Vitamin E Reduces Superficial Bladder Cancer Recurrence: A Randomized Controlled Trial

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ABSTRACT

Background: Most patients with superficial bladder cancer who undergo transurethral resection of bladder tumor show recurrence of the disease. So far, there have been numerous studies on ways to decrease bladder cancer recurrence, including the intake of vitamins and antioxidants. The goal of this study was to investigate the effect of vitamin E on the recurrence of non-invasive bladder cancer.

Methods: In this randomized controlled trial, 46 patients with a single, low-grade, superficial bladder cancer, less than 3 cm in diameter, were randomly divided into two groups of vitamin E intake (400 IU daily) and no intake of vitamin E. Ultrasound and urinalysis were performed every three months to detect bladder cancer recurrence.

Results: There was no significant difference between the groups in age, tumor size, mean time to recurrence, and follow-up time. There recurrence rate was 28.3% throughout the follow-up period (19% in the study group and 36% in the controls) (CI=0.19 – 0.92, RR=0.53, CI=0.11 – 0.94, OR=0.42, *P*=0.04). In both groups, most (69.2%) of the recurrences occurred during the first year. The rate of recurrence decreased in smokers from 50% in the study group to 25% in the control group (*P*=0.06) and from 26.7% to 15.4% in the non-smokers in the control and study groups, respectively (*P*=0.15).

Conclusion: Intake of vitamin E significantly decreased bladder cancer recurrence, especially among smokers, possibly due to higher levels of oxidants, which vitamin E may target in smokers. The trial registry code: IRCT201105235527N2

Keywords: Antioxidant, bladder cancer, recurrence, vitamin E

INTRODUCTION

About 60% of the cases of bladder transitional cell carcinoma (TCC) are non-invasive and low-grade when diagnosed for the first time,[1] and the standard current treatment is transurethral resection of the bladder tumor (TURB). Unfortunately, most

(50 – 80%) patients with superficial TCC who just undergo Transurethral Resection of Bladder (TURB) face recurrence. In 16 to 25% of these cases, superficial tumors recur with a higher grade, mostly within the first year post TURB.[1-3]

The predisposing factors for bladder cancer include occupational contact with chemicals, smoking, coffee, sweeteners, sedatives, bacteria, parasites, fungi, bladder stone, and chemotherapeutic medications.[1,3] Smoking seems to be the most important risk factor for bladder cancer and it increases the risk of bladder cancer four-fold.[3]

About one-third of bladder cancers are thought to be related to smoking.[1,3] It is suggested that at least some bladder cancers are caused by carcinogens. These carcinogens cause DNA damages in the target cells.[4-7]

Oxidants and free radicals are inevitably produced during most physiological and metabolical processes, and the human body has defensive antioxidant mechanisms.[8]

These mechanisms vary according to the cell and tissue type and they may act antagonistically or synergistically. They include antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, as well as antioxidant vitamins like vitamin C, E, and beta-carotene.[8]

In our previous study, we compared 52 patients with bladder cancer and 58 healthy persons, and observed that the level of total antioxidant activity (TAC) was significantly lower (P<0.001) and the level of malondialdehyde was significantly higher (P<0.001) in bladder cancer patients than in controls.[9]

Vitamin E is a lipid-soluble vitamin with an antioxidant effect like that of vitamin C. It was discovered in 1920, and was extracted from wheat germ in 1936, and was named alpha-tocopherol. This vitamin prevents the cell wall from destruction.[10]

Vitamin E can be found in plant oils such as sunflower, olive, corn, and almond oil, fresh nuts (hazelnut, almond, and walnuts), spinach, cabbage, asparagus, soya beans, and potatoes, as well as fruits like peach. Synthetic vitamin E is available as tablets and injections. Even as the daily vitamin E requirement is 7 – 9 mg, up to 1000 units daily may be tolerated.[11]

Considering the low levels of antioxidants in patients with bladder cancer, we hypothesized that the intake of vitamin E by patients with bladder cancer might result in a decrease in tumor recurrence. This hypothesis has been investigated with a variety of antioxidants in the previous studies.[1,2,12-14]

METHODS

This randomized controlled trial (The registry code in WWW.IRCT.IR is IRCT201105235527N2) was conducted from 2006 to 2010 in Isfahan, Iran. Patients diagnosed with a single, low-grade, superficial bladder tumor, less than 3 cm in diameter, who had undergone TUR were included in the study. Patients with accompanying carcinoma *in situ* (CIS) were excluded from the study. The Research and Ethics Committee of the School of Medicine, Isfahan University of Medical Sciences approved the study (project code 388477); informed consent was obtained from all the adult participants.

The patients were randomly divided into two groups (Treatment and Control groups). The patients in the treatment group took vitamin E (E-Zavit capsules, 400 IU, made in Iran, daily at night before sleep) and the control group did not received vitamin E. None of the patients received intravesical chemotherapy.

