

Multiplicities in the Assessment of Multiple Vitamins

Is It Too Soon to Tell Men That Vitamins Prevent Cancer?

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IN THIS ISSUE OF JAMA, GAZIANO AND COLLEAGUES¹ report one of several analyses of data from the Physicians' Health Study II (PHS II) randomized controlled trial. Among more than 14 000 male physicians who participated in this study, the authors report a marginally statistically significant ($P=.04$) inverse relationship between taking a daily multivitamin (Centrum Silver) and the occurrence of cancer.¹ The authors did not find that the supplement prevented any particular cancer preferentially, and there was no evidence of an association between adherence and the protective effect. The vitamin supplement was not demonstrated to reduce overall or cancer-specific mortality, although the authors observed nonsignificant reductions in both.¹

Following online publication to coincide with a presentation at a national meeting, the study results were reported widely in the media. Importantly, this report is a single entry in a crowded field of studies. The majority of these studies (many of which are cited by the authors) suggest no effect of vitamin supplementation on cancer risk and some, notably, show evidence of harm.^{2,3} Given this context, the marginal statistical significance and the perplexing and somewhat counterintuitive nature of the study findings make drawing any firm conclusion premature. Thus, it may be inappropriate to recommend that men take multivitamins to prevent cancer. There are several reasons for this perspective.

First, it is important to consider the nature of the PHS II end point of "all cancers," given the lack of an apparent effect in preventing any of the common cancer types, including prostate cancer, colorectal cancer, and lung cancer. Cancers are not a homogeneous group of disorders, but differ in terms of risk factors, epidemiology, treatment, and outcome. These varied diseases—and this study considered the incidence of all cancers except nonmelanomatous skin cancer as the outcome—are mostly bound together by an ancient taxonomy, not by any known single causal pathway. Thus, it seems unlikely that a common characteristic across all diseases included under this wide category of cancer would be a protective effect from multivitamins. Likewise, multivitamins are not composed of a single entity but, as their name implies, in-

clude multiple substances. The multivitamin used in the intervention group of the PHS II study contained 30 different vitamins and minerals in a single pill. It is plausible that some components of the multivitamin matter, whereas other components probably can be ignored. However, knowing which components fall into each category is important in understanding the biological plausibility of any potential mechanism for cancer prevention. This point is emphasized by several studies that have shown that some mineral and vitamin supplements are harmful and cause cancer. For instance, carotene and retinol supplementation caused smokers to develop and die from lung cancer,² and vitamin E supplementation increased the risk of prostate cancer in men.³

Second, the biological plausibility of the study hypothesis—that a multivitamin would be protective in a well-nourished population—is also limited. This matters, because the chance that the study finding of a protective effect is true is intrinsically related (by Bayes theorem) to the plausibility of the hypothesis. The plausibility of a protective effect is reduced by the absence of a clear path through which 30 different vitamins and minerals would cause a decline in the risk of multiple cancers and, especially, by the negative pattern of prior results. If the men in the study had adequate levels of vitamins and minerals, as seems likely for most of these apparently otherwise healthy male physicians, it seems unlikely that supplementation to reach super-normal levels would reduce cancer risk. Similarly, the investigators observed no difference in effect whether the study participants were or were not adherent to the multivitamin intervention. This is an unlikely observation with a true treatment effect, considering that a "dose response" is one of the seminal features of studies that convincingly demonstrate cause-effect relationships, although there are examples of effectiveness with a plateau or threshold effect.

Third, the multiple treatments and end points addressed by the PHS II study in its entirety must be considered when interpreting the results presented in the current report. The PHS II study randomized participants across 4 different nutritional supplements (vitamin E, vitamin C, beta carotene,

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See also p 1871.

and multivitamins) and evaluated 1 or more end points in each of 4 categories of outcomes in the domains of cardiovascular disease, cancer, ocular disease, and neurocognitive function.

To date, statistical evaluations of treatment effects associated with 7 primary and 13 secondary end points evaluated in the PHS II study have been reported.^{1,4-10} Evaluations of 8 additional secondary end points are planned according to information available at clinicaltrials.gov.¹¹ Thus, the complete planned analysis of the primary and secondary end points in the PHS II study will entail 28 tests of association. Previously reported results include findings of no effect of vitamin E supplementation on the risk of major cardiovascular events, stroke, myocardial infarction, total cancer, prostate cancer, cataracts, and macular degeneration; a similar set of negative results regarding the effect of vitamin C supplementation on these same end points; the recent negative results regarding the effect of multivitamin supplementation on cardiovascular end points¹⁰; and the 3 analyses presented in the current report.¹

The additional analyses that are not published along with the report on cancer prevention in this issue of *JAMA* may create a problem of “hidden multiplicity.”¹² In the PHS II study, and in any study, each analysis has some possibility of yielding a statistically significant result by chance alone, even when there is no true treatment effect. In evaluating the evidence arising from this particular study, a single analysis yielding a positive statistical result may appear to represent strong evidence. However, when this finding is considered in the context of the number of already completed and planned analyses of the same study, the strength of the inference is weaker, because the likelihood of a randomly occurring finding that appears to be statistically significant (particularly at a marginal significance level) is much greater. According to Berry, “an apparently extraordinary observation becomes quite ordinary when there are many opportunities to observe something unusual.”¹³

Statistical corrections are available to address the problem of multiplicities, and arcane controversies exist involving which approach is more suitable in what setting. Regardless, all approaches share the feature that the reported *P* value is likely to exaggerate the true strength of the evidence if that evidence is not considered in light of both apparent and hidden multiplicities.^{12,13} Because the *P* value in the PHS II study of .04 is close to the conventional *P* value cutoff of .05, any of the available corrections for multiple comparisons would eliminate the apparent “statistical significance” of the results.

The PHS II study was a well-done, large-scale, blinded, randomized trial with objective verification of cancer outcomes. Yet before drawing a definitive conclusion from this study that daily multivitamins reduce the risk of cancer in men, physicians and other readers must be convinced that the observed treatment effect is real and thus is likely to be reproduced in future experience, rather than a random event that is unlikely to recur. Making this determination requires considering the details of the study design, the biological foundation for the observed effect, prior results from similar efforts, the apparent strength of the evidence, the consistency of the results with known aspects of the diseases in question, and overt and hidden multiplicities. That assessment seems to point to remaining uncertainty regarding the effect of multivitamin supplementation on the risk of cancer in men.

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