.00 (0.46-2.18)	0.83	
HPFS men	1.00	0.59 (0.34-1.03)	0.86 (0.56-1.33)	0.59 (0.26-1.34)	0.26	
Pooled	1.00	0.72 (0.50-1.04)	0.96 (0.71-1.30)	0.78 (0.44-1.37)	0.51	0.36
Cruciferous vegetables, no. of cases (women; men)	<2/wk (39; 54)	2-2.9/wk (43; 25)	3-4.9/wk (33; 18)	≥5/wk (17; 19)		
RR (95% CI)						
NHS women	1.00	1.55 (1.00-2.40)	1.16 (0.72-1.86)	1.04 (0.58-1.86)	0.92	
HPFS men	1.00	0.79 (0.49-1.28)	0.48 (0.27-0.83)	0.67 (0.39-1.16)	0.06	
Pooled	1.00	1.12 (0.58-2.15)	0.75 (0.31-1.79)	0.82 (0.54-1.26)	0.25	0.28
Green leafy vegetables, no. of cases (women; men)	<3/wk (42; 36)	3-4.9/wk (34; 35)	5-6.9/wk (29; 25)	≥1/d (27; 20)		
RR (95% CI)						
NHS women	1.00	1.26 (0.78-2.03)	1.45 (0.88-2.39)	1.49 (0.90-2.48)	0.09	
HPFS men	1.00	1.24 (0.77-2.00)	1.09 (0.65-1.84)	0.72 (0.41-1.27)	0.23	
Pooled	1.00	1.25 (0.89-1.75)	1.26 (0.88-1.81)	1.05 (0.51-2.13)	0.87	0.06
Vitamin C–rich fruits and vegetables, no. of cases (women; men)	<4/wk (22; 25)	4-6.9/wk (17; 16)	1-1.9/d (69; 52)	≥2/d (24; 23)		
RR (95% CI)						
NHS women	1.00	0.52 (0.27-0.98)	0.83 (0.50-1.37)	0.78 (0.41-1.45)	0.97	
HPFS men	1.00	0.48 (0.25-0.90)	0.53 (0.32-0.87)	0.43 (0.24-0.79)	0.04	
Pooled	1.00	0.49 (0.32-0.78)	0.66 (0.43-1.02)	0.58 (0.32-1.03)	0.32	0.18
Legumes, no. of cases (women; men)	<1/wk (47; 47)	1-2.9/wk (72; 53)	≥3/wk (13; 16)			
RR (95% CI)						
NHS women	1.00	1.27 (0.86-1.86)	1.26 (0.66-2.40)		0.41	
HPFS men	1.00	0.97 (0.64-1.47)	0.61 (0.34-1.12)		0.11	
Pooled	1.00	1.12 (0.84-1.48)	0.87 (0.43-1.76)		0.76	0.11
Potatoes, no. of cases (women; men)	<2/wk (39; 34)	2-3.9/wk (59; 45)	4-4.9/wk (15; 16)	≥5/wk (19; 21)		
RR (95% CI)						
NHS women	1.00	1.09 (0.71-1.66)	0.84 (0.45-1.57)	0.73 (0.40-1.34)	0.26	
HPFS men	1.00	1.00 (0.63-1.58)	0.93 (0.49-1.75)	0.69 (0.38-1.26)	0.22	
Pooled	1.00	1.05 (0.77-1.43)	0.88 (0.56-1.38)	0.71 (0.46-1.09)	0.09	0.89

NOTE: In the NHS, multivariate RRs were adjusted for BMI (<25, 25-26.9, 27-29.9, or ≥30 kg/m^2), history of hypertension (yes, no), parity (continuous), history of diabetes (yes, no), smoking status (never, 1-19, 20-39, ≥40 pack-years), multivitamin use (never, past, current <5 yr, current ≥5 yr of use), alcohol intake (continuous), and total energy intake (continuous). In the HPFS, multivariate RRs were adjusted for BMI (<25, 25-26.9, 27-29.9, or ≥30 kg/m^2), history of hypertension (yes, no), smoking status (never, 1-19, 20-39, ≥40 pack-years), multivitamin use (never, past, current <5 yr, current ≥5 yr of use), and total energy intake (continuous).