The patients were followed up every three months with urinalysis and bladder ultrasound for two years and in cases with no recurrence, semi-annually thereafter. Cystoscopy was performed for microscopic hematuria or urinary symptoms during follow-up. Cystoscopy was done for all patients in the third- and twelfth-month follow-up. Patients without regular follow-up or medication intake were excluded form the study. Patients with recurrence of bladder cancer were taken off the study, to receive standard therapy.[15]

The obtained data were analyzed by Chi-square, Fisher's exact, and independent sample t tests using the Statistical Package for Social Sciences software version 19.0 (SPSS Inc, Chicago, IL, USA). The significance level was set at P<0.05.

RESULTS

From 2006 through 2010, forty-six patients with the inclusion criteria were followed up (25 and 21 patients in the control and study groups, respectively).

The demographic characteristics of the two groups are compared in Table 1. There was no significant difference between the study and control groups in terms of the patients' sex and age, tumor size, and mean duration of follow-up.

In the control and study groups, 40 and 38.1% of the patients were smokers, respectively (*P*=0.42).

There were 13 cases (28.3%) of recurrence during follow-up, of which 19 and 36% were in the study and control groups, respectively (CI=0.19 – 0.92, RR=0.53, CI=0.11 – 0.94, OR=0.42, *P*=0.04).

Recurrences of 66.7 and 75%, respectively, in the control and study groups occurred within the first year. The mean time to recurrence was not significantly different in the study and control groups (9 ± 8.1 vs. 8.33 ± 6.1 months, respectively, *P*=0.9).

The patients were divided into two groups, smokers (18 patients) and non-smokers (28 patients). The recurrence rate was not significantly different in non-smokers in the study group and in the controls (15.4% vs. 26.7%, respectively, *P*=0.15). In smokers, the corresponding Figure was 25 and 50%, respectively (*P*=0.06) [Figure 1].

Table 1: Demographic characteristics of the patients in the groups under study

Variable	Treatment group	Control group	*P* - value
Age (years)	8.35 ± 60.62	15.92 ± 59.16	0.71*
Female/male ratio	2/19	3/22	0.8**
Tumor size (cm)	0.4 ± 2.1	0.6 ± 1.9	0.45*
Mean period of follow-up (months)	16.22 ± 24.57	12.1 ± 17.8	0.1*

*Sample *T* test Independent; **Chi-square

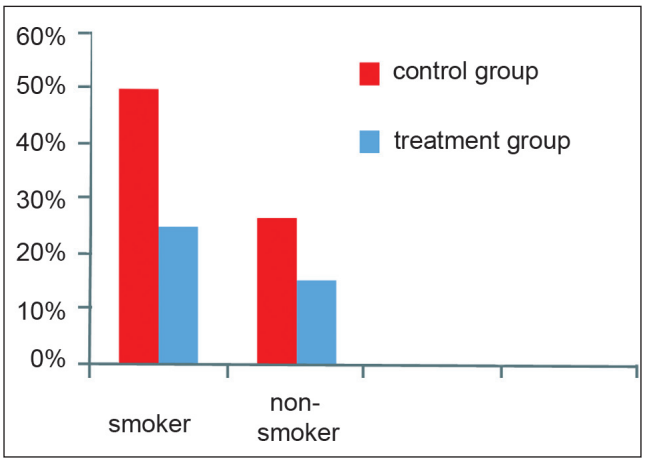

Figure 1: Recurrence rate in non-smokers and smokers in two groups

DISCUSSION

The anti-tumor effect of vitamin E may be related to several mechanisms. Oxidative injury may induce gene mutation and promote carcinogenesis.[16] Vitamins E is a potent antioxidant and can inhibit carcinogenesis in the bladder by neutralizing the reactive oxygen species, which can damage the DNA,[17] or by inhibiting the formation of nitrosamines,[18] which may be bladder carcinogens.[19] Vitamins E could also plausibly reduce bladder cancer risk by enhancing the immune function.[20] Studies in breast and prostate cancer cells have shown that the vitamin E decreases proliferation and induces apoptosis.[21] These effects make vitamin E appealing for the chemoprevention of bladder cancer.

Many observational epidemiological studies have shown that a high intake of fruit and vegetables, rich in antioxidants is associated with a lower incidence of cancer.[22,23] Another study has reported an association between the serum levels of vitamin E and the risk of urinary tract cancer among Finnish men.[24]

Several epidemiological studies suggest that vitamin E is protective against bladder cancer. Jacob *et al*. evaluated the impact of Vitamin C and Vitamin E supplement use and bladder cancer mortality in a large cohort of US men and women.[12] After adjusting for variables, including patient sex, age, vegetable intake, and smoking, only patients receiving vitamin E supplements for at least 10 years demonstrated a decreased risk of death from bladder cancer (RR = 0.60, 95% CI = 0.37 to 0.96).

