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Effects of supplemental alpha-tocopherol and beta-carotene on urinary tract cancer: incidence and mortality in a controlled trial (Finland)

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Abstract

Objectives: Epidemiological studies have suggested a protective effect of vegetables and fruits on urinary tract cancer but the possible protective nutrients are unknown. We studied the effect of alpha-tocopherol (a form of vitamin E) and beta-carotene supplementation on urinary tract cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.
Methods: A total of 29,133 male smokers aged 50–69 years from southwestern Finland were randomly assigned to receive alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or a placebo daily for 5–8 years (median 6.1 years). Incident urothelial cancers (bladder, ureter, and renal pelvis; n = 169) and renal cell cancers (n = 102) were identified through the nationwide cancer registry. The diagnoses were centrally confirmed by review of medical records and pathology specimens. The supplementation effects were estimated using a proportional hazards model.
Results: Neither alpha-tocopherol nor beta-carotene affected the incidence of urothelial cancer, relative risk 1.1 (95% confidence interval (CI) 0.8–1.5) and 1.0 (95% CI 0.7–1.3), respectively, or the incidence of renal cell cancer, relative risk 1.1 (95% CI 0.7–1.6) and 0.8 (95% CI 0.6–1.3), respectively.
Conclusion: Long-term supplementation with alpha-tocopherol and beta-carotene has no preventive effect on urinary tract cancers in middle-aged male smokers.

Introduction

There are about half a million new cases of urinary tract cancer worldwide annually, with the highest incidence rates in Europe and North America [1]. Smoking and occupational exposure to arylamines are established causes of bladder and renal pelvic cancer [2], and it is estimated that cigarette smoking accounts for 50% of the male cases and 25% of the female cases in the general population [3]. Smoking is also causally related to renal cell cancer and contributes to as many as one-third of all cases [4]. Otherwise the etiology of urinary tract cancers is largely undefined. Several epidemiological studies have investigated the role of diet in the etiology of these cancers but their findings are equivocal [5, 6]. Available data suggest that a diet rich in vegetables and fruits may protect against urinary tract cancer. Micronutrients have been examined in a limited number of studies which suggest potential protection for carotenoids against bladder cancer [5], but a recent large cohort study found no association between intake of alpha-carotene, beta-carotene, lycopene, lutein, or beta-cryptoxanthin, and the risk of bladder cancer [7].

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) is a controlled trial to test the hypothesis that supplementation with alpha-

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tocopherol or beta-carotene reduces cancer incidence. We report here the effects of these supplements on the incidence of and mortality from urinary tract cancer.

Materials and methods

The ATBC Study participants were male smokers (five or more cigarettes per day at entry) aged 50–69 years, who were recruited from the total male population of this age group in southwestern Finland (n = 290,406) from 1985 through 1988. Subjects with prior cancer, or serious disease limiting long-term participation, or who used vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses were excluded. The rationale, methods, participant characteristics, compliance, and main results of the ATBC Study have been reported [8, 9].

At baseline, medical, dietary, smoking, and other background data were obtained, along with height and weight, and a serum sample. Dietary intakes of vitamin E and beta-carotene were estimated from a diet history questionnaire [10], while serum concentrations of alpha-tocopherol and beta-carotene were determined by high-pressure liquid chromatography [11] and serum total cholesterol measured enzymatically (CHOD/PAP, Boehringer Mannheim, Mannheim, Germany).

Participants (n = 29,133) were randomly assigned to receive either alpha-tocopherol (50 mg), or beta-carotene (20 mg), or both agents, or placebo in one capsule daily. A two-by-two factorial design allowed assessment of the two agents independently, with one-half of the participants receiving alpha-tocopherol (n = 14,564) and one-half not (n = 14,569); similarly half received beta-carotene (n = 14,560) and half did not (n = 14,573). Intervention continued for 5–8 years (median 6.1 years) until April 1993.

Participants had three follow-up visits annually, during which information regarding illnesses, symptoms, and smoking were collected and a new capsule pack given. The remaining capsules were returned at each visit, and overall capsule compliance was estimated by dividing the total number of nonreturned capsules by the number of days in the trial. Capsule compliance (median 99% of on-study capsules taken) and dropout rate (31%) were similar across the four intervention groups.

