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## Original Contribution

# Multivitamin Use and the Risk of Mortality and Cancer Incidence

## The Multiethnic Cohort Study

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Although multivitamin/mineral supplements are commonly used in the United States, the efficacy of these supplements in preventing chronic disease or premature death is unclear. To assess the relation of multivitamin use with mortality and cancer, the authors prospectively examined these associations among 182,099 participants enrolled in the Multiethnic Cohort Study between 1993 and 1996 in Hawaii and California. During an average 11 years of follow-up, 28,851 deaths were identified. In Cox proportional hazards models controlling for tobacco use and other potential confounders, no associations were found between multivitamin use and mortality from all causes (for users vs. nonusers: hazard ratio = 1.07, 95% confidence interval: 0.96, 1.19 for men; hazard ratio = 0.96, 95% confidence interval: 0.85, 1.09 for women), cardiovascular diseases, or cancer. The findings did not vary across subgroups by ethnicity, age, body mass index, preexisting illness, single vitamin/mineral supplement use, hormone replacement therapy use, and smoking status. There also was no evidence indicating that multivitamin use was associated with risk of cancer, overall or at major sites, such as lung, colorectum, prostate, and breast. In conclusion, there was no clear decrease or increase in mortality from all causes, cardiovascular disease, or cancer and in morbidity from overall or major cancers among multivitamin supplement users.

cohort studies; mortality; neoplasms; vitamins

Abbreviations: ICD-9, *International Classification of Diseases*, Ninth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision.

Multivitamin/mineral supplements are commonly used in the United States in part because people expect this type of supplement to improve their health (1, 2). However, the efficacy of these supplements to prevent chronic disease or premature death is not proven (3, 4), and the National Institutes of Health do not recommend multivitamin/mineral supplements for this purpose (5). A small number of clinical trials to date have shown that multivitamin use was effective in reducing the risk of some chronic disease including cancer and cardiovascular diseases (4, 6). However, these trials tested specific combinations of vitamins with or without minerals rather than commonly used multivitamin products. In addition, subjects were not generally drawn from healthy populations and/or the sample sizes were small. The Physicians' Health Study II, an ongoing large clinical trial, has the potential to provide more definitive evidence of the effects of a widely used multivitamin product on the risk of chronic disease, but the findings are not yet available (2, 7, 8).

Although many observational studies have examined the associations between dietary supplements and risk of disease or mortality, only a small number of them investigated multivitamin use. Recently, a large Women's Health Initiative cohort study with a median follow-up of 8 years reported no association of multivitamin use with the risk of incidence of cancer and cardiovascular disease and with mortality among more than 161,000 postmenopausal women (9).

To further assess the relation of multivitamin use with mortality and cancer incidence among both men and women, we examined these associations for participants in the Multiethnic Cohort, which was established to study diet and chronic disease in Hawaii and California. Multivitamin use is closely related to healthy lifestyle factors, which are major confounders in observational studies (10). Therefore, we carefully considered health-related factors for adjustment and/or stratification in the analyses.

## MATERIALS AND METHODS

### Study population

In 1993–1996, the Multiethnic Cohort Study enrolled more than 215,000 adults aged 45–75 years, living in Hawaii and California, who were mostly African Americans, Native Hawaiians, Japanese Americans, Latinos, or Whites (11). The participants completed a 26-page mailed questionnaire on diet, medical history, and lifestyle when they entered the cohort. The study was approved by the review boards of the University of Hawaii and the University of Southern California. For the analyses, we excluded participants who were not in one of the targeted 5 ethnic groups ($n = 13,991$) or who reported invalid dietary intakes based on total energy intake or its components ($n = 8,264$) (12). We also excluded those with missing information on multivitamin use ($n = 4,451$) or smoking ($n = 7,013$). Therefore, the analysis included 182,099 participants (82,405 men and 99,694 women).

### Assessment of multivitamin use and potential confounders

The baseline questionnaire included questions about the use of multivitamins (with/without minerals) and 7 single vitamin/mineral supplements. Subjects were asked to indicate whether they had used any of these supplements at least weekly during the previous year. Subjects were also asked about the frequency and duration for each supplement they had used. In a validation study (13), weighted kappa statistics ($\kappa$) for agreement between three 1-day recalls of multivitamin supplement use and the questionnaire across 6 categories of frequency of use (never use, 1–3/week, 4–6/week, 1/day, 2/day, and $\geq$3/day) was 0.65, and the $\kappa$ for reproducibility of questionnaire responses at 2 time points was 0.54 for multivitamin supplements.

