Can daily multivitamin prevent cancer? Results from the Physicians' Health Study

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A well-balanced diet including fruit and vegetables has been associated with a reduced risk of cancer in some, but not all, epidemiological trials.[1,2] Since multivitamins contain a combination of nutrients and minerals which may mimic a diverse diet, it is hypothesized that a daily multivitamin may be associated with a reduced risk of cancer. The use of multivitamin supplementation has been increasing over the last several years, especially among elderly patients.[3] However, this use is not supported by solid evidence and there is controversy about its safety.[4] The recent results from the Iowa Women's Health Study, an observational cohort, suggest that multivitamin use can be associated with increased risk of mortality in elderly women.[5] These results were potentially biased by factors including indication[4] and the tendency for supplement use to be higher in those with previous exposure to disease.

In 2013, investigators at the Harvard Medical School, Boston, Massachusetts, United States, reported the results of the Physicians' Health Study (PHS) II, which indicated that daily multivitamin supplement significantly reduced the risk of total cancer.[6] The PHS II is a randomized, double-blind, placebo-controlled trial, which included 14,641 patients to test the effect of 4 different supplements (multivitamin, vitamin C, vitamin E, β-carotene) on cancer incidence and mortality as well as the incidence of cardiovascular events, eye diseases, and cognitive decline. Men with a history of cirrhosis, active liver disease, those taking anticoagulants, or with a serious illness that might have precluded participation, were excluded. Men with a history of cancer or myocardial infarction or stroke were eligible for enrollment. This report focused particularly on cancer outcomes including total cancer incidence, cancer mortality, and total mortality.

Because of the mentioned prevalent use of multivitamin supplement among older individuals, the study included male physicians aged 50 years or older who were recruited in 2 different study phases. In the first phase, 7000 patients were recruited from a group of living participants of the previously conducted PHS I study, a randomized trial of low-dose aspirin and β-carotene in male physicians.[7] In the second phase, 7641 male physicians were recruited via a list provided by the American Medical Association. Both the multivitamin and placebo groups were well-balanced for patient characteristics. Approximately 9% of the patients in each group had a self-reported history of cancer, not further validated. The mean age of participants was 64.2 years in the active group and 64.3 years in the placebo groups. Over half of the participants were never-smokers (56.7% and 56.1% in the treatment and placebo groups, respectively). A large proportion of participants were aspirin users (77.5% and 77.3% in the treatment and placebo groups, respectively). There was a parental history of cancer in 52.9% and 54.1% of the subjects in the treatment and placebo groups, respectively.

Patients were followed for a mean period of 11.2 years. The results of the study showed that the incidence for total cancer in the trial was 17.0 per 1000 person-years in the intervention group and 18.3 for the placebo group with a statistically significant hazard ratio (HR) of 0.92 (95% confidence interval [CI], 0.86–0.998, $P = 0.04$). However, the incidence of prostate cancer, the most frequent cancer in this study, was not affected by multivitamin use. The majority of the prostate cancers diagnosed were early-stage, low-grade, and characterized by high survival. One of the challenges in interpreting the study results was the lack of information on prostate cancer mortality. Data on mortality may explain the absence of effect of multivitamin use on prostate cancer. When the investigators considered the incidence of total cancer with the exclusion of prostate cancer, the effect of multivitamin use was more pronounced (HR, 0.88; 95% CI, 0.79–0.98, $P = 0.02$). However, when they analyzed the effect of multivitamin use by different cancer sites,

the effect was weak and not statistically significant probably because of the small sample size of the subgroups.

Finally, cancer mortality was not reduced by multivitamin use. However, the "protective" HR was close to the statistical significance (HR, 0.88; 95% CI, 0.77–1.01; $P = 0.07$) even in consideration of the limited number of the counted events (multivitamin vs. placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years). Similarly, total mortality was not significantly reduced (HR, 0.94; 95% CI, 0.88–1.02; $P = 0.13$).

An interesting result from one of the subgroup analysis showed that men with no parental history of cancer showed the reduction in cancer incidence with multivitamin use (HR, 0.86, 95% CI, 0.76–0.98; $P = 0.02$). No such reduction was observed in men with a parental history of cancer (HR, 1.05; 95% CI, 0.94–1.17; $P = 0.37$) although the investigators did not specify how parental history was determined. Furthermore, among the 1312 men with a self-reported baseline history of cancer (not further validated), there was a significant reduction in the total cancer incidence (HR, 0.73, 95% CI, 0.56–0.96; $P = 0.02$). In men without a history of previous cancer, the reduction was not statistically significant (HR, 0.94; 95% CI, 0.87–1.02; $P = 0.15$). The overall rates of total cancer in men with or without a history of cancer were 18.4 and 17.6 per 1000 person-years, respectively.

Adherence was measured at different times of the study and remained high throughout. At the end of the follow-up period, the adherence rates were similar in both groups: 67.5% in the multivitamin group and 67.1% in the placebo group.

The strengths of this study include the study design and high adherence rates. As stated by the authors, this is the only large-scale, randomized, double-blind, placebo-controlled trial testing the effects of multivitamin in cancer prevention. There was a sufficiently large sample size to evaluate cancer outcomes. The incidence of cancer among all participants was 18.2% (2669 cancer cases of 14,641 men). The incidence of cancer mortality was 5.8% (859 of 14,641). The follow-up period of 11.2 years could have been insufficient to look efficiently at cancer mortality and total mortality.

The findings of this study are not easily generalizable. The PHS II study is comprised of physicians who are presumably well-nourished. Perhaps this may not be the best population when looking at the benefits of multivitamin supplementation. Theoretically, undernourished individuals might derive the greatest benefit from vitamin supplementation rather than those who have adequate baseline levels of various nutrients. Conducting a similar trial in an undernourished population would be of great interest.

Furthermore, there are multiple components in a multivitamin pill, and it is impossible to know which might have cancer prevention properties in this study. Although some components may be beneficial in cancer prevention, some may be harmful. We know from the SELECT study that vitamin E is associated with increased risk of prostate cancer.[8] In addition, using all cancers as the outcome implies that all cancers are identical in their biology but this is untrue. Different cancers have different pathophysiology and different mechanisms of proliferation. Each cancer has unique pathways of prevention and using one pill to prevent all cancers is not biologically plausible.

Previous studies have included observational data, and results have been mixed. In the Nurses' Health Study, women who took multivitamin supplements had decreased risk of colon cancer (relative risk [RR], 0.25; 95% CI, 0.13–0.51).[9] This benefit was seen at 15 years of follow-up, but not at the 5- or 10-year follow-up. In the Cancer Prevention Study II, a history of multivitamin use 10 years before enrollment was associated with the reduced risk of colorectal cancer in men and women (RR, 0.71, 95% CI, 0.57–0.89).[10] However, this study did not show any benefit in cancer mortality. The Women's Health Initiative included over 160,000 women followed for a mean of 8 years, and multivitamin use did not show any association with breast, colon, or other cancers.[11] In a Swedish study of 35,000 women followed for 10 years, multivitamin use was actually associated with an increased risk of breast cancer.[12]

The PHS II study is intriguing because it was a large trial that showed a statistically significant reduction in cancer incidence with multivitamin use. However the size of the effect was small (8% reduction) and there was no improvement in cancer mortality.

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