Re: Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health—AARP Diet and Health Study

The results reported by Lawson et al. (1) on the association of multivitamin use and prostate cancer are open to multiple interpretations. Contrary to prevailing myths, large statistical studies such as the one conducted by the authors are weak investigative tools and provide indications of relative risks. When the number of cases is large, the absolute magnitude of a statistically significant effect may be tiny.

In the study, multiple statistical testing of subgroups was performed but the number of tests was not stated. Thus, it is impossible to validate the statistical significance of the associations between cancer risk and the supplements that were investigated (2). In addition, the tables of results listed nutrients with a negative effect, but did not, for example, include vitamin C, for which no effect was noted. Additional limitations, such as the fact that the period of multivitamin–mineral supplementation was unknown and the possibility of detection bias, were noted by the authors.

There are additional reasons why the results and general conclusions of this
study, suggesting that increased vitamin use in cancer may be harmful, are incomplete and potentially unreliable. First, both the dose and quality of supplements affect how cells will respond. For example, vitamin E, one of the vitamins studied in the paper, has both synthetic and natural forms, and the term covers at least eight molecular classes of tocopherols and tocotrienols (3). Some forms of vitamin E might protect against prostate cancer, while others might not (4). Lawson et al. (1) employed an experimental instrument that lacked the potential to identify specific molecular components and was thus unable to illuminate nutrient effects in detail.

Second, in studying the effects of nutrients, it is essential to separate nutritional effects from pharmacologic intakes. Hickey and Roberts’ microevolutionary model for cancer (5) describes how cells undergoing carcinogenesis respond to redox (antioxidant/oxidant) signaling and changes in redox state. The model predicts that nutritional doses of antioxidant supplements, required daily for maintenance of normal health, inhibit carcinogenesis. The Lawson paper is consistent with this prediction. Once a cancer is established, however, the model suggests that nutritional doses of antioxidants may be contraindicated as they could accelerate tumor growth. Since the intakes studied in the Lawson paper were all in the nutritional range, this prediction is also supported.

Large pharmacologic doses of nutrients, which produce specific physiologic or biochemical effects, are indicated for the treatment of cancer or other diseases. For example, pharmacologic doses of ascorbate range from 10 to 300 g and are given intravenously or orally (sometimes as liposomal formulations). Such doses do not correspond to the intakes described by Lawson, nor is there an extensive record of investigation of the effects of pharmacologic doses on cancer in the literature. In the oxidizing environment of a developing tumor, nutritional doses of antioxidants could lower oxidation levels and inhibit cancer cell death. By contrast, pharmacologic doses of redox-active substances that alter the antioxidant–oxidant balance, such as vitamin C (acting as a pro-oxidant), have been shown to destroy cancer cells in vitro and in animal experiments (6).

Our interpretation of this study suggests that people in good health should select only high-quality, natural, antioxidant supplements, or molecularly identical counterparts, avoiding synthetic forms such as DL-alpha-tocopherol (synthetic vitamin E). Furthermore, until we gain accurate data on individual nutrient molecules and suitable dose levels, results such as those presented by Lawson do not support widespread generalizations.

Such generalizations require solid scientific support, which has not been provided. Meanwhile, people with cancer clearly need appropriate nutrition. In metastatic cancer, only those supplements that have been shown to provoke a differential redox response in cancer cells, such as vitamin C, r-alpha-lipoic acid, and vitamin K3, are appropriate. Research into the use of pharmacologic doses of nutrients against cancer is long overdue, and failure to initiate it may eventually be revealed as one of the greatest oversights of modern medicine.

References


Notes

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Response

Hickey et al. suggest that our results have limited public health relevance. However, we observed a substantial increase in risk for fatal prostate cancer (relative risk = 1.98; 95% confidence interval = 1.07 to 3.66) among men reporting excessive use of multivitamins (1). If, as in our study, 5% of men older than age 50 take multivitamins more than once a day, then, in light of the large number of prostate cancer–related deaths in the United States (2), our findings have potentially important consequences for public health.

With respect to multiple testing of subgroups, our results section did include a list of the total number of nutrients and foods tested. In addition, our discussion section noted the possibility of chance findings due to multiple comparisons.

We did not evaluate vitamin C because there is no a priori hypothesis linking vitamin C to prostate cancer risk. In contrast, we did examine vitamin E and its isoforms in detail in a separate recent publication (3) because vitamin E holds promise for prostate cancer prevention.

Our study was not designed to address the effect of pharmacologic doses of nutrients on cancer prognosis or survival. We did, however, find strong epidemiologic evidence against a protective effect of excessive use of multivitamins on prostate carcinogenesis. The conclusion that people should use natural antioxidant supplements and avoid synthetic forms does not follow from our study. Our study did not compare the effect of natural versus synthetic ingredients contained in multivitamin supplements.

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References

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DOI: 10.1093/jnci/djm139
Published by Oxford University Press 2007.