The study was approved by the review boards of the participating institutions. Participants gave written informed consent before randomization, and their interests were upheld by an outside Data and Safety Monitoring Committee twice a year throughout the trial.

Urinary tract cancers were identified through the Finnish Cancer Registry and the Register of Causes of Death. Cases known to have been diagnosed up to the end of the intervention period, 30 April 1993, were included in this article. There were 152 cases of bladder cancer, six of ureter cancer, 11 of renal pelvis cancer, and 102 of renal cell cancer; no case of cancer of the urethra was diagnosed. Since the uroepithelium from renal pelvis through ureter to bladder is considered one contiguous tissue, these sites were combined for analysis (n = 169 urothelial cancers). Two men had urothelial and renal cell cancer, thus both men were included in the respective analyses of urothelial and renal cell cancer. After the initial publication of the ATBC Study [9], one bladder cancer case was reclassified as non-malignant (inverted papilloma) in a subsequent pathology review and two cases were found to have been diagnosed with cancer of renal pelvis prior to the bladder malignancy.

Histopathologic and cytologic specimens from patients with urinary tract cancers were obtained for central review. At least one specimen was received from all cases of urothelial cancer; 166 cases (98%) had histologic specimen and three cases (2%) had only cytologic. The slides were reviewed independently by two pathologists for malignancy, histologic type, grade, and the extent of the primary tumor. The diagnosis was transitional cell carcinoma in 165 cases and squamous cell carcinoma in one case. In the three cases with cytologic specimens only, the review suggested transitional cell carcinoma. In 94 (92%) of the 102 renal cell cancer cases, the diagnosis was based on histologic evidence; in central review adenocarcinoma was verified in all the cases.

The medical records of the patients with urinary tract cancer were reviewed centrally for diagnostic confirmation and staging by two clinical oncologists who worked independently but who used the results of the central pathologic review. A random sample of 50 urothelial and 17 renal cell cancer cases was re-reviewed by a urologist who confirmed all the diagnoses.

Staging was based on the 1992 criteria for urinary tract cancers of the American Joint Committee on Cancer and was undertaken during 1992 through 1994 [12]. Stage 0a tumors of the urothelial cancers include non-invasive papillary carcinoma, and 0is tumors include carcinoma *in situ* ("flat tumor"). Stage I tumors include those invading subepithelial connective tissue, stage II include those invading deep muscle, stage III include those invading perivesical fat or the prostate, and stage IV include those invading the pelvic wall or the abdominal wall and all tumors with regional lymph node or distant metastasis. Stage I renal cell cancer includes tumors 2.5 cm or less within the kidney, stage II

tumors include those more than 2.5 cm but within the kidney, stage III include those extending into major veins or invading the adrenal gland or perinephric tissue, or having a metastasis, 2 cm or less, in a single regional lymph node, and stage IV tumors include those invading beyond Gerota's fascia or having multiple metastases or one greater than 2 cm in regional lymph nodes, or distant metastasis.

The analyses estimating the effect of supplementations on urothelial and renal cell cancer incidences and mortalities were based on the intention-to-treat principle; *i.e.* follow-up and case count continued irrespective of dropout from trial participation. In the analyses of urothelial cancer (169,400 person-years through 30 April 1993), other cancers, including renal cell cancer, were ignored as well as correspondingly in the analyses of renal cell cancer (169,625 person-years). Kaplan–Meier cumulative incidence curves and two-sided p values from the unweighted logrank statistic are presented separately for the alpha-tocopherol and beta-carotene recipients and nonrecipients, after testing the interaction of the agents by the likelihood ratio test. The supplementation effects were estimated by the proportional hazards model and are reported with 95% confidence intervals [13]. The supplementation effects, possibly modified by baseline current smoking and alcohol consumption – because of their reported interaction with beta-carotene in relation to lung cancer incidence [14, 15] – were analyzed accordingly, with smoking divided into three categories (less than 20, 20–29, and more than 29 cigarettes per day) and alcohol consumption by median. Difference in the frequency distributions of categorical variables was compared with the χ^2 test.

The associations between quartiles of baseline dietary intakes and serum concentrations of alpha-tocopherol and beta-carotene and the incidences of urinary tract cancers were calculated by the proportional hazards model adjusting for baseline age, number of cigarettes smoked daily, years of smoking, body mass index, daily coffee consumption, serum total cholesterol, education, and intervention group.