In a follow-up questionnaire approximately 5 years after baseline (1999–2003), participants were asked the same question on multivitamin use but without duration of use. To examine long-term effects of multivitamin use on mortality, we defined long-term users as those who had taken multivitamins for 5 or more years at cohort entry and also currently took them at the time of the follow-up survey. We then compared them with those who were nonusers at both time points. This analysis was limited to 144,195 participants who provided information on multivitamin use for both surveys.

On the baseline questionnaire, participants also provided information on sociodemographic factors, dietary intake (a quantitative food frequency questionnaire), weight/height, personal behaviors, and history of medical conditions, as well as, for women, menopausal status and use of hormone replacement therapy. For this analysis, preexisting illness was defined as self-reported, physician-diagnosed heart attack or angina, stroke, diabetes, high blood pressure, and/or cancer. Preexisting cancer was additionally identified by linking to the Surveillance, Epidemiology, and End Results tumor registries covering the states of Hawaii and California.

### Ascertainment of outcomes

We linked the cohort to the death certificate files in Hawaii and California and to the National Death Index through December 31, 2005. During an average 11 years of follow-up, we identified 28,851 deaths (15,962 men and 12,889 women). Death from all causes was the primary endpoint in the analyses. In addition, according to the *International Classification of Diseases*, Ninth Revision (ICD-9) and Tenth Revision (ICD-10), we categorized the primary cause of death into cardiovascular diseases (ICD-9 codes 390–434, 436–448; ICD-10 codes I00–I78), cancer (ICD-9 codes 140–208; ICD-10 codes C00–C97), and all other causes. We also linked the cohort to the Surveillance, Epidemiology, and End Results cancer registries covering Hawaii and California through December 31, 2004, in order to identify incident cases of cancer.

### Statistical analysis

We compared baseline characteristics between multivitamin users and nonusers separately for men and women. Cox proportional hazards models, with age as the time metric, provided estimates of hazard ratios and 95% confidence intervals of mortality or cancer incidence related to multivitamin use. Because smoking is related to dietary supplement use and the outcomes of mortality and cancer incidence, we used a comprehensive base model for the relation between smoking and the outcomes that was based on the model developed to study tobacco use and lung cancer incidence in the Multiethnic Cohort (14). The model explicitly included 4 indicator variables for race/ethnicity; average number of cigarettes; average number of cigarettes squared; indicator variables for former and current smokers; number of years smoked (time dependent); number of years since quitting (time dependent); and interactions of race/ethnicity with the following variables: average number of cigarettes, average number of cigarettes squared, smoking status, and number of years smoked.

The models were further adjusted for the following strata variables: age at cohort entry (<50, 50–54, 55–59, 60–64, 65–69, 70–74, $\geq$75 years), body mass index (<18.5, 18.5–22.4, 22.5–24.9, 25–29.9, 30–34.9, $\geq$35 kg/m$^2$, and missing), alcohol consumption (ethanol; 0, 1–<5.2, 5.2–<23, $\geq$23 g/day for men; 0, 1–<3, $\geq$3 g/day for women), education (12th grade or less, vocational school/some college, college graduate or postgraduate, and missing), physical activity (hours spent in vigorous activity per day; <0.1, 0.1–<0.25, 0.25–<0.80, $\geq$0.80, and missing for men; <0.1, 0.1–<0.25, $\geq$0.25, and missing for women),

**Table 1.** Baseline Characteristics of Multivitamin Supplement Users and Nonusers in the Multiethnic Cohort Study, 1993–1996[a]