*For the highest category.

† Number of cases (women; men): a number of cases for women in the NHS and for men in the HPFS.

‡ Potatoes and legumes were excluded from total fruit and vegetable group and total vegetable group.

strategy, cumulative average intakes were calculated from all available questionnaires up to the end of each 2-year follow-up interval. For example, in the NHS, fruit intake in 1980 was used for the analyses of renal cell cancer diagnosed from 1980 to 1984, and the average of fruit intake in 1980 and 1984 was used for the analyses of renal cell cancer diagnosed from 1984 to 1986. Additional analyses were done using a simple update of dietary intake and using only baseline intake. Simple updated intakes were calculated using the most recent SFFQs prior to the diagnosis. For example, fruit intake in 1980

Table 3. Multivariate RRs for intakes of vitamins A, C, and E, and carotenoids

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* test for trend	*P* test for between-studies heterogeneity*
Total vitamin A †						
Median, IU/d (women; men) ‡	(6,644; 7,306)	(10,210; 11,284)	(13,852; 15,872)	(20,320; 24,856)		
RR (95% CI)						
NHS women	1.00	1.03 (0.58-1.81)	1.48 (0.86-2.52)	1.40 (0.80-2.47)	0.17	
HPFS men	1.00	0.78 (0.47-1.29)	0.82 (0.49-1.35)	0.41 (0.22-0.78)	0.009	
Pooled	1.00	0.88 (0.60-1.28)	1.09 (0.61-1.95)	0.77 (0.23-2.54)	0.78	0.005
Dietary vitamin A						
Median, IU/d (women; men)	(5,852; 6,451)	(8,582; 9,368)	(11,358; 12,628)	(16,134; 18,724)		
RR (95% CI)						
NHS women	1.00	1.04 (0.61-1.76)	1.12 (0.67-1.87)	1.37 (0.83-2.27)	0.17	
HPFS men	1.00	1.05 (0.65-1.71)	0.71 (0.42-1.19)	0.47 (0.26-0.84)	0.003	
Pooled	1.00	1.05 (0.73-1.49)	0.89 (0.57-1.39)	0.81 (0.28-2.33)	0.72	0.006
Total vitamin C †						
Median, mg/d (women; men)	(96; 114)	(154; 190)	(242; 328)	(633; 907)		
RR (95% CI)						
NHS women	1.00	1.05 (0.63-1.76)	0.91 (0.53-1.57)	0.89 (0.51-1.56)	0.60	
HPFS men	1.00	0.75 (0.45-1.26)	0.77 (0.44-1.35)	0.97 (0.55-1.71)	0.64	
Pooled	1.00	0.89 (0.62-1.29)	0.84 (0.57-1.24)	0.93 (0.62-1.38)	0.95	0.84
Dietary vitamin C						
Median, mg/d (women; men)	(79; 91)	(116; 137)	(148; 177)	(196; 243)		
RR (95% CI)						
NHS women	1.00	0.81 (0.48-1.38)	0.94 (0.57-1.55)	1.20 (0.74-1.95)	0.29	
HPFS men	1.00	0.58 (0.34-0.98)	0.70 (0.43-1.15)	0.51 (0.30-0.88)	0.03	
Pooled	1.00	0.69 (0.47-0.99)	0.81 (0.57-1.15)	0.79 (0.35-1.82)	0.76	0.02
Total vitamin E †						
Median, mg/d (women; men)	(6; 8)	(9; 11)	(14; 18)	(103; 162)		