Results

There were no differences in the background factors between the intervention groups at baseline (Table 1). The median age of the trial participants was 57.1 years, they had smoked 36 years, they smoked 20 cigarettes daily currently, and their body mass index was 26.0 kg/m^2.

Urothelial cancer (bladder, renal pelvis, and ureter)

Of the 169 incident cases of urothelial cancer, 47 were in the alpha-tocopherol-alone group, 42 in the alpha-tocopherol plus beta-carotene group, 43 in the beta-carotene-alone group, and 37 were in the placebo group. The differences in incidences between the four groups were not statistically significant (p = 0.87). There was no interaction between alpha-tocopherol and beta-carotene supplementation effects (likelihood ratio test, p = 0.39).

The cumulative incidence of urothelial cancer was similar among men receiving and not receiving alpha-tocopherol, relative risk 1.1 (95% CI 0.8–1.5) (Figure 1). Similarly, beta-carotene supplementation had no effect on the incidence of urothelial cancer, relative risk 1.0 (95% CI 0.7–1.3). Neither was the effect of beta-carotene modified by the number of cigarettes smoked daily, or average daily alcohol consumption.

The majority of urothelial cancers were of stage 0a (54%) when diagnosed, 5% were of stage 0is, 14% of

Table 1. Baseline characteristics (median or proportion) of the men by the intervention group in the ATBC study

Characteristic	Alpha-tocopherol	Alpha-tocopherol and beta-carotene	Beta-carotene	Placebo
Number of subjects	7286	7278	7282	7287
Age (years)	57.1	57.3	57.2	56.9
Serum total cholesterol (mmol/l)	6.15	6.18	6.14	6.15
Cigarettes smoked/day	20	20	20	20
Years of smoking	36	36	37	36
Body mass index (kg/m^2)	26.0	26.0	25.9	26.0
Coffee consumption (ml/day)	560	550	550	550
Education, ≥junior high school (%)	15	16	15	15
Dietary vitamin E (mg/day)	10.7	10.8	10.8	10.6
Dietary beta-carotene (mg/day)	1.70	1.73	1.70	1.72
Serum alpha-tocopherol (mg/l)	11.5	11.6	11.5	11.5
Serum beta-carotene (μg/l)	168	172	170	171