| | Men ($n$ = 82,405) | | | | Women ($n$ = 99,694) | | | |
|---|---|---|---|---|---|---|---|---|
| | Users ($n$ = 39,214) | | Nonusers ($n$ = 43,191) | | Users ($n$ = 53,738) | | Nonusers ($n$ = 45,956) | |
| | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % |
| Age, years | 60.4 (8.8) | | 59.9 (8.9) | | 59.8 (8.8) | | 59.4 (8.9) | |
| Race/ethnicity | | | | | | | | |
| African American | | 13.5 | | 13.6 | | 19.4 | | 19.5 |
| Native Hawaiian | | 5.1 | | 8.8 | | 5.9 | | 9.3 |
| Japanese American | | 30.5 | | 30.1 | | 27.8 | | 27.9 |
| Latino | | 23.6 | | 23.3 | | 20.4 | | 20.7 |
| White | | 27.4 | | 24.3 | | 26.5 | | 22.5 |
| Body mass index, kg/m$^2$ | 26.3 (4.0) | | 26.9 (4.4) | | 26.0 (5.5) | | 27.0 (6.1) | |
| Smoking status at baseline | | | | | | | | |
| Never | | 31.7 | | 30.1 | | 57.3 | | 56.0 |
| Former | | 51.9 | | 50.3 | | 29.5 | | 28.2 |
| Current | | 16.5 | | 19.6 | | 13.2 | | 15.8 |
| Alcohol intake, g/day | 14.1 (30.5) | | 15.3 (34.1) | | 4.4 (14.5) | | 4.2 (15.3) | |
| Education | | | | | | | | |
| 12th grade or less | | 37.2 | | 43.9 | | 42.9 | | 48.4 |
| Vocational/some college | | 30.2 | | 28.7 | | 31.0 | | 28.8 |
| College graduate/postgraduate | | 32.6 | | 27.4 | | 26.1 | | 22.8 |
| Physical activity, hours/day[b] | 0.58 (1.01) | | 0.57 (1.02) | | 0.23 (0.57) | | 0.19 (0.52) | |
| Preexisting illness[c] | | 51.9 | | 53.1 | | 48.1 | | 51.9 |
| Single supplement use[d] | | 72.2 | | 20.3 | | 81.7 | | 38.3 |
| Vegetable intake, servings/day | 4.9 (3.1) | | 4.6 (3.0) | | 4.9 (3.3) | | 4.5 (3.2) | |
| Fruit intake, servings/day | 3.4 (3.1) | | 3.0 (2.9) | | 3.9 (3.5) | | 3.4 (3.2) | |
| Energy from fat, % energy/day | 29.8 (7.1) | | 30.4 (7.2) | | 29.2 (7.0) | | 30.3 (7.2) | |
| Postmenopause | | | | | | 86.3 | | 84.7 |
| Hormone replacement therapy use[e] | | | | | | | | |
| No current or past estrogen use | | | | | | 42.0 | | 51.3 |
| Past estrogen use with or without progesterone | | | | | | 20.7 | | 19.0 |
| Current estrogen-only use | | | | | | 16.9 | | 14.0 |
| Current estrogen use with past/current progesterone | | | | | | 20.5 | | 15.7 |

Abbreviation: SD, standard deviation.

[a] Users were defined as subjects who had used multivitamin supplements at least weekly during the previous year.

[b] Hours spent in vigorous activity per day.

[c] Self-reported heart attack or angina, stroke, diabetes, high blood pressure, and cancer (or from tumor registries).

[d] Used 1 or more of the following supplements at least once a week during the past year: vitamin A, vitamin C, vitamin E, β-carotene, calcium, selenium, or iron.

[e] Among postmenopausal women only.

preexisting illness (yes, no), single supplement use (yes, no), vegetable intake (<2.3, 2.3–<3.4, 3.4–<4.6, 4.6–<6.6, and ≥6.6 servings/day for men; <2.3, 2.3–<3.4, 3.4–<4.6, 4.6–<6.7, and ≥6.7 servings/day for women), and fruit intake (<1, 1–<1.9, 1.9–<3, 3–<4.8, and ≥4.8 servings/day for men; <1.3, 1.3–<2.3, 2.3–<3.5, 3.5–<5.5, and ≥5.5 servings/day for women). For women, the models were additionally adjusted for menopausal status (premenopause, postmenopause, and missing) and hormone replacement therapy use (no current or past estrogen use, past estrogen use with or without progesterone, current estrogen use without progesterone, current estrogen use with past/current progesterone, and missing).