RR (95% CI)						
NHS women	1.00	0.94 (0.54-1.65)	1.16 (0.65-2.08)	1.20 (0.66-2.16)	0.55	
HPFS men	1.00	0.98 (0.59-1.63)	0.65 (0.36-1.19)	0.67 (0.36-1.24)	0.38	
Pooled	1.00	0.96 (0.66-1.40)	0.88 (0.49-1.55)	0.90 (0.51-1.60)	0.74	0.18
Dietary vitamin E						
Median, mg/d (women; men)	(6; 8)	(7; 9)	(8; 11)	(10; 13)		
RR (95% CI)						
NHS women	1.00	1.46 (0.85-2.49)	1.66 (0.99-2.81)	1.31 (0.75-2.28)	0.41	
HPFS men	1.00	1.32 (0.78-2.23)	0.88 (0.50-1.54)	0.97 (0.56-1.70)	0.56	
Pooled	1.00	1.38 (0.95-2.02)	1.22 (0.65-2.28)	1.13 (0.76-1.67)	0.97	0.46
α-Carotene						
Median, μg/d (women; men)	(254; 351)	(444; 577)	(707; 898)	(1,327; 1,668)		
RR (95% CI)						
NHS women	1.00	0.82 (0.49-1.38)	1.23 (0.77-1.96)	0.90 (0.54-1.49)	0.89	
HPFS men	1.00	1.36 (0.83-2.22)	0.99 (0.59-1.67)	0.53 (0.29-0.98)	0.007	
Pooled	1.00	1.07 (0.65-1.74)	1.12 (0.79-1.58)	0.71 (0.42-1.19)	0.26	0.19
β-Carotene †						
Median, μg/d (women; men)	(1,963; 2,371)	(3,244; 2,718)	(4,678; 5,293)	(7,242; 8,518)		
RR (95% CI)						
NHS women	1.00	1.08 (0.63-1.84)	1.38 (0.83-2.29)	1.24 (0.74-2.09)	0.36	
HPFS men	1.00	0.91 (0.55-1.50)	0.81 (0.49-1.36)	0.57 (0.32-0.99)	0.04	
Pooled	1.00	0.98 (0.68-1.42)	1.06 (0.63-1.78)	0.84 (0.39-1.82)	0.70	0.04
β-Cryptoxanthin						
Median, μg/d (women; men)	(24; 21)	(53; 52)	(86; 94)	(152; 179)		
RR (95% CI)						
NHS women	1.00	0.87 (0.52-1.47)	1.11 (0.68-1.82)	1.02 (0.61-1.69)	0.76	
HPFS men	1.00	0.84 (0.52-1.38)	0.72 (0.44-1.19)	0.48 (0.27-0.84)	0.008	
Pooled	1.00	0.86 (0.60-1.23)	0.90 (0.59-1.37)	0.70 (0.34-1.47)	0.43	0.05
Lutein/zeaxanthin						
Median, μg/d (women; men)	(1,552; 1,523)	(2,623; 2,629)	(4,111; 3,794)	(7,248; 6,044)		
RR (95% CI)						
NHS women	1.00	1.22 (0.71-2.08)	1.54 (0.93-2.57)	1.36 (0.81-2.29)	0.30	
HPFS men	1.00	0.77 (0.46-1.27)	0.92 (0.57-1.48)	0.46 (0.26-0.82)	0.02	
Pooled	1.00	0.96 (0.61-1.51)	1.18 (0.70-1.97)	0.80 (0.28-2.30)	0.62	0.006
Lycopene§						
Median, μg/d (women; men)	(3,668; 4,192)	(5,936; 7,082)	(8,308; 10,220)	(12,296; 16,180)		
RR (95% CI)						
NHS women	1.00	0.90 (0.51-1.57)	0.88 (0.51-1.54)	0.90 (0.51-1.57)	0.76	

(*Continued on the following page*)

Table 3. Multivariate RRs for intakes of vitamins A, C, and E, and carotenoids (Cont'd)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* test for trend	*P* test for between-studies heterogeneity*
HPFS men	1.00	0.90 (0.55-1.49)	0.77 (0.46-1.29)	0.71 (0.42-1.20)	0.18	
Pooled	1.00	0.90 (0.62-1.31)	0.82 (0.56-1.20)	0.79 (0.54-1.16)	0.20	0.56