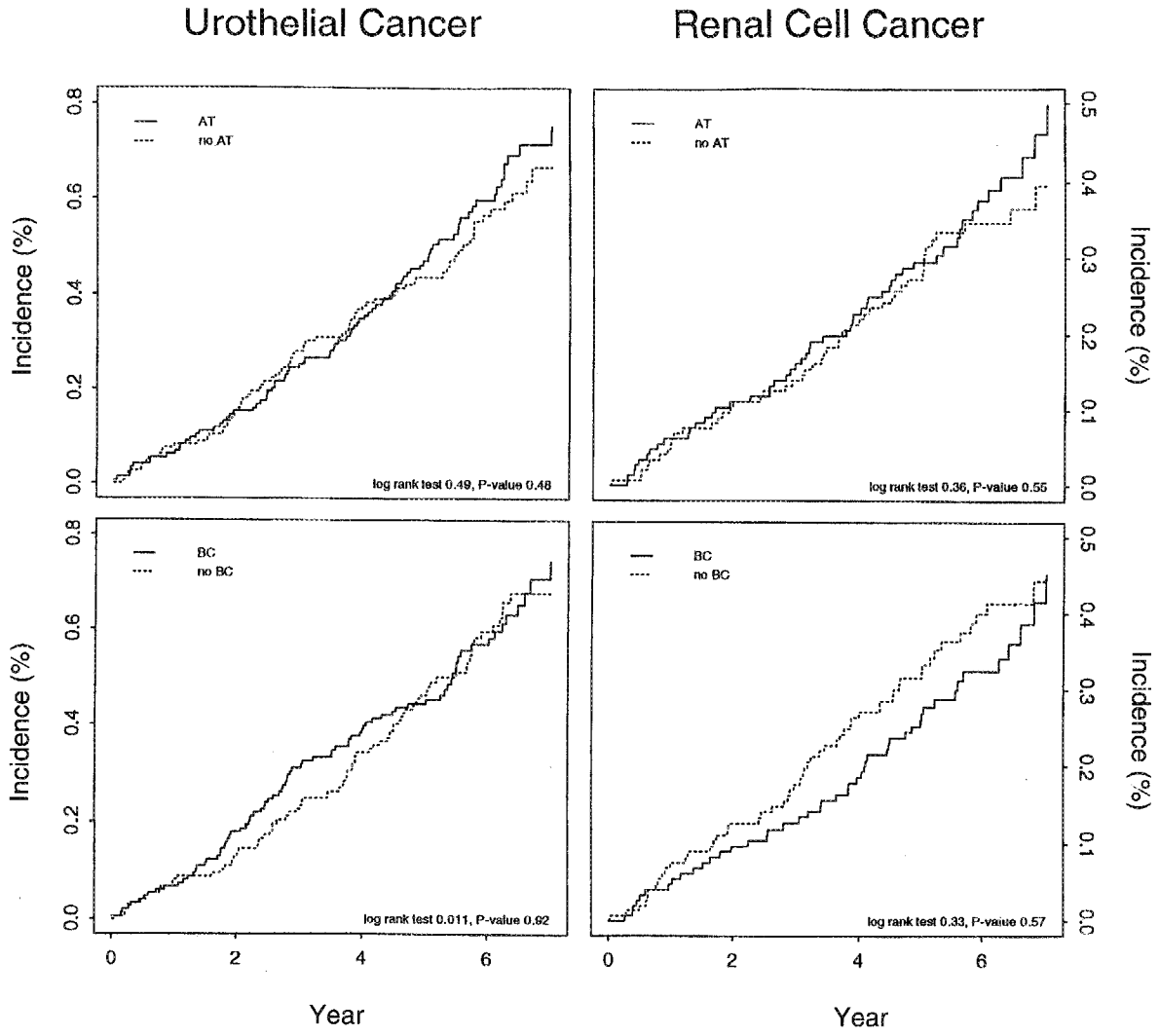

Fig. 1. Kaplan–Meier curves of the cumulative incidence (%) of urothelial (bladder, ureter, and renal pelvis) cancer and renal cell cancer among participants who did and did not receive alpha-tocopherol and beta-carotene, respectively.

stage I, 12% of stage II, 5% of stage III, and 8% of stage IV; 2% could not be staged due to only cytologic specimen (n = 3). The distribution of stages was similar among recipients and nonrecipients of alpha-tocopherol (χ^2 test, $p = 0.17$), and beta-carotene (χ^2 test, $p = 0.47$), respectively. Neither alpha-tocopherol nor beta-carotene affected significantly the risk of subgroups of urothelial cancer: relative risks of 0.9 (95% CI 0.6–1.5) and 0.8 (95% CI 0.5–1.2) for low and moderate grade superficial papillary tumors, respectively, and 1.2 (95% CI 0.8–1.9) and 1.2 (95% CI 0.8–1.9) for other bladder cancers (potentially invasive or invasion already present), respectively.

There were 24 deaths from urothelial cancer: six in the alpha-tocopherol-alone group, eight in the alpha-tocopherol plus beta-carotene group, five in the beta-carotene-alone group, and five in the placebo group. The corresponding mortality rates did not differ ($p = 0.91$).

Some 55% of urothelial cancer cases visited their physician primarily due to macroscopic hematuria, 26% due to urinary discomfort, and 19% because of other symptoms. Hematuria, either macroscopic or microscopic, was reported in 87% of cases of urothelial cancer prior to the diagnosis. Reasons to visit a physician and the presence of hematuria were similar in all four intervention groups.

Analyses were also repeated for bladder cancer separately, with similar results as for the urothelial cancers combined; thus their results are not presented.

Renal cell cancer

Of the 102 incident cases of renal cell cancer, 27 were in the alpha-tocopherol-alone group, 27 in the alpha-tocopherol plus beta-carotene group, 21 in the beta-carotene-alone group, and 27 were in the placebo group. The differences in incidences between the groups were not statistically significant ($p = 0.89$). There was no interaction between alpha-tocopherol and beta-carotene supplementation effects (likelihood ratio test, $p = 0.52$).

