Published in final edited form as:
J Urol. 2011 April ; 185(4): 1210–1215. doi:10.1016/j.juro.2010.11.081.

Long-Term Use of Supplemental Vitamins and Minerals Does Not Reduce the Risk of Urothelial Cell Carcinoma of the Bladder in the VITamins And Lifestyle Study

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Abstract

Purpose—Urothelial Carcinoma (UC) has the highest lifetime treatment cost of any cancer making it an ideal target for preventative therapies. Previous work has suggested that certain vitamin and mineral supplements may reduce the risk of UC. We sought to use the prospective VITamins And Lifestyle (VITAL) cohort to examine the association of all commonly taken vitamin and mineral supplements as well as 6 common anti-inflammatory supplements with incident UC in a United States population.

Materials&Methods—77,050 eligible VITAL participants completed a detailed questionnaire at baseline on supplement use and cancer risk factors. . After 6 years of follow-up, 330 incident UC cases occurring in the cohort were identified via linkage to the Seattle-Puget Sound Surveillance, Epidemiology and End Results (SEER) cancer registry. We analyzed use of supplemental vitamins (multivitamins, beta-carotene, retinol, folic acid, vitamins B1, B3, B6, B12, C, D and E), minerals (calcium, iron, magnesium, zinc, and selenium), and anti-inflammatory supplements (glucosamine, chondroitin, saw-palmetto, ginko-biloba, fish oil and garlic). For each supplement, the hazard ratios (risk ratios) for UC comparing each category of users to nonusers, and 95% confidence intervals, were determined using Cox proportional hazards regression., adjusted for potential confounders.

Results—None of the vitamin, mineral or anti-inflammatory supplements was significantly associated with UC risk in either age-adjusted or multivariate models.

Conclusions—The results of this study do not support the use of commonly taken vitamin or mineral supplements or 6 common anti-inflammatory supplements for chemoprevention of UC.

Keywords

Urothelial Carcinoma; Supplement; Diet; Nutrition; Cancer Prevention

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INTRODUCTION1

UC of the bladder has an age adjusted incidence of 21.1 cases per 100,000 people, is the fifth most common cancer among both sexes in the United States and has the highest lifetime cost of treatment for any cancer.[1] These features of UC make it an ideal target for preventative strategies.[2] Some have postulated that intake of supplemental vitamins or minerals may help to prevent cancer; large scale trials for other genitourinary malignancies have been undertaken.[3, 4]

Interest in primary and secondary prevention of UC by use of dietary supplements began after a small randomized controlled trial by Lamm et al from 1994.[5] This study examined 65 patients with biopsy proven UC who were randomized to Bacillus Calmette-Guerin (BCG) versus BCG + megadoses of vitamins A, B6, C, E and zinc. That study found that those given the vitamin treatment had significantly lower 5 year estimates of recurrence (41% in megadose group vs. 91% in the control group; p=0.0014). Because higher fruit and vegetable consumption may be associated with a reduction in the risk of UC,[6] this suggests that intake of vitamin and mineral supplements at physiologic doses might be protective. In addition, several epidemiologic studies have found use of supplemental vitamin C and vitamin E to be associated with reduced bladder cancer risk, possibly due to their anti-oxidant effects[7–10] However, other epidemiologic studies have found conflicting results for the association between vitamin supplement use and UC.[118]

Also DNA hypomethylation, a loss of global DNA methylation resulting in genomic instability, has been associated with increased risks of UC[12, 13] suggesting that factors involved in the production of methyl groups including folic acid and B-vitamins may reduce UC risk. Folic acid and B-vitamin supplements, however, have generally not been studied in relation to UC risk. Finally, the use of anti-inflammatory supplements (e.g., glucosamine, chondroitin, and fish oil) is of interest given some evidence to suggest that anti-inflammatory drugs such as COX-2 inhibitors may reduce the risk of UC progression.[2, 14, 15]

We sought to use the prospective VITAL cohort to examine the association of all commonly taken vitamin and mineral supplements as well as 6 common anti-inflammatory supplements with incident UC in a United States population. VITAL was specifically designed to assess the associations of supplement use with cancer risk.