In a prospective study, Michaud *et al*. investigated the effect of vitamin E on 320 patients with newly diagnosed bladder cancer, with a 12-year follow up. This study in American men was conducted by checking on the food habits and intake of food supplements. Conclusion: Vitamin E (alpha-tocopherol) was found to significantly diminish the recurrence of bladder cancer (95% C1 = 0.31-0.45, RR = 68%). There was an inverse association between the intake of vitamin E and bladder cancer mortality.[25]

Virtamo *et al*., in a controlled trial, reported the effects of supplemental alpha-tocopherol and beta-carotene on the incidence and mortality of urinary tract cancer. Participants in the intervention arm received 50 IU of vitamin E (alpha-tocopherol) daily for five to eight years. No reduction in bladder cancer incidence was observed (RR = 1.1, 95% CI = 0.8 – 1.5).[14] The absence of reduced risk in this trial could be due to differences in treatment duration or dosage. Only short-term intake of vitamin E could be examined in this trial. In addition, the 50 IU dose of vitamin E used is several times lower than the 400 IU that was used in our study.

The total recurrence rate in the present study (28.3%) is consistent with that reported in other studies. In a large epidemiological study on low-grade and low-stage (stage Ta, T1), non-invasive bladder cancer, 1745 patients were followed up in the Netherlands. In 60% of the patients, at least one recurrence was seen within the first five years after primary treatment of the tumor (95%, C1 = 0.58 – 0.62). The risk of a three-year recurrence in patients with minor cancer (grade 1, Ta) was 37%, whereas, this rate rose to 71% in major T1 multifocal tumors in spite of intravesical chemotherapy.[3]

In another study, the three-month recurrence rate after grade I bladder tumor resection was studied in 18 centers. This rate was 0 – 36% for single tumors and 7 – 75% for multifocal tumors.[11]

We found fewer recurrences with the use of vitamin E, but considering the longer follow-up period in this group than in the controls (25 months vs. 18 months); this difference might actually have been larger. In both groups, most of the recurrences were detected within the first year (69.2%).

Importantly, we observed no significant difference in the first-year recurrences and the time-to-recurrence between the two groups. In other words, although vitamin E had decreased bladder cancer recurrence, it was less effective in early (i.e., within the first year) recurrence, suggesting that vitamin E might have to be taken for longer periods.

Comparison of the recurrence rate in the two groups in our study revealed that in smokers taking vitamin E, this rate diminished from 50% in the controls to 25% in the study group, suggesting a trend toward statistical significance (P=0.06), but it diminished from 26.7 to 15.4% in non–smokers taking vitamin E (P=0.15). It can be concluded that intake of vitamin E might be effective in reducing bladder cancer recurrence, especially in smokers. Smoking results in an increase in oxidants, which vitamin E can counteract, thus leading to an almost significant decrease in bladder cancer recurrence in smokers.

In Michaud's study mentioned previously, regular vitamin E supplement use of 10 or more years was associated with the greatest reduction in bladder cancer mortality among participants who were cigarette smokers at enrollment, whereas, smaller, statistically insignificant risk reductions were observed among non- or former smokers.[25] They also found that smokers with higher fluid intake (2,531 ml vs. 1,290 ml) had fewer recurrences (RR = 0.31).[26]

Castelao *et al*. studied the nutritional factors in 1592 patients with bladder cancer, from 1987 to 1996. They showed that the incidence of bladder cancer had an inverse association with the intake of vitamin C (P=0.02) and carotenoid (P=0.04). This protective effect was especially high among smokers, even more in current smokers compared to quitters.[27]

Study limitations

On account of the small numbers of patients enrolled, these trials should be viewed as preliminary and must not generalize the results to the entire community.

Another design issue that may have better tested the purely chemopreventive effectiveness of vitamin E, would have been to continue the study drug after the first recurrence until some prearranged time point had been reached, or a second recurrence had occurred.

CONCLUSION

Although most of bladder tumors are not a threat to the life of the patient, the potential for frequent recurrences and the ensuing investigations add to the morbidity, resulting in bladder cancer becoming the single most expensive disease, if diagnosis, surveillance, and repeat treatments are factored in. With its indolent course, a need for repeated interventions, and a long natural history, bladder cancer is a poster child for chemopreventable cancer. One of prophylaxis methods is vitamins

and antioxidant drugs.

Vitamin E is safe and effective, with low price and low side effects. Intake of vitamin E significantly decreases bladder cancer recurrence, especially among smokers.

However, it was less effective in early (i.e., within the first year) recurrence, suggesting that vitamin E might have to be taken for longer periods. Larger studies with a longer follow-up are warranted to determine the exact role vitamin E might play in the chemoprevention of bladder cancer.

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