The cumulative incidence of renal cell cancer was similar among men receiving and not receiving alpha-tocopherol, relative risk 1.1 (95% CI 0.7–1.6) (Figure 1). Similarly, beta-carotene supplement had no effect on the incidence of renal cell cancer, relative risk 0.8 (95% CI 0.6–1.3). Neither was the effect of beta-carotene modified by the number of cigarettes smoked daily or average daily alcohol consumption.

Nine percent of renal cell cancers were stage I when diagnosed, 37% stage II, 11% stage III, and 43% stage IV. The distribution of stages was similar among recipients and non-recipients of alpha-tocopherol (χ^2 test, $p = 0.95$), and beta-carotene (χ^2 test, $p = 0.52$), respectively. Hematuria, either macroscopic or microscopic, was reported in 25% of cases prediagnostically, as often in all four intervention groups.

There were 41 deaths from renal cell cancer: 11 in the alpha-tocopherol-alone group, 10 in the alpha-tocopherol plus beta-carotene group, six in the beta-carotene-alone group, and 14 in the placebo group. The corresponding mortality rates did not differ ($p = 0.50$).

Association of baseline dietary intake and serum level of alpha-tocopherol and beta-carotene

No association was observed between the baseline dietary intake of vitamin E or serum level of alpha-tocopherol, and the risk of urothelial cancer or renal cell cancer. Dietary intake of beta-carotene was positively associated with the risk of urothelial cancer; relative risks (95% CI) for beta-carotene quartiles (cut-off points 1.1, 1.7, and 2.7 mg/day) were 1.0 (referent), 1.1 (0.7–1.9), 1.7 (1.0–2.8), and 1.7 (1.0–2.9), p for trend = 0.005. No association was found between serum beta-carotene and the risk of urothelial cancer. Neither was there an association between dietary or serum beta-carotene, and renal cell cancer.

Discussion

We found no effect of alpha-tocopherol or beta-carotene supplementation on the incidence of urothelial (bladder, ureter, and renal pelvis) or renal cell cancer. This is in line with the finding of the CARET study, in which the relative risk of bladder cancer (n = 78 cases) was 1.0 (95% CI 0.6–1.7) among those supplemented with the daily combination of 30 mg beta-carotene and 25,000 IU retinyl palmitate for an average of 4.0 years compared with those who received placebo [15]. In the Physicians' Health Study there were 62 cases of bladder cancer among those supplemented with beta-carotene, 50 mg every second day for 12 years, and 41 cases among those receiving placebo, but after adjustment for multiple comparisons this difference was not statistically significant at the 0.05 level [16]. Neither the CARET Study nor the Physicians' Health Study reported findings regarding beta-carotene and renal cell cancer. There are no previous controlled data on the effect of alpha-tocopherol on urinary tract cancers.

Beta-carotene is an important precursor of vitamin A which has been found to promote differentiation of normal and neoplastic cells in tissue culture. Vitamin A and its derivatives effectively inhibit the development of carcinogen-induced bladder cancer in experimental animals [17]. Accordingly the more potent but less toxic vitamin A derivatives have been tested in prevention of recurrence of superficial bladder tumors in humans; only etretinate has shown some efficacy in prevention of recurrence of superficial tumors [18, 19] but not in all trials [20]. We found a non-significant 19% reduction in low and moderate grade superficial papillary tumors among those who received beta-carotene compared with those who did not receive beta-carotene.

Bias is an unlikely explanation for our lack of effect of alpha-tocopherol and beta-carotene supplementation on the incidence of urinary tract cancers. The study population was large, the intervention groups were balanced in all relevant characteristics, and the case ascertainment was essentially complete. The first symptom of urinary tract cancer is often hematuria [21]; in this study 55% of urothelial cancer cases visited their physician primarily due to macroscopic hematuria. Since alpha-tocopherol can affect platelet function, and thus possibly cause increased bleeding tendency [22], it could be speculated that those receiving alpha-tocopherol have more hematuria; consequently they have bladder cancer diagnosed more frequently. However, we found no difference in the frequency of prediagnostic hematuria between the cases who received alpha-tocopherol and those who did not; nor did we find any difference between the intervention groups in the frequencies of other primary reasons to visit a physician prior to cancer diagnosis. Bladder cancer is infrequently diagnosed at autopsy only, suggesting that

nearly all patients will present clinically during their lifetime [23]; also in our population none of the bladder cancer cases was diagnosed at autopsy only. Thus it is likely that there is no bias in detection of urothelial cancer between supplementation groups. The paucity of bladder cancer cases found only at autopsy also implies that the preclinical latency is rather short; thus the possible bleeding tendency related to alpha-tocopherol, if true, will not much advance the diagnosis of bladder cancer.

