A New Role for Multivitamins?

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Study Overview

Objective. To determine the effect of a daily multivitamin (Centrum Silver) on total and site-specific cancer incidence and mortality in men.

Design. Large-scale, randomized, double-blind, placebo-controlled trial (Physicians Health Study II [PHS II])

Setting and participants. Recruitment, enrollment, and randomization took place in 2 phases. In the first phase, participants from PHS I (a randomized controlled trial studying effects of aspirin 81 mg and beta carotene among 22,071 male physicians) were invited to participate. Exclusion criteria included serious illness, cirrhosis, active liver disease, and use of anticoagulants or vitamin supplements. Participants with history of cancer, myocardial infarction, or stroke remained eligible. In the second phase, researchers sent letters to 254,597 US male physicians 50 years and older through a list provided by the American Medical Association. Of 42,165 men who responded, 11,128 were eligible. Only those who were adherent, as determined in a 12-week placebo run-in period, were included in the study. In total, 14,641 PHS II participants (7641 from phase I, 7000 from phase II) underwent randomization in blocks of 16, stratified by age, prior cancer, and cardiovascular disease, and beta-carotene assignment from PHS I.

Intervention. Participants received monthly calendar packs with Centrum Silver or placebo every 6 months for the first year then annually thereafter.

Main outcome measures. The primary endpoints were total cancer incidence (excluding non-melanoma skin cancers) and major cardiovascular events. Secondary endpoints included prostate, colorectal, epithelial cell cancers (excluding leukemia/lymphoma), total mortality, cancer mortality, and cancer site-specific mortality. Total cancer incidence excluding prostate cancer was also evaluated as an endpoint because of increased incidence of prostate cancer associated with prostate specific antigen screening during the study period. Cancer diagnoses were primarily based on pathology or cytology reports (96.9%). Otherwise, strong clinical, radiologic, or laboratory evidence was used. Mortality was determined by review of death certificates. Morbidity and mortality follow-up were 98.2% and 99.9% respectively and median follow-up time was 11.2 years.

Results. The groups were similar with regard to baseline characteristics, including age, BMI, smoking history, self and parental history of cancer, exercise, and diet. Mean age and BMI were 64.3 years and 26.0. Few participants were current smokers (3.6%), but many had former cigarette use (40%). Current aspirin use was high (77.4%) because of median age and participation in PHS I.

Of the participants, 9% (n = 1312) had a baseline history of cancer. Adherence in both groups remained adequate at various timepoints throughout the study (76.8% vs. 77.1%, P = 0.71 at 4 years; 67.5% vs. 67.1%, P = 0.70 at end of study).

The study found a statistically significant reduction in incidence of total cancer (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.86–0.998; P = 0.04) and total epithelial cell cancer (HR, 0.92; CI, 0.85–0.997; P = 0.04). The effect of the intervention was most notable in the incidence of total cancer excluding prostate cancer (HR, 0.88; CI, 0.79–0.98; P = 0.04). There was no significant difference in total mortality or cancer mortality. No detectable difference was observed in site-specific cancers including prostate cancer, colorectal cancer, lung cancer, or melanoma, although the low number of events limited the power in these groups.

Subgroup analysis in patients with a baseline history of cancer (n = 1312) revealed a greater reduction in incidence of total cancer (HR, 0.73; CI, 0.56–0.96; P = 0.02) and epithelial cell cancer (HR, 0.66; CI, 0.50–0.88; P = 0.004). Patients without a baseline history of cancer (n = 13,329) did not have a significant reduction in cancer incidence or mortality when stratified: incidence of total cancer (HR, 0.94; CI, 0.87–1.02; P = 0.15) and total epithelial cell cancer (HR, 0.95; CI, 0.87–1.03; P = 0.21). However, the P value for interaction was only significant for total epithelial cell cancer (P = 0.02).

Few adverse effects were observed in participants randomized to the active intervention. Investigators found no gastrointestinal tract symptoms, fatigue, drowsiness, skin discoloration, or migraines. Participants did have increased incidence of rash (HR, 1.07; CI, 1.01–1.14; P = 0.03) and epistaxis (HR, 1.10; CI, 1.02–1.18; P = 0.01) although no other effects on bleeding were observed.