We evaluated models for total mortality and for cause-specific mortality (cardiovascular diseases, cancer, and all other causes), as well as models for the incidence of specific

**Table 2.** Hazard Ratios of Total Mortality According to Multivitamin Supplement Use in the Multiethnic Cohort Study, 1993–2005

| Multivitamin Use | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Subjects | No. of Deaths | HR[a] | 95% CI | HR[b] | 95% CI | No. of Subjects | No. of Deaths | HR[a] | 95% CI | HR[b] | 95% CI |
| No use | 43,191 | 8,458 | 1.00 | | 1.00 | | 45,956 | 6,140 | 1.00 | | 1.00 | |
| Use | 39,214 | 7,504 | 0.99 | 0.96, 1.03 | 1.07 | 0.96, 1.19 | 53,738 | 6,749 | 0.96 | 0.93, 0.99 | 0.96 | 0.85, 1.09 |
| Frequency of use | | | | | | | | | | | | |
| No use | 43,191 | 8,458 | 1.00 | | 1.00 | | 45,956 | 6,140 | 1.00 | | 1.00 | |
| 1–6/week | 8,610 | 1,238 | 0.91 | 0.85, 0.96 | 1.00 | 0.81, 1.22 | 11,253 | 1,074 | 0.84 | 0.79, 0.90 | 0.86 | 0.69, 1.07 |
| 1/day | 21,324 | 4,493 | 1.02 | 0.98, 1.05 | 1.08 | 0.96, 1.23 | 30,329 | 4,165 | 0.99 | 0.95, 1.03 | 0.98 | 0.86, 1.12 |
| ≥2/day | 8,633 | 1,601 | 1.00 | 0.95, 1.05 | 0.98 | 0.81, 1.18 | 11,051 | 1,314 | 0.95 | 0.89, 1.01 | 0.95 | 0.77, 1.17 |
| Duration of use | | | | | | | | | | | | |
| No use | 43,191 | 8,458 | 1.00 | | 1.00 | | 45,956 | 6,140 | 1.00 | | 1.00 | |
| <5 years | 15,900 | 3,041 | 1.05 | 1.01, 1.10 | 1.13 | 0.98, 1.30 | 22,447 | 2,789 | 1.01 | 0.96, 1.05 | 0.93 | 0.80, 1.09 |
| ≥5 years | 22,050 | 4,149 | 0.94 | 0.91, 0.98 | 0.99 | 0.86, 1.13 | 29,460 | 3,670 | 0.92 | 0.88, 0.95 | 1.00 | 0.87, 1.15 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The following variables were included to rigorously control for the effects of smoking: ethnicity, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoked. The models also included age at cohort entry.

[b] The models were further adjusted for body mass index, alcohol consumption, education, physical activity, preexisting illness, single supplement use, vegetable intake, fruit intake, energy from fat, hormone replacement therapy use, and menopausal status (for women only).

cancers, which were additionally adjusted for family history of the corresponding cancer. We performed subgroup analyses to investigate whether the associations between multivitamin use and mortality varied by ethnicity, age group (<65 and ≥65 years), body mass index (18.5–<25, 25–<30, and ≥30 kg/m$^2$), preexisting illness (yes, no), single vitamin/mineral supplement use (yes, no), hormone replacemen therapy use (ever, never use among postmenopausal women), and smoking status (never, former, current smokers at baseline). We also examined the joint effect of duration and frequency of multivitamin use. Tests for interaction were based on the Wald statistics for cross-product terms. All statistical tests were 2 sided, and $P < 0.05$ was considered statistically significant. Analyses were conducted by using SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

Compared with men and women who took no multivitamin supplements, multivitamin users, in general, were more likely to be older, white, and better educated (Table 1). They were also more likely to use single vitamin/mineral supplements and to eat vegetables and fruit. They were less likely to be Native Hawaiian, obese, or current smokers and less likely to have preexisting illness or to have high fat intake. Female multivitamin users also were more likely to be postmenopausal women and to currently use hormone replacement therapy, compared with women who did not use multivitamins.

Overall associations between multivitamin use and total mortality are presented in Table 2. No significant associations were observed for multivitamin use, either for frequency or duration of use. Mortality from cardiovascular diseases or cancer also was not associated with multivitamin use (Table 3). However, compared with nonusers, men who took multivitamins twice or more per day and those who were short-term users (<5 years) showed an increased risk of mortality from all causes other than cardiovascular diseases or cancer. In the analyses for long-term multivitamin use (using baseline and follow-up surveys), no significant association was found with duration of use for overall, cardiovascular diseases, and cancer mortality; the hazard ratios of overall mortality were 0.98 (95% confidence interval: 0.74, 1.29) in men and 0.78 (95% confidence interval: 0.58, 1.06) in women for long-term users versus nonusers (data not shown).