NOTE: Multivariate RRs were adjusted for the same covariates listed in Table 2.
*For the highest category.
† From food and supplement.
‡ Median (women; men): median for quartile from women in the NHS and median for quartile from men in the HPFS.
§In the NHS, the analysis for lycopene was started in 1984, and 106 cases were included because the main food sources were not assessed in 1980.

was used for the analyses of renal cell cancer diagnosed from 1980 to 1984, and fruit intake in 1984 was used for the analyses of renal cell cancer diagnosed from 1984 to 1986. In the baseline analyses, we used only the baseline SFFQs. Vitamins and carotenoids were energy-adjusted using the residuals from the regression of nutrient intake on total energy intake (28). The relative risks (RR) were calculated using the Cox proportional hazards model (29) with SAS PROC PHREG (30). By stratifying according to age in months at the start of each questionnaire cycle and calendar year of the current questionnaire cycle, we controlled as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales. In the multivariate models, we also adjusted for possible risk factors, including body mass index (BMI; <25, 25-26.9, 27-29.9, ≥30 kg/m^2), smoking (never, 1-19, 20-39, ≥40 pack-years of smoking), history of hypertension (yes, no), multivitamin use (never, past, current <5 years, and current ≥5 years of use), alcohol intake (continuous), and total energy intake (continuous) in both men and women. We adjusted for parity (continuous) and history of diabetes (yes, no) in women. Because history of diabetes in men was not associated with risk of renal cell cancer, we did not include it in the study-specific multivariate models. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; 1 pack-year is equivalent to having smoked one pack per day for 1 year. Information on BMI, smoking, history of hypertension, history of diabetes and multivitamin use were updated every 2 years. Parity among women was updated until 1984. Duration of multivitamin use was calculated based on the reported duration at baseline and the subsequent responses to current multivitamin use. Two-sided 95% confidence intervals (95% CIs) were obtained for the RRs. To calculate the *P* values for the test for trend, participants were assigned the median value of their intake category, and this variable was treated as a continuous term in the model.

After obtaining RRs from each cohort, we combined $\log_e$ RRs using a random effects model (31, 32). Heterogeneity between the two studies was assessed by the Q statistic (33, 34). We also did several subgroup analyses and examined whether the association varied by BMI (<25, ≥25 kg/m^2), history of hypertension (yes, no), smoking habits (ever, never), multivitamin use (ever users, never users), or age (<65, ≥65 years). Tests for heterogeneity were conducted using a Wald test based on the pooled estimates of the cross-product term of a continuous exposure variable with a binary modifier variable.

Results

During 1,708,260 person-years of follow-up in the NHS, and 608,265 person-years of follow-up in the HPFS, we documented 132 incident renal cell cancer cases in the NHS, and 116 cases in the HPFS. Women and men who consumed more fruit and vegetables were generally older, smoked less, consumed less animal fat, were more physically active, and were more likely to use multivitamins compared with those who consumed less fruit and vegetables (Table 1). Median intakes of total fruits in 1986 were 2.3 servings/d for women and 2.1 servings/d for men, and median intakes of total vegetables in 1986 were 2.9 servings/d for women and 3.0 servings/d for men.

The consumption of total fruits and vegetables was inversely associated with the risk of renal cell cancer in men, but not in women (Table 2). For men, compared with <3 servings/d, the multivariate RR was 0.45 (95% CI, 0.25-0.81; *P* test for trend = 0.02) for ≥6 servings/d of fruit and vegetable intake. A similar pattern was observed when fruit and vegetable intake was modeled as a continuous variable; the multivariate RR for an increment of one serving of total fruits and vegetables per day was 0.91 (95% CI, 0.84-0.99) in men. Baseline intake of total fruits and vegetables was also associated with a lower risk of renal cell cancer only in men (multivariate RR for ≥6 servings/d versus <3 servings/d = 0.43; 95% CI, 0.24-0.76; *P* test for trend = 0.004). In the simple updated analyses, which used intakes closest to but prior to diagnosis, a significant inverse association was observed in men (data not shown). Neither baseline intake nor recent intake (simple update analysis) of total fruits and vegetables was associated with renal cell cancer risk in women (data not shown). Additional adjustment for physical activity (tertiles) and meat intake (<1, 1-1.9, ≥2 servings/d) did not markedly change the results in either men or women (data not shown).