Materials and Methods

Selection of Study Participants

Study participants are members of the VITAL cohort study of 77,719 men and women ages 50 to 76 years living in a 13-county area of western Washington State. The study proposal was approved by the institutional review board of the Fred Hutchinson Cancer Research Center. Methods of cohort recruitment, data collection and follow-up of outcomes have been described.[7] Briefly, cohort recruitment occurred from October 2000 to December 2002 by using a purchased commercial mailing list which identified 364,418 individuals.

79,300 questionnaires were returned, and among them 77,719 met eligibility and quality control checks. For the present analysis we excluded 665 participants who reported a diagnosis of bladder cancer prior to entering the study or had missing data on prior bladder cancer. Participants (n = 4) with incident non-urothelial bladder cancer (pure squamous cell carcinoma or pure adenocarcinoma) were also excluded, leaving 77,050 eligible participants.

[1]Additional tables found at url: (will be provided)

Baseline Data Collection

Baseline data were obtained from a 24-page self-administered questionnaire that included items on dietary supplement use, diet, medical history, personal characteristics and cancer risk factors. We analyzed multivitamins, beta-carotene, retinol, folic acid, vitamin B1, B3, B6, B12, C, D and E as well as the following minerals: calcium, iron, magnesium, zinc, and selenium. For each vitamin and mineral we ascertained intake from single supplements and multivitamins, including the frequency and duration of use of each supplement in the 10 years prior to baseline and the average dose per day.

Information was also recorded on the duration and frequency of multivitamin use and the current brand and most commonly used brand of multivitamin. The amount of each vitamin or mineral contained in the multivitamin was obtained from the *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements 2002*[16] or from the manufacturer (for the 16 multivitamin brands listed in the questionnaire), or the amount reported by the participant (if the multivitamin was not one of the 16 brands listed). Multivitamin use was classified as "pill years": (days per week)/7 × years.

Ten-year average daily intake of each supplemental vitamin and mineral was calculated as: years/10 × days per week /7 × dose per day, and summed over the individual supplement and multivitamin. Vitamin and mineral supplement use was divided into no use and tertiles of ten-year average dose for the common supplements (vitamin C, vitamin E and calcium). For the less common supplements, users were segregated into one of three groups of 10-year average daily intake(units/day): (1) the first tertile, (2) more than the first tertile up to the amount of that nutrient that would be obtained from 10-year daily use of the multivitamin pill Centrum Silver (Wyeth; Madison NJ, USA), or (3) more than the amount of that nutrient that would be obtained from 10-year daily use of the multivitamin pill Centrum Silver (Wyeth; Madison NJ, USA). Thus, participants in the highest category of use only included persons who used an individual supplement with a relatively high amount of that nutrient.

Ten-year average daily intake of anti-inflammatory supplements was divided into three groups based on frequency and duration of use; dose per day was not assessed for these supplements due to inaccuracy of information on supplement bottles. The categories were: (1) no use, (2) a low-use category that included those with a duration of less than 3 years or a frequency of less than 4 days per week, or (3) a high-use category that included those with a duration of at least 3 years and a frequency during that time of at least 4 days per week. A few brands of multivitamins contain saw palmetto, ginko biloba, and/or garlic but in doses of 10–50% of the amount in individual supplements. Individuals who only obtained these compounds from one of those brands of multivitamins were classified into the low-use category.

Follow-Up of Subjects for Urothelial Cancer and Censored Data

Incident cases of UC were ascertained by linkage to the Seattle-Puget Sound SEER cancer registry. A total of 330 incident UC cases were identified. For each subject, the end of follow-up was the earliest of: date of UC (0.43%), date withdrew from the study(0.03%), date moved out of the 13 counties of Western Washington covered by SEER(5.44%), date died (5.69%), or date of last cohort follow-up(December 31, 2007) (88.42%). Deaths were ascertained by linkage to the Washington State death files and moves out of area monitored via the US Post Office National Change of Address system and follow-up letters and phone calls to participants.