Table 4 shows the associations between multivitamin use and mortality for each ethnic group. The associations did not differ among the 5 groups (tests for interactions were not statistically significant), although there was a suggestive increase in mortality among white females (for white vs. all other females: $P_{\text{interaction}} = 0.06$ for use and 0.05 for duration). When associations between multivitamin use and mortality were examined among subgroups of the cohort participants, there were no differences by age group, body mass index group, preexisting illness, single supplement use, hormone replacement therapy use (among postmenopausal women), and smoking status (data not shown).

In an analysis for joint effects of frequency and duration of multivitamin use, there was no significant interaction between these 2 variables for total mortality or for mortality from cardiovascular diseases, cancer, or all other causes (data not shown).

We observed no significant association between multivitamin use and cancer incidence either for major sites or overall (Table 5). For other cancer sites with smaller numbers of

**Table 3.** Hazard Ratios of Cause-specific Mortality According to Multivitamin Supplement Use in the Multiethnic Cohort Study, 1993–2005[a]

| Multivitamin Use | CVD | | | Cancer | | | All Other Causes | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI |
| Men | | | | | | | | | |
| No use | 3,303 | 1.00 | | 2,898 | 1.00 | | 2,210 | 1.00 | |
| Use | 2,803 | 1.06 | 0.88, 1.27 | 2,588 | 0.98 | 0.81, 1.19 | 2,076 | 1.15 | 0.92, 1.44 |
| Frequency of use | | | | | | | | | |
| No use | 3,303 | 1.00 | | 2,898 | 1.00 | | 2,210 | 1.00 | |
| 1–6/week | 467 | 1.08 | 0.76, 1.54 | 433 | 1.02 | 0.74, 1.40 | 331 | 0.81 | 0.53, 1.26 |
| 1/day | 1,674 | 1.06 | 0.87, 1.29 | 1,557 | 1.06 | 0.86, 1.32 | 1,245 | 1.09 | 0.85, 1.39 |
| ≥2/day | 597 | 0.89 | 0.65, 1.22 | 538 | 0.72 | 0.51, 1.01 | 454 | 1.49 | 1.02, 2.17 |
| Duration of use | | | | | | | | | |
| No use | 3,303 | 1.00 | | 2,898 | 1.00 | | 2,210 | 1.00 | |
| <5 years | 1,125 | 1.12 | 0.89, 1.41 | 1,025 | 0.97 | 0.76, 1.25 | 876 | 1.33 | 1.01, 1.76 |
| ≥5 years | 1,556 | 0.95 | 0.76, 1.19 | 1,455 | 0.96 | 0.76, 1.20 | 1,117 | 0.97 | 0.74, 1.28 |
| Women | | | | | | | | | |
| No use | 2,227 | 1.00 | | 2,158 | 1.00 | | 1,723 | 1.00 | |
| Use | 2,346 | 0.95 | 0.77, 1.17 | 2,512 | 1.08 | 0.87, 1.33 | 1,867 | 0.90 | 0.72, 1.13 |
| Frequency of use | | | | | | | | | |
| No use | 2,227 | 1.00 | | 2,158 | 1.00 | | 1,723 | 1.00 | |
| 1–6/week | 367 | 1.05 | 0.73, 1.51 | 452 | 0.76 | 0.53, 1.10 | 253 | 0.74 | 0.48, 1.16 |
| 1/day | 1,463 | 0.94 | 0.74, 1.18 | 1,514 | 1.16 | 0.91, 1.47 | 1,174 | 0.90 | 0.70, 1.16 |
| ≥2/day | 438 | 0.89 | 0.62, 1.27 | 490 | 1.01 | 0.72, 1.42 | 379 | 1.02 | 0.67, 1.56 |
| Duration of use | | | | | | | | | |
| No use | 2,227 | 1.00 | | 2,158 | 1.00 | | 1,723 | 1.00 | |
| <5 years | 1,003 | 0.88 | 0.68, 1.15 | 1,020 | 1.09 | 0.84, 1.42 | 760 | 0.91 | 0.68, 1.22 |
| ≥5 years | 1,233 | 1.04 | 0.81, 1.33 | 1,394 | 1.07 | 0.83, 1.38 | 1,027 | 0.89 | 0.67, 1.17 |

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] The following variables were included to rigorously control for the effects of smoking: ethnicity, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoked. The models were further adjusted for age at cohort entry, body mass index, alcohol consumption, education, physical activity, preexisting illness, single supplement use, vegetable intake, fruit intake, energy from fat, hormone replacement therapy use, and menopausal status (for women only).

cases, no evidence was found that multivitamin use either increased or decreased cancer risk (data not shown).