To address the possibility that the inverse association observed for total fruit and vegetable consumption in men was due to confounding by other healthy lifestyles, we excluded men (58 renal cell cancer cases were excluded in the analysis) who had vigorous physical activity [>36 metabolic equivalents (METS) of physical activity/wk], and never smoked. The association for fruit and vegetable consumption was still inverse, although the confidence intervals were wider based on the smaller sample size. Compared with <3 servings/d, the multivariate RRs were 0.71 (95% CI, 0.32-1.55) for 3 to 4.9 servings/d, 0.39 (95% CI, 0.14-1.11) for 5 to 5.9 servings/d, and 0.57 (95% CI, 0.24-1.31) for ≥6 servings/d (*P* test for trend = 0.23).

Fruit intake and vegetable intake were individually associated with a lower risk of renal cell cancer in men, but not in women, in analyses using cumulative average intakes (Table 2), baseline intake (data not shown), and most recent intake (data not shown). For men, when we simultaneously adjusted for total fruit and total vegetable intakes, similar patterns were still observed for total fruit intake (multivariate RR for ≥3 serving/d versus <1 serving/d = 0.58; 95% CI, 0.29-1.14; *P* test for trend = 0.11) and for total vegetable intake (multivariate RR ≥4 serving/d versus <2 servings/d = 0.50; 95% CI, 0.28-0.89; *P* test for trend = 0.03). We also examined associations with specific fruit and vegetable groups. For men, a significant inverse association was seen only for vitamin C–rich fruits and vegetables; the other groups examined had nonsignificant inverse associations (*P* test for trend >0.1) and cruciferous vegetables had a borderline significant inverse association (*P* test for trend = 0.06). No

clear associations for specific fruit and vegetable groups were observed in women.

To explore a potential explanation for the different results between women and men, we examined whether reproductive factors such as postmenopausal hormone therapy use (past and current use, never use and premenopausal), number of children (0-2, ≥3 children), and oral contraceptive use (ever user, nonuser) modified the risk of renal cell cancer in women. We did not find any clear association of total fruit and vegetable consumption with renal cell cancer risk in each subgroup, although we had limited statistical power (data not shown). Also, when we limited our analyses to only postmenopausal women, and when we used 1986 as the starting point of follow-up time in the NHS to make the age distribution and SFFQs used in the NHS (86 renal cell cancer cases were included) compatible with those of the HPFS, no clear associations were observed in women (data not shown).

As observed for fruit and vegetable consumption, intakes of dietary and total vitamin A were inversely associated with renal cell cancer risk only in men (Table 3). When we examined total retinol (preformed vitamin A) intake, of which the primary contributors in our cohorts were multivitamins, liver, vitamin A–fortified milk, and cereals, in relation to renal cell cancer risk, no association was found (data not shown). Given our findings and a high correlation between dietary vitamin A and vegetable intake ($r \approx 0.7$ across the follow-up period), we cannot rule out the possibility that the inverse association observed for vitamin A in men could be due to other nutrients or bioactive compounds in vegetables that we did not examine.

Dietary vitamin C intake from food only was associated with a lower risk of renal cell cancer only in men, but total vitamin C intake (from food and supplements) was not significantly associated with the risk of renal cell cancer in either men or women. Current vitamin C supplement use was not associated with the risk of renal cell cancer; compared with nonusers, the multivariate RRs for vitamin C supplemental users were 1.09 (95% CI, 0.68-1.73) in men and 0.82 (95% CI, 0.54-1.24) in women.

