

## Platinum Priority

### Rebuttal from Authors re: Marko Babjuk. The Search for the Etiology of Bladder Cancer: Are Achievements Sufficient? *Eur Urol* 2009;56:771–2

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In his editorial in this issue of *European Urology*, Babjuk [1] presents an excellent overview of the research on bladder cancer (BCa) etiology conducted during the last two centuries. He summarizes what is already known in the field and highlights areas that he considers frontiers for pursuing the etiology of the disease.

A deep understanding of disease etiology is important for developing enhanced preventive initiatives against this widespread disease. I am pleased to note that Dr. Babjuk agrees that micronutrients are relevant as a focus for future prevention of BCa.

Such a deepened understanding of disease etiology relies on extensive and thorough research. Only a few other studies, however, consider the relationship between micronutrient consumption and risk of BCa. Our finding of a protective effect of dietary beta-carotene in BCa [2] is not supported presently by other studies and should thus be considered merely advisory until further studies have been conducted. I would therefore like to take this opportunity to encourage future research in the field and to address areas that would be relevant to consider in such future studies.

One issue relates to timing. Dr. Babjuk highlights micronutrients as possible anticarcinogens in relation to primary, secondary, and tertiary prevention of BCa [1], based on our study [2]. It is, however, important to be careful not to extrapolate a preventive effect of beta-carotene in primary prevention of BCa, as seen in our study, to a similar effect in secondary and tertiary prevention of BCa without further studies supporting this claim.

In studies of micronutrients and colorectal cancer, the association has been found to be modified by the timing of the micronutrient intake. Folate has a protective effect among participants without preneoplastic lesions but increases risk among those with colorectal polyps, indicating that when the folate consumption followed a pre-cancerous lesion, the micronutrient enhanced the development of the polyp into a colorectal tumor [3]. It is possible that a similar effect of timing could exist in BCa. Thorough studies on the secondary and tertiary preventive effects of micronutrients on BCa are warranted before any conclusions are drawn regarding the effects of micronutrients. The potential beneficial effect of micronutrients in secondary and tertiary prevention of BCa, however, is highly

relevant to further inquiry, due to the very high recurrence rate of BCa, even after complete resection of the primary tumor [4].

The optimal study design to approach the association between micronutrients and BCa must also be considered. The randomized, controlled trial (RCT) is deemed the highest standard in medical research. We have identified only two RCTs exploring the effect of beta-carotene supplementation on the risk of developing BCa. Contrary to our study [2], one showed no effect of beta-carotene [5] and one found a borderline increased risk of disease (risk ratio: 1.5; 95% confidence interval [CI], 1.0–2.2;  $p = 0.04$ ) [6].

Two crucial differences between these study designs are the different beta-carotene doses considered in the studies and the sources of the micronutrient, with observational studies considering dietary beta-carotene and experimental studies considering supplemental beta-carotene.

In our study, in which we found a protective effect, study participants had a median total beta-carotene consumption of 3.3 mg/d [2], compared to a supplemental dosage of 50 mg on alternate days, which showed an increased risk in the Physicians' Health Study [6]. In the Alpha-Tocopherol, Beta Carotene study, which found no association between beta-carotene and BCa, the dosage administered was 20 mg/d [5]. The different results may be explained by these large differences in dose, but it is also possible that the source in itself is what rendered the different effect. The diet consists of a balanced composition of different nutrients, the beneficial effects of which may not be retained once a sole micronutrient is singled out of this compound in a supplement.

This discrepancy between an RCT showing an increased risk and our observational study finding a beneficial effect of beta-carotene is a pattern that, as also mentioned in our article, parallels the research on the effects of beta-carotene in lung cancer prevention. Here observational studies found beneficial effects of beta-carotene, but subsequent tests of this association in two large RCTs found, surprisingly, an increased disease risk with supplements [5,7]. The lack of a protective effect of supplemental micronutrients on cancer risk in experimental trials, however, is not confined to lung cancer and BCa; increasingly, the lack of a protective effect seems to be a general pattern for all types of cancer [8].

Whether this lack of effect can be explained by the difference in dose or source needs further research to understand. With regard to BCa, future RCTs could test this by administering a much smaller dose of beta-carotene in the intervention group to mimic dietary beta-carotene intake more closely and to avoid the potential harmful effect of pharmacologic doses. It is also possible, however, that beta-carotene does not exert beneficial effects when singled out from those dietary components with which it usually coexists in fruits and vegetables. Consequently, we would also encourage studies focusing on dietary beta-carotene, despite the fact that these studies will not generate evidence that beta-carotene is the true active anticarcinogen, such as RCTs can.

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Hopefully, this editorial reply has highlighted some of the more complex areas that might be relevant to consider in future research on micronutrients and BCa prevention. In conclusion, I agree with Dr. Babjuk's optimism regarding preventive effects of micronutrients, especially beta-carotene, in BCa prevention. Cautious optimism, however, is encouraged until further studies in the field have been conducted to explore in depth the nature of the relationship between beta-carotene and BCa.

**Conflicts of interest:** The author has nothing to disclose.

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