Statistical Analyses

For each supplement, the hazard ratios (risk ratios) for UC comparing each category of users to nonusers, and 95% confidence intervals, were determined using Cox proportional hazards regression with age as the time variable. Participants became at risk of UC from their age at completion of the baseline questionnaire through age at end of follow-up. The statistical significance of each supplement variable was tested using a likelihood ratio test for trend with the variable in ordinal form. A base model adjusting for age and gender was performed. Variables to include in the multivariate model were selected a priori including age, gender, race (white, black, other), education, family history of bladder cancer, smoking (never; former, quit>10yrs prior to start of VITAL; former, quit <10 yrs prior to start of VITAL; current), pack years (never smoker and tertiles), and fruit and vegetable intake (quartiles). For all supplements examined, we tested for effect modification by smoking status, by interaction of the ordinal supplement variable with smoking status as current/ever/never. All analyses were performed in STATA v11 (STATACORP, College Station, TX USA).

Results

After a median follow-up of 6 years, 330 incident cases of UC were identified among the 77,050 eligible participants. Participants developing incident UC were significantly more likely to be male, both recency and pack-years of smoking were positively associated with UC risk. Fruit and vegetable intake did not show a statistically significant association with risk of UC (data not shown).

Multivitamin and vitamin supplement use were examined for an association with UC (Table 1). None of the vitamin supplements had a statistically significant association with UC in the age-adjusted or multivariate models. We also found no association between 5 commonly used mineral supplements (calcium, iron, magnesium, zinc, or selenium) and UC (HR for Ca >=319 mg/day vs. non-use 1.00 CI 0.71,1.40, p-trend=0.66; HR for Se >=20 mcg/day vs. non-use 0.97 CI 0.72,1.31, p-trend=0.740) (data not shown). Similarly, six commonly used anti-inflammatory supplements (glucosamine, chondroitin, saw palmetto, ginko biloba, garlic and fish oil) failed to show any statistically significant reduction in incident UC in the multivariate model (HR for high use glucosamine vs. non-use 0.99 CI 0.65,1.50, p-trend=0.432; HR for high use chondroitin vs. non-use 1.06 CI 0.65,1.73, p-trend=0.622; HR for high use fish oil vs. non-use 0.87 CI 0.50,1.51, p-trend=0.497) (data not shown). There was no evidence for effect modification by smoking status for the relationship between any of the supplements and UC risk (data not shown).

Discussion

We found no association between commonly taken vitamin supplements, mineral supplements or 6 common anti-inflammatory supplements and incident UC in a large, contemporary United States cohort.

Past research on supplement use and bladder cancer risk has focused only on the most commonly used supplements: mutivitamins and vitamins A,C and E. In the 1990's, case-control studies of UC found a protective effect associated with use of supplemental vitamins C and E[7] and vitamin A[17] and a small cohort study reported a reduced risk with use of vitamin C supplements among women only[10].

Several large cohort studies have subsequently examined vitamin and mineral supplement use and incident UC.[8, 9, 18] The Health Professional Study was initiated in 1986, had 51,500 white men aged 40–75 and 320 incident cases of UC. They found a reduced risk associated with >10 years of use of vitamin E supplements (RR=0.68, 95%CI 0.45–1.03, p for trend =

0.03) and a borderline reduced risk associated with > 10 years of supplemental vitamin C use (RR=0.73; 95%CI 0.52–1.03, p for trend 0.08).[8] No association was found for multivitamin use or use of supplemental vitamin A. The Cancer Prevention Study II, a cohort of 991,552 U.S. adults with a high proportion of smokers followed from 1982–1998 with 1289 UC deaths, found that >10 years of regular vitamin E use was associated with a decreased risk of UC mortality (OR 0.60, 95%CI 0.37–0.96).[9] No associations with vitamin C supplement use were found. Among members of the large Netherlands Cohort Study (N= 120,852), neither use of vitamin A, C, or E supplements was associated with reduced risk of UC.[19] Similarly, in a Danish cohort of 55,500 with a high proportion of smokers followed from 1993–1997 with 332 cases of incident UC, there was no effect for supplemental vitamins C, or E.[18] Finally, cohort studies of women, who have a lower risk of UC, have found no association between multivitamin use[2021] or use of vitamin A, C or E supplements and incident UC. [20]

Randomized trials of supplements have generally been too small to yield sufficient numbers of UC cases. The Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study of 50 mg alpha-tocopherol and 20 mg beta-carotene reported no association of the interventions with UC risk.[22] In contrast, a meta-analysis of four trials of anti-oxidant supplements found a significantly increased risk of bladder cancer for those randomized to the supplements (RR=1.52 (1.06–2.17). [23]