Epidemiological studies have suggested that diets rich in vegetables, and possibly also in fruit, confer some protection against bladder carcinogenesis [5]. Among the micronutrients there is evidence suggesting potential protection for carotenoids [5]. Findings from studies associating prediagnostic serum beta-carotene and vitamin E concentration with bladder cancer risk show no significant associations [24]. Thus epidemiological studies give only weak support to the hypothesis that vitamin E and beta-carotene are related to the development of bladder cancer. Also we found no evidence that high dietary intake or serum level of alpha-tocopherol or beta-carotene was protective against urothelial cancer, but rather a suggestion of increased risk with increasing intake of beta-carotene; however, we have no plausible explanation for this. We cannot, however, exclude the possible effect of residual confounding, since we had no data on lifetime occupations, which have been shown to account for up to one-fifth of bladder cancer risk [25].

Participants of the ATBC Study were current smokers with a history of an average of 36 years of smoking. Since smoking is a well-established risk factor of bladder cancer, causing about half of the cases, it is likely that a large proportion of bladder cancers in the ATBC Study were caused by smoking. The mechanism through which smoking induces bladder cancer is unknown, but aromatic amines present in small amounts in tobacco, and known to be carcinogenic, are primary candidates as the specific agents [2]. These aromatic amines, however, require metabolic activation to become carcinogenic. The balance of the genetically determined activity of enzymes involved in either formation of these carcinogens, or their detoxification, will determine the actual concentrations of activated carcinogenic compounds reaching the bladder where they damage the genome of mucosal cells. Cigarette smoke also contains substances which increase proliferation of the bladder epithelium and thus contribute to the increased risk of bladder cancer [26]. Other processes, such as injuries caused by urinary calculi, may also increase the risk of bladder cancer by inducing proliferation. Whether vitamin E or beta-carotene could affect urothelial carcinogenesis through involvement in these events is unknown. Our finding of no supplemental effect of these agents on urothelial cancer does not support this possibility. It is likely that the inverse association of dietary carotenoids or vegetables and fruit with bladder cancer in epidemiological studies reflects either incomplete control of cigarette smoking, other compounds of vegetables and fruit, or some other lifestyle factor associated both with high intake of vegetables and fruit and low risk of bladder cancer.

Smoking and obesity are causally related to renal cell cancer; otherwise the risk factors for this site are not well known [27]. Case–control studies have observed an inverse or no association between beta-carotene intake and risk of renal cell cancer [6, 28–30], but no data from prospective cohort studies are so far available. A recent report indicated that low intake of vitamin E (below the lowest decile) increased the risk of renal cell cancer significantly [28]. The mechanism of renal cell carcinogenesis is not known, but it can be hypothesized that the many potentially carcinogenic compounds excreted via the kidney have a role. There is no evidence of the involvement of vitamin E or beta-carotene in such carcinogenesis; this, coupled with our finding of no preventive effect of alpha-tocopherol and beta-carotene supplements on renal cell cancer, suggests that neither agent has any notable role in the prevention of renal cell cancer.

Both the ATBC Study and the CARET Study provided some evidence that current heavy smoking and alcohol consumption may increase the risk of lung cancer among those who received beta-carotene compared with those who did not receive it [14, 15]. In the present study we found no indication that the number of cigarettes smoked daily, or average daily alcohol consumption, would modify the effect of beta-carotene on the risk of urothelial or renal cell cancer.

In conclusion, neither alpha-tocopherol nor beta-carotene supplements reduce the risk of urinary tract cancers in smokers. Smoking cessation is the most effective means to prevent urinary tract cancers, particularly bladder cancer. For renal cell cancer, more epidemiological studies are needed to understand better those factors that may be the target of preventive actions.

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