## DISCUSSION

In this large multiethnic cohort, we found no associations between multivitamin use and mortality from all causes, cardiovascular diseases, or cancer. The findings did not vary across subgroups by ethnicity, age, body mass index, preexisting illness, single vitamin/mineral supplement use, hormone replacement therapy use, and smoking status. In addition, there was no evidence indicating that multivitamin use increased or decreased risk for cancer, overall or at major sites, such as lung, colorectum, prostate, and breast.

The findings from cohort studies that have examined multivitamin use in relation to risk of cancer incidence or mortality are mixed: Most of them were null, while some showed direct associations, and others found inverse associations. In the First National Health and Nutrition Examination Survey (1971–1975) followed through 1987, vitamin and mineral supplement use was not related to mortality (15). The Physicians' Health Study reported no association between multivitamin use and cardiovascular disease mortality among low-risk healthy males (16). The Women's Health Initiative cohorts also provided no evidence that multivitamin use was related to either the risk of incidence of cancer and cardiovascular diseases or total mortality among postmenopausal women (9).

The Cancer Prevention Study II investigators have reported on the effects of vitamin supplements on mortality from cardiovascular diseases and from cancer overall or of specific sites. Multivitamin use alone was not associated

**Table 4.** Hazard Ratios of Mortality According to Multivitamin Supplement Use and Ethnicity in the Multiethnic Cohort Study, 1993–2005[a]