We did not find an association between dietary or total vitamin E intake and the risk of renal cell cancer in either women or men. When examining vitamin E supplements alone, we found no clear associations in either men (multivariate RR for current user versus nonuser, 0.80; 95% CI, 0.49-1.30) or women (multivariate RR for current user versus nonuser, 1.21; 95% CI, 0.80-1.86).

We found that individual carotenoids except lycopene were significantly associated with a lower risk of renal cell cancer in men only (Table 3). The proportion of β-carotene supplemental users was low (average of 3.1% in women and 7.0% in men across the follow-up periods) and the main sources of carotenoids were fruits and vegetables ($r \approx 0.7$ with fruits for β-cryptoxanthin; $r = 0.6$-0.8 with vegetables for α-carotene, β-carotene, lycopene, and lutein/zeaxanthin).

When we examined the most recent intake (closest to but prior to diagnosis for renal cell cancer cases) or baseline intake, we found similar associations as observed for the cumulative average intakes (data not shown). We simultaneously modeled total carotenes (including α-carotene, β-carotene, and β-cryptoxanthin) and dietary vitamin C as continuous variables, and found that the intake of total carotenes was significantly associated with a lower risk of renal cell cancer (for an increment of 4,000 IU/d, multivariate RR, 0.83; 95% CI, 0.71-0.97), but dietary vitamin C was not (for an increment of 100 mg/d, multivariate RR, 0.92; 95% CI, 0.68-1.24).

To examine whether carotenoids and vitamin C accounted for the inverse association of fruit and vegetable consumption in men, we adjusted for total carotenes (continuous), lutein/zeaxanthin, and vitamin C (continuous), although they were correlated with fruit and vegetables. In these analyses, the inverse association for total fruit and vegetable consumption was still observed (multivariate RR comparing ≥6 servings/d versus <3 servings/d = 0.66; 95% CI, 0.32-1.36; P test for trend = 0.31).

We also examined whether the associations between fruit and vegetable intakes and renal cell cancer risk varied by multivitamin use (ever users, never users), smoking status (never, ever), BMI (<25, ≥25 kg/m^2), history of hypertension (yes, no), and age (<65, ≥65 years; Table 4). For men, the inverse association was more pronounced in men who were older, who had never smoked, and who had ever used multivitamins.

Discussion

We found that the consumption of fruits and vegetables was associated with a lower risk of renal cell cancer in men. In contrast, a clear association was not observed in women. Similarly, the inverse associations for vitamins A and C from food and individual carotenoids were limited to men, which may be due to the effects of fruits and vegetables. However, no clear association was observed for vitamin E intake.

A statistically significant inverse association (12, 35-37) or nonsignificant inverse association (10) between total vegetable intake and renal cell cancer risk has been observed in some, but not all (38, 39), case-control studies. Although the

Table 4. Multivariate RRs for one increment of serving of fruits and vegetables per day by multivitamin use, smoking status, BMI, history of hypertension, and age

	Multivitamin use		Smoking status		BMI (kg/m^2)		History of hypertension		Age (y)	
	Ever	Never	Never	Ever	<25	≥25	No	Yes	<65	≥65
Person-years										
Women	1,035,515	672,658	784,466	923,707	927,832	780,340	1,206,382	501,790	1,437,421	270,752
Men	411,082	197,072	309,200	298,980	264,044	344,136	428,390	179,790	262,317	59,155
No. of cases										
Women	93	39	53	79	59	73	63	69	88	44
Men	70	46	45	71	43	73	58	58	78	38
Total fruits and vegetables										
Women	1.06 (0.96-1.18)	1.14 (0.97-1.33)	1.08 (0.94-1.23)	1.09 (0.97-1.22)	1.16 (1.03-1.30)	1.01 (0.89-1.14)	1.14 (1.02-1.27)	1.01 (0.88-1.15)	1.11 (1.00-1.23)	1.02 (0.88-1.19)
Men	0.84* (0.74-0.94)	1.01* (0.91-1.13)	0.82* (0.71-0.95)	0.96* (0.87-1.06)	0.96 (0.84-1.09)	0.89 (0.80-0.99)	0.95 (0.85-1.06)	0.87 (0.77-0.99)	0.96* (0.88-1.05)	0.80* (0.68-0.94)
Pooled	0.94 (0.75-1.17)	1.07 (0.94-1.23)	0.94 (0.72-1.22)	1.02 (0.90-1.14)	1.05 (0.87-1.27)	0.94 (0.83-1.06)	1.04 (0.87-1.24)	0.94 (0.82-1.07)	1.03 (0.89-1.18)	0.90 (0.71-1.15)