Conclusion. Multivitamins may provide an incremental but statistically significant decrease in the risk of total cancers in middle-aged and older men with a history of cancer.

Commentary

It is well-established that oxidative damage is linked to DNA damage and is also associated with mutations resulting in the pathogenesis of cancers [1]. A diet high in fruits and vegetables may be associated with a lower cancer risk, likely due to the presence of antioxidants. Observational studies have correlated lower antioxidant levels with an increased risk for many cancers [2,3]. For these reasons, vitamin and antioxidant supplementation has been a popular area of interest in cancer prevention.

Up until this point, there have been numerous large-scale observational and cohort studies studying the association between vitamin supplementation and cancer prevention. Many studies concluded that there is no association between multivitamin use and cancer incidence or mortality. The Multiethnic Cohort Study (n = 215,000) found no association between vitamin use and morbidity or mortality from cancer over average 11 years of follow-up [4]. Similarly, the Women's Health Initiative, another large cohort study with median follow-up of 8 years (n = 161,000), reported no change in cancer of cardiovascular disease incidence in those taking multivitamins [5]. Additionally, the Cancer Prevention Study II (n = 1.2 million) showed no reduction in mortality in multivitamin use [6].

Despite these results, some studies have shown a significant decrease in mortality with multivitamin use. For example, the Linxian Chinese Cancer Prevention Trial was a study in rural China investigating the effects of combinations of vitamin/mineral supplements over 5 years (n = 29,584). Results showed 9% lower mortality (RR, 0.91; CI, 0.84–0.99; P = 0.03) and 13% lower cancer mortality (RR, 0.87; CI, 0.75–1.0). Esophageal/gastric cancer rates were reduced by 10%, with stomach cancer showing a more dramatic decrease than esophageal cancer (RR, 0.79; CI, 0.64–0.99).

This study is the first large-scale randomized, placebo-controlled trial evaluating multivitamins on cancer incidence and mortality in the United States. There was an incremental decrease in risk for cancer but no specific difference was noted in site-specific cancers. The absolute differences for total cancer, total epithelial cancer, and total cancer excluding prostate cancer were small at best, with absolute risk reductions of 1.2%, 1.2%, and 1.0%, respectively. Despite this incremental decrease, the number needed to treat was 83, 83, and 100, respectively. Given that the study revealed only minor adverse reactions, the study suggests multivitamin supplementation could benefit the population without producing significant harm.

Participants in the Linxian Chinese Cancer Prevention Trial included those who had greater exposures to

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tobacco, pickled vegetables, and moldy foods. Many had a family history of esophageal or stomach cancer, no education, and nutritional deficiencies. In contrast, the PHS II participants were male US physicians who were presumably high-income, highly educated, and well-nourished. The greater effects seen in the Linxian study participants might be attributable to their poorer nutritional status.

While the study had a long follow-up period (median, 11.2 years), previous studies have demonstrated a latency effect with continued multivitamin use over time. The Nurses Health Study, a prospective cohort study from 1980 to 1994, showed a dramatic decrease in colon cancer incidence when comparing high-dose folate use at 4 years (relative risk [RR], 1.02) with use after 15 years (RR, 0.25; CI, 0.13–0.51) [9]. Furthermore, the Linxian study showed a greater effect on mortality and cancer incidence after incorporating a 1-year lag-time into the analysis. Total cancer mortality decreased (RR, 0.87 to 0.85) and stomach cancer (RR, 0.79 to 0.77). Thus, a greater effect of multivitamin use on cancer incidence and mortality might be found by increasing the follow-up time of the study or incorporating lag-time into analysis.

Applications for Clinical Practice

Overall, the results of the study reveal there is likely little harm in recommending multivitamin supplements to the general patient population, given the few severe adverse events. However, the impact on cancer incidence is likely to be small. The study results represent the rather narrow demographic of older male physicians, so applicability to younger populations and women is questionable. Furthermore, there is no published breakdown of the ethnicities of participants, so it is unclear whether this can be generalized to minority populations. Despite these limitations, it appears vitamin supplementation may decrease cancer incidence in select populations, especially those with a history of previous cancers.

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