| Multivitamin Use | African Americans | | | Native Hawaiians | | | Japanese Americans | | | Latinos | | | Whites | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI | No. of Deaths | HR | 95% CI |
| Men | | | | | | | | | | | | | | | |
| No use | 1,929 | 1.00 | | 796 | 1.00 | | 2,134 | 1.00 | | 1,756 | 1.00 | | 1,843 | 1.00 | |
| Use | 1,581 | 0.95 | 0.85, 1.05 | 363 | 0.95 | 0.74, 1.21 | 2,056 | 1.03 | 0.95, 1.12 | 1,626 | 1.03 | 0.93, 1.14 | 1,878 | 1.05 | 0.96, 1.16 |
| $P_{interaction}$ | | | 0.41 | | | | | | | | | | | | |
| Frequency of use | | | | | | | | | | | | | | | |
| No use | 1,929 | 1.00 | | 796 | 1.00 | | 2,134 | 1.00 | | 1,756 | 1.00 | | 1,843 | 1.00 | |
| 1–6/week | 320 | 0.90 | 0.76, 1.07 | 50 | 0.71 | 0.41, 1.20 | 235 | 0.93 | 0.79, 1.09 | 347 | 1.05 | 0.89, 1.23 | 286 | 0.92 | 0.77, 1.09 |
| 1/day | 887 | 0.95 | 0.84, 1.07 | 207 | 0.94 | 0.71, 1.24 | 1,361 | 1.03 | 0.94, 1.12 | 916 | 1.01 | 0.91, 1.13 | 1,122 | 1.06 | 0.96, 1.18 |
| ≥2/day | 311 | 0.98 | 0.82, 1.18 | 100 | 1.21 | 0.82, 1.80 | 423 | 1.12 | 0.98, 1.28 | 329 | 1.12 | 0.95, 1.32 | 438 | 1.09 | 0.94, 1.27 |
| $P_{interaction}$ | | | 0.25 | | | | | | | | | | | | |
| Duration of use | | | | | | | | | | | | | | | |
| No use | 1,929 | 1.00 | | 796 | 1.00 | | 2,134 | 1.00 | | 1,756 | 1.00 | | 1,843 | 1.00 | |
| <5 years | 743 | 0.96 | 0.85, 1.10 | 170 | 1.09 | 0.80, 1.47 | 664 | 1.10 | 0.99, 1.23 | 814 | 1.06 | 0.94, 1.19 | 650 | 1.09 | 0.97, 1.23 |
| ≥5 years | 746 | 0.93 | 0.81, 1.06 | 180 | 0.77 | 0.55, 1.06 | 1,340 | 0.98 | 0.89, 1.07 | 717 | 0.96 | 0.85, 1.09 | 1,166 | 1.00 | 0.90, 1.12 |
| $P_{interaction}$ | | | 0.79 | | | | | | | | | | | | |
| Women | | | | | | | | | | | | | | | |
| No use | 1,965 | 1.00 | | 664 | 1.00 | | 1,086 | 1.00 | | 1,133 | 1.00 | | 1,292 | 1.00 | |
| Use | 2,145 | 1.03 | 0.94, 1.13 | 378 | 0.95 | 0.73, 1.23 | 1,333 | 1.03 | 0.93, 1.15 | 1,163 | 0.98 | 0.87, 1.11 | 1,730 | 1.20 | 1.07, 1.35 |
| $P_{interaction}$ | | | 0.36 | | | | | | | | | | | | |
| Frequency of use | | | | | | | | | | | | | | | |
| No use | 1,965 | 1.00 | | 664 | 1.00 | | 1,086 | 1.00 | | 1,133 | 1.00 | | 1,292 | 1.00 | |
| 1–6/week | 401 | 0.96 | 0.82, 1.13 | 49 | 0.83 | 0.48, 1.43 | 150 | 0.87 | 0.70, 1.08 | 225 | 0.92 | 0.75, 1.12 | 249 | 1.15 | 0.94, 1.40 |
| 1/day | 1,249 | 1.04 | 0.94, 1.15 | 227 | 0.84 | 0.62, 1.13 | 897 | 1.02 | 0.91, 1.15 | 703 | 1.03 | 0.90, 1.19 | 1,089 | 1.22 | 1.07, 1.39 |
| ≥2/day | 398 | 0.93 | 0.79, 1.10 | 87 | 1.32 | 0.81, 2.14 | 252 | 1.21 | 1.02, 1.44 | 209 | 0.91 | 0.74, 1.13 | 368 | 1.22 | 1.02, 1.46 |
| $P_{interaction}$ | | | 0.26 | | | | | | | | | | | | |
| Duration of use | | | | | | | | | | | | | | | |
| No use | 1,965 | 1.00 | | 664 | 1.00 | | 1,086 | 1.00 | | 1,133 | 1.00 | | 1,292 | 1.00 | |
| <5 years | 991 | 0.99 | 0.89, 1.11 | 184 | 1.02 | 0.74, 1.41 | 423 | 1.10 | 0.95, 1.27 | 633 | 1.02 | 0.89, 1.18 | 558 | 1.17 | 1.00, 1.36 |
| ≥5 years | 1,038 | 1.03 | 0.92, 1.16 | 182 | 0.99 | 0.70, 1.40 | 868 | 1.00 | 0.89, 1.12 | 468 | 0.93 | 0.79, 1.09 | 1,114 | 1.20 | 1.06, 1.37 |
| $P_{interaction}$ | | | 0.29 | | | | | | | | | | | | |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The following variables were included to rigorously control for the effects of smoking: smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), and number of years since quitting (time dependent). The models were further adjusted for age at cohort entry, body mass index, alcohol consumption, education, physical activity, single supplement use, vegetable intake, fruit intake, energy from fat, hormone replacement therapy use, and menopausal status (for women only).

with cardiovascular diseases and cancer mortality, but the combined use with vitamin A, C, or E decreased cardiovascular disease mortality by 15% compared with nonusers (17). They found no associations with mortality from non-Hodgkin's lymphoma (18) and stomach cancer (19), while they found a small increase in risk of mortality from prostate cancer (20) and a moderate decrease of colon cancer mortality among long-term (≥15 years) users (21). They also found an inverse association for colorectal cancer incidence among past users (10 years before baseline) (22). An inverse association with colon/colorectal cancer that was observed only after a substantial latency period was also reported by the Health Professionals Follow-up Study (23) and the Nurses' Health Study (24) investigators, where the authors speculated that folic acid contained in multivitamins might contribute to the risk reduction. For breast cancer incidence, the Nurses' Health Study found no association regardless of the duration of multivitamin use (25). The