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CORRESPONDENCE

Re: Lifestyle and bladder cancer prevention: no consistent evidence from cohort studies

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We thank Dr. Vrieling for her knowledgeable comments on our study [1]. Her concern was the use of estimates based on case–control and cohort studies combined.

In our systematic review of meta-analyses we choose to review the most comprehensive meta-analyses for all modifiable risk factors for bladder cancer, published up to September 2015. In our criteria list we prioritized adjustment for confounding, including adjustment for smoking, over study design.

Both case–control and cohort studies are susceptible to confounding bias, which can influence the magnitude of the relationship between the independent variable and outcome drastically. Therefore, unadjusted estimates are often considered incorrect.

Regarding the modifiable risk factor "physical activity" this criterion has led to report an estimate based on case–control and cohort studies separately, rather than cohort studies only. Although Keimling et al. [2], did report an estimate for physical activity based on cohort studies only, this estimate was not restricted to primary studies that adjusted for important confounders, e.g. four cohort studies were not adjusted for the most important risk factor for bladder cancer; smoking [3–6]. We, therefore, believe that our reported "more adjusted estimated" risk estimate, including both case–control and cohort studies, is more correct than reporting the risk estimate based on cohort studies only.

In nutritional epidemiology, most individual studies have insufficient sample sizes and thus lacked adequate statistical power to find all true associations. Therefore, meta-analyses, in which results of independent studies are integrated into a more precise estimate, play an important role in this area of research. However, the examination of variability or heterogeneity in methodological diversity is crucial to this approach. In our review, the reported significant risk estimates for vegetables, vitamin E, vitamin C, antioxidant supplementation, obesity and folate showed low levels of heterogeneity. Although low levels of heterogeneity do not appear to be predictive of the accuracy of the meta-analysis result, they do suggest low methodological diversity. The role of recall bias is therefore likely to be present but with minimal influence on the results.

Regarding the remaining reported risk estimates that showed a significant association (i.e. processed meat, selenium, cruciferous vegetables, fruit and citrus) we do agree with Vrieling that results should be interpreted with caution, since methodological diversity among the included individual studies may play a significant role. However, for consistent reporting, we opted to use similar criteria/use a similar approach for all investigated modifiable risk factors. In addition, although the form of bias addressed by Vrieling (i.e. recall bias) has also been addressed and analyzed for its consequences in many epidemiological/methodological papers [7–10], no clear answer on the magnitude of the effect of this specific type of bias could be draw. Furthermore, the magnitude and direction of recall bias might differ for different exposure factors, and concern are especially expected for those exposures that attracted public attention, since the knowledge of an

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unhealthy or healthy effect of such an exposure is a prerequisite for study subjects to change their reporting behavior of individual exposure. In this regard, it is expected that especially fruit and vegetables intake would be effected by recall bias. However, the positive effect of fruit remains significant even after restricting to cohort studies only. Apart from methodological considerations and consistent real-life observational data, it may be worth pointing that the results on processed meat, cruciferous vegetables and (citrus)fruit are supported by strong biological evidence, which are reported in our discussion section.

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