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European Association of Urology

## Letter to the Editor

### Re: John L. Gore, Jonathan L. Wright. Can We Prevent Bladder Cancer Recurrences? *Eur Urol* 2019;75:602–3

In their interesting editorial [1] discussing the recently published BOXIT trial [2], Gore and Wright commented on ways urologists can prevent non-muscle-invasive bladder cancer (NMIBC) recurrences. These included a diet abundant in fruits and vegetables, maintaining an ideal weight, and smoking cessation. Importantly, one factor not mentioned was the avoidance of a high intake of synthetic folic acid, since it has been shown that excessive folic acid (but not natural folate) promotes the recurrence of NMIBC in patients [3].

Regarding cancer, folic acid is a double-edged sword. On one hand, it may prevent the initiation of cancer via its involvement in DNA repair, and on the other hand, it may actually promote the progression of established and clinically unapparent cancers via several mechanisms [3,4]. These include speeding cell division, decreasing natural killer cell function, and enhancing hypermethylation in promoter regions of tumor suppressor genes.

Folate is the natural form of the essential water-soluble B vitamin found in green leafy vegetables, fruits, and legumes, and is oxidized and hydrolyzed before absorption. Folic acid is a synthetic form of the vitamin that exists in an oxidized state, making it highly bioavailable; dietary sources of folic acid include vitamin pills, fortified grains and cereals, and supplemented beverages [4]. Notably, folic acid is reduced in the liver by dihydrofolate reductase, but folic acid intake in excess of 400  $\mu\text{g}/\text{d}$  probably saturates this enzyme, leading to unreduced folic acid in the circulation [4]. Since the mandatory fortification of flour and grain products with synthetic folic acid in the USA and many other countries to prevent neural tube defects, it is not uncommon to have unreduced folic acid in the circulation [4].

Cancer cells, including bladder cancer cells, are replete with folic acid receptors [3,4]. Disturbingly, many cancer patients take folic acid supplements in the form of vitamins and fortified beverages [3]. Moreover, the kidney excretes excess folic acid, resulting in bladder urothelium and residual bladder cancer cells being directly exposed to relatively high concentrations of folic acid [3]. Therefore, it is not surprising

that in a cohort of NMIBC patients, a high intake of synthetic folic acid has been associated with a significant twofold increase in the recurrence of tumors over 5 yr [3]. Reassuringly, in that same cohort, natural folate intake was associated with a trend towards a reduction in tumor recurrence.

In conclusion, to prevent the recurrence of NMIBC, in addition to encouraging patients to intake a diet abundant in fruits, vegetables, and legumes, urologists should advise against excess synthetic folic acid intake from vitamins and supplements. This advice might prevent the promotion of other urologic cancers as well [5].

**Conflicts of interest:** The authors have nothing to disclose.

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