NOTE: Multivariate RRs were adjusted for the same covariates listed in Table 2.
*$P < 0.05$ for interaction by stratification.

results from case-control studies regarding fruit intake have been inconclusive (10, 12, 35-39), case-control studies which included >1,000 RCC cases showed a statistically significant or nonsignificant inverse association for total fruits (10), total vegetables (10), and subgroups of vegetables (11, 12), corresponding with our results.

Five prospective cohort studies (6-8, 14, 40) have examined the associations between total fruit and vegetable consumption. One U.S. prospective study (40) that included 14 cases of RCC found a RR of 0.21 (95% CI, 0.05-1.45) for three or more times a week compared with less than three times a week of fruit intake, and a RR of 0.34 (95% CI, 0.11-1.10) for the same contrast of intake of green salads. The Iowa Women's Health Study (14) reported an age-adjusted RR of 1.56 (95% CI, 0.83-2.92) for >42 servings/wk of fruits and vegetables compared with <28 servings/wk. In the same study with a longer follow-up, there was no association for total fruit and vegetable consumption (but RRs were not reported; ref. 5). The European Prospective Investigation into Cancer and Nutrition study found no association (RR, 1.02; 95% CI, 0.93-1.11) for an increment of 80 g/d of fruit and vegetable consumption (7), and nonsignificant inverse associations for total fruits and vegetables were observed in the Netherlands Cohort Study (RR, 0.78; 95% CI, 0.50-1.21; ref. 6) and in the Swedish Mammography Cohort (RR, 0.59; 95% CI, 0.26-1.34; ref. 8). The inconsistency of our findings with the other studies regarding fruit and vegetable consumption could be due to chance, follow-up time, different types of vegetables, the range of intakes of vegetables, different food frequency questionnaires, and different lifestyle factors such as multivitamin use, smoking habits, or postmenopausal hormone therapy.

However, Swedish women with ≥12 servings of vegetables per month (3 servings/wk) had a lower risk of renal cell cancer compared with those with ≤11 servings per month (8). In the European Prospective Investigation into Cancer and Nutrition study, the cubic spline regression curve showed an increased risk of renal cell cancer at very low vegetable consumption levels (90-130 g/d; ~1 serving/d).

There are individual fruits and vegetables that have been associated with renal cell cancer risk in these studies. Intake of root vegetables (e.g., carrots, beets) was associated with a lower risk of renal cell cancer in the European Prospective Investigation into Cancer and Nutrition study (7) and the Swedish Mammography Cohort (8), and banana consumption decreased renal cell cancer risk in the Swedish Mammography Cohort (8) and the Netherlands Cohort Study (6). In agreement with other studies, a significant inverse association for carrot intake and a borderline significant inverse association for banana intake were observed in men in our data (data not shown).

We found that the association for vegetables was more pronounced among men who used multivitamins or did not smoke. In three case-control studies (10-12) examining interactions between vegetable consumption and smoking habits, two of these studies found that the inverse association was stronger among nonsmokers (10, 11).

Because the inverse associations for total fruits and vegetables in men were consistently observed in our data after excluding men who had healthy lifestyles and after controlling for physical activity and meat consumption, it is unlikely that residual confounding by healthy lifestyles explains our findings. In addition, whereas men with greater total vitamin C intake were also more likely to have healthy lifestyles, we did not find any clear protective effect of total vitamin C intake.

