Randomised controlled trial

Modest cancer prevention benefit with long-term multivitamin supplementation: Physicians' Health Study II results warrant cautious interpretation

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Commentary on **Gaziano JM**, Sesso HD, Christen WG, *et al*. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomised controlled trial. *JAMA* 2012;**308**:1871–80.

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Context

Various vitamins and minerals have been shown to inhibit carcinogenesis or reduce cancer risk in preclinical experiments and observational studies. Such work has given rise to several chemoprevention trials of isolated nutrients, many of which (eg, Alpha-Tocopherol and Beta-Carotene (ATBC) Trial, Carotene and Retinol Efficacy Trial (CARET) and Selenium and Vitamin E Cancer Prevention Trial (SELECT)) have produced disappointing findings.[1] Multivitamin supplements, however, may yield greater benefit and less risk, since the nutrient profile more closely approximates a healthy, balanced diet. A randomised controlled trial (RCT) of multivitamin supplements is significant since over one-third of US adults regularly take these preparations.[2]

Methods

Gaziano and colleagues recently reported the results of the Physicians' Health Study II (PHS II) that relate to cancer-associated outcomes. The present study provides data that augment results related to cardiovascular disease reported in *JAMA* in 2012.[3] The PHS II RCT tested the effect of Centrum Silver (original formula: Pfizer, New York City) versus placebo on cancer prevention.[3] The present study was part of a larger 2×2×2×2 factorial trial that also tested β-carotene, vitamin C and α-tocopherol; however, these components were previously phased out. The study sample included a total of 14 641 physicians aged over 49 who were not taking anticoagulants, and did not have active liver disease, a history of cirrhosis or other serious illnesses, and those who agreed not to take supplements that exceeded 100% of the recommended dietary allowance for vitamins E, C, A and β-carotene. To achieve this sample, 2 73 360 physicians were mailed invitations and then screened for eligibility. Eligible men then participated in a 12-week placebo run-in to assess adherence; those taking at least two-thirds of the placebos were enrolled into the study and assigned with equal allocation to either the multivitamin (n=7317) or placebo (n=7324) arms. Total cancer events (excluding non-melanoma skin cancer) were recorded over a median follow-up of 11.2 years. Intention-to-treat, two-sided analyses (α=0.05) were performed using Cox proportional hazards regression models. Power was estimated at 80% and calculations assumed 75% adherence and a 10% reduction in cancer events in the multivitamin versus the placebo arms.[3]

Findings

Compared with men assigned to placebo, those receiving multivitamins had a statistically significant reduction in total cancer events; 17 vs 18.3 events/1000 person-years, respectively (HR=0.92, 95% CI 0.86 to 0.998, p=0.04). Likewise, a statistically significant between-arm difference was found for total cancers minus prostate cancer (HR=0.88, 95% CI 0.79 to 0.98, p=0.02) and total epithelial carcinomas (HR=0.92, 95% CI 0.85 to 0.997, p=0.04). No differences were found for events expressed per capita, site-specific cancers or cancer-related mortality. While multivitamin use was associated with a reduction in total cancer among 1312 men who reported a baseline history of cancer (HR=0.73, 95% CI 0.56 to 0.96, p=0.02), the interpretation of these data calls for caution since events did not differ from those who reported no cancer history (n=13 329), nor were they lower among supplement takers who reported a parental history of cancer. The high prevalence of self-reported cancer history at baseline relative to cardiovascular disease was most unusual and was about twofold higher than the data presented in a previous publication that documented the baseline characteristics of this study sample.[4]

Commentary

This study was well designed, well controlled and adherence to both interventions was good (>70% throughout most of the study period). Also, the interpretation of the results was measured, with the conclusions stating 'a modest effect'. It is important to note however that this same trial showed no benefit for cardiovascular disease which tends to be an even more prevalent concern among middle-aged and older men (though it seems that within this sample the proportion of men with a cancer history was higher than that for cardiovascular disease, higher than that reported at baseline and higher than that of population norms).[3] Thus, even though this was a very good study, these modest results and issues related to the representativeness of the study population and generalisability of findings call for caution. Moreover, it is questionable whether a difference of 1.3 events/1000 patient-years is clinically significant, especially when supplementation would cost roughly $1800 over the balance of an average life, and the costs associated with additional visits to the chemist.

Competing interests None.

References

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