Thus while early studies gave some support for a chemoprotective effect of supplemental vitamin C and E, the emerging evidence from all studies to date including ours is for no effect of the common supplements and UC risk. Little literature exists on the effects of less common vitamin and mineral supplements and anti-inflammatory supplements in relation to UC, even though there are reasons to expect that some may reduce the risk of UC. Specifically, folic acid and other B vitamin supplements are of interest for cancer chemoprevention because serum levels of B vitamins have been associated with reduced risk of colorectal and lung cancers likely due the role of these nutrients in reducing DNA hypomethylation and maintenance of DNA integrity.[2425] DNA hypomethylation as measured in blood has been associated with increased risk of bladder cancer in two recent case-control studies. [12, 13] However, as with the Danish study, we found no protective effect for folic acid.[18] Anti-inflammatory supplements such as fish oil, chondroitin or glucosamine have been associated with reduced risk of lung, colorectal or breast cancers in this cohort.[14, 26] and may work by a mechanism similar to that of how NSAIDs potentially attenuate UC progression in animal models. [27] However, none of the less commonly used vitamin, mineral or anti-inflammatory supplements were significantly associated with UC risk in the present study.

Advantages of our study include its prospective design, the focus on supplements and cancer risk including recruitment of a high proportion of supplement users, and the large sample size.[28] In addition, our assessment instrument for ascertaining supplement use included more types of supplements and more detail on their use than prior studies, and our study of the measurement properties of this questionnaire found it to have very good reliability and validity.[28] Nonetheless, non-differential measurement error due to inaccuracies of self-report would have attenuated our results and we do not know how long participants continued supplement use.

Other potential limitations of the study include the relatively low rate of use of some of the less common vitamin, mineral and anti-inflammatory supplements and the modest number of UC cases (n=330) limiting power. Another significant limitation is that while we have DNA on approximately 54,000 individuals we have yet to examine genetic polymorphisms in carcinogenesis and metabolic pathways that may modify our results. Recent work has

suggested that stratification by genetic polymorphisms of enzymes in the metabolic and carcinogenesis pathways is necessary to identify populations in which supplements could attenuate UC risk.[29, 30] Potentially, these could allow us to identify a sub-group of patients who might benefit significantly from supplement use.

CONCLUSIONS

We have found no evidence for reduced risk of incident UC associated with vitamin, mineral or anti-inflammatory supplement use. While further genetic work may help to elucidate sub-populations of patients who may decrease their risk of UC from the supplements tested here, we cannot endorse routine use of these supplements to prevent UC.

Acknowledgments

This work was supported in part by grants K05CA154337 and R01CA154512 from the National Cancer Institute.

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STANDARD ABBREVIATIONS

SEER	Surveillance Epidemiology and End Results
UC	Urothelial Carcinoma
VITAL	VITamins and Lifestyle Study

TABLE 1

Hazard ratios of urothelial carcinoma in relation to use of vitamin supplements during the 10 years before baseline, western Washington, 2000–2007.

	Number of controls s (N = 76,720)		Number of cases of UC (N = 330)		Multivariate-adjusted[a]		
Ten-year average daily supplement use[b]	**No.**	**%**	**No.**	**%**	**HR**	**95% CI**	
Multivitamins (pill -years)*							
None	26,451	34	125	38			Referent
>0–2.5	13,245	17	49	15	0.98	0.70	1.37
>2.5–8	13,584	18	47	14	0.89	0.63	1.25
>8–10	23,430	31	109	33	0.98	0.76	1.28
P trend							0.809
Beta carotene (mcg/day)							
None	26,247	35	125	38	1.00		Referent
6.4 to 377.0	16,303	22	61	19	0.93	0.68	1.27
377.1 to 600.0	10,821	14	47	15	0.95	0.71	1.28
600.1 to 13,554.0 [c]	22,416	29	92	28	0.93	0.69	1.26
P trend							0.632
Retinol (mcg/day)							
None	24,873	33	118	37	1.00		Referent
19.3 to 510.0	17,093	22	66	21	1.03	0.76	1.41
510.1 to 1200.0	25,882	34	111	35	0.94	0.72	1.22
1200.1 to 8790.0 [c]	7,614	10	26	8	0.80	0.52	1.23
P trend							0.343
Folic acid (mcg/day)							
None	24,412	32	119	36	1.00		Referent
8.6 to 200.0	21,539	28	82	25	0.95	0.71	1.27
200.1 to 400.0	24,577	32	111	34	0.96	0.74	1.25
400.1 to 1400.0 [c]	5,634	7	17	5	0.73	0.44	1.22
P trend							0.390