We did not find clear associations for fruit and vegetable consumption in women. There are several possible explanations for the lack of a clear association. First, it could be a chance finding. Secondly, it is possible that the effects of fruit intake and vegetable intake are modified by hormones such as estrogen and progesterone. More than twice as many men develop renal cell cancer than do women, which suggests the possibility of a gender difference. The difference in magnitude or direction of association by gender varied across studies. The majority of studies adjusted for gender or combined both genders when examining fruit and vegetable intake in relation to renal cell cancer. One case-control study found an inverse association for the intake of vegetables only in women (12), but another study found an inverse association for the intake of fruits and vegetables only in men (35). There is little prior research to support an interaction between diet and hormones. In our data, the association did not vary by postmenopausal hormone therapy use, parity, or oral contraceptive use, although we had limited statistical power in these subgroup analyses. The joint effect of diet and hormones merits further study. Third, fruit and vegetable intakes may have been too high in our female study participants to observe an effect if only low vegetable intake is associated with an increased risk of renal cell cancer in women. We were not able to examine the effect of <1 serving/d of vegetables due to the limited number of participants with low intake.

Furthermore, random misclassification, which is inherent when collecting dietary information, may have obscured an association if the true effect in women is not as strong as that in men. However, because an inverse association between fruit intake and ischemic stroke was found in our female cohort (multivariate RR, 0.69; 95% CI, 0.49-0.98 for the highest quintile versus the lowest; ref. 16) and because the use of repeated assessments of diet reduces measurement error (41), the lack of association observed in women is not likely to be entirely due to random misclassification.

Although our findings in the subgroup analyses are not conclusive due to limited power, fruit intake or vegetable intake may be more beneficial to those who are older and overweight, or to those with renal cell cancer risk factors such as high blood pressure and insulin resistance (2).

Our data suggests that preformed vitamin A, or vitamins C and E are not responsible for the reduction in renal cell cancer risk in men. Because we were not able to separate the effect of each carotenoid from the effects of fruits and vegetables due to high correlations between carotenoids and fruits and vegetables, we cannot exclude the possibility of independent effects of α-carotene, β-carotene, β-cryptoxanthin, and lutein/zeaxanthin on renal cell cancer risk. Information on antioxidants in relation to renal cell cancer risk from prospective studies is sparse. The Iowa Women's Health Study (5) found that vitamin C (from both food and supplements) was positively associated with renal cell cancer risk, but vitamin E (from both food and supplements) was inversely associated with renal cell cancer risk. In the same study with a shorter follow-up period, vitamin A and carotene were not associated with risk (14). The majority of case-control studies have found nonsignificant inverse associations for vitamin C (10-12), and β-carotene (10, 12, 13). The associations from only a few case-control studies for vitamin E (12, 42), β-carotene (11), and vitamin C (among nonsmokers; ref. 10) reached statistical significance.

The strengths of this study include a prospective design with a long and high rate of follow-up. Therefore, we minimized the potential for information and selection bias. Repeated measurements of nondietary and dietary factors allowed for good control for confounding and for assessments of long-term and recent intake. In addition, we were able to reduce the measurement error. Because we had collected comprehensive information on supplement use, we were able to examine whether each of these vitamins had an effect on renal cell cancer risk independent of fruits and vegetables. We had a limited number of cases to examine whether these associations were modified by reproductive factors. Because of the limited number of participants who had low intakes of

fruits and vegetables in our study, we could not examine the effect of very low intake.

In conclusion, we found that the consumption of fruits and vegetables was inversely associated with the risk of renal cell cancer in men, but not in women. Carotenoids may partly contribute to the inverse associations observed for fruit and vegetable consumption in relation to renal cell cancer risk, but components other than carotenoids in fruit and vegetables should be considered.

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Intakes of Fruits, Vegetables, Vitamins A, C, and E, and Carotenoids and Risk of Renal Cell Cancer

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