J Urol. Author manuscript; available in PMC 2012 April 1.

Ten-year average daily supplement use[b]	Number of controls s (N = 76,720) No.	%	Number of cases of UC (N = 330) No.	%	Multivariate-adjusted[a] HR	95% CI	
Vitamin B1 (mg/day)							
None	25,165	33	118	36	1.00		Referent
0.032 to 0.750	18,081	24	72	22	1.06	0.78	1.42
0.751 to 1.50	19,279	25	87	27	1.02	0.77	1.36
1.51 to 104.65 [c]	13,598	18	49	15	0.90	0.64	1.26
P trend							0.649
Vitamin B3 (mg/day)							
None	24,896	33	116	35	1.00		Referent
0.4 to 10.0	20,554	27	84	26	1.08	0.81	1.44
10.1 to 20.0	23,696	31	99	30	0.94	0.72	1.24
20.1 to 1024.0 [c]	6,963	9	28	9	0.94	0.62	1.42
P trend							0.612
Vitamin B6 (mg/day)							
None	24,400	32	115	35	1.00		Referent
0.04 to 1.40	17,301	23	64	20	0.97	0.71	1.33
1.41 to 3.00	19,956	26	99	31	1.07	0.81	1.40
3.01 to 270.00 [c]	14,501	19	49	15	0.88	0.62	1.24
P trend							0.761
Vitamin B12 (mcg/day)							
None	24,387	32	115	35	1.00		Referent
0.1 to 5.0	18,035	24	67	21	0.98	0.72	1.33
5.1 to 25.0	25,447	33	109	33	0.95	0.73	1.24
25.1 to 300.0 [c]	8,173	11	36	11	1.12	0.77	1.64
P trend							0.875
Vitamin C (mg/day)							
None	20,437	27	99	30	1.00		Referent
0–60.05	19,110	25	76	23	0.94	0.69	1.27

	Number of controls s (N = 76,720)		Number of cases of UC (N = 330)		Multivariate-adjusted[a]		
Ten-year average daily supplement use[b]	**No.**	**%**	**No.**	**%**	**HR**	**95% CI**	
60.06–322.05	18,048	24	75	23	0.97	0.72	1.33
322.06–1600	18,499	24	76	23	0.90	0.67	1.23
P trend							0.584
Vitamin D (mcg/day cholecalciferol)							
None	24,316	32	114	35	1.00		Referent
0.2 to 5.0	21,741	29	87	27	1.07	0.80	1.42
5.1 to 10.0	24,742	33	107	33	0.98	0.75	1.28
10.1 to 30.0[c]	5,071	7	19	6	1.02	0.63	1.67
P trend							0.914
Vitamin E (mg/day dl alpha-tocopherol)							
None	19,985	26	96	30	1.00		Referent
1.3–42.0	18,928	25	72	22	0.92	0.67	1.25
42.1–215.0	18,721	25	74	23	0.94	0.69	1.28
215.1–1000.0	18,496	24	83	26	0.95	0.70	1.29
P trend							0.784

Abbreviations: CI, confidence interval; HR, hazard ratio; UC urothelial carcinoma

[a] Adjusted for the following variables: sex; age; race/ethnicity; education; family history of bladder cancer; smoking status/recency of smoking, pack-years of smoking; servings per day of fruits; and servings per day of vegetables (excluding potatoes).

[b] From single supplements (and mixtures other than multivitamins) plus multivitamins.

[c] Greater than amount of that nutrient that could be obtained from 10-year daily use of the multivitamin Centrum Silver (Wyeth; Madison NJ, USA).

* Pill-years = days per week/7 × years of use in 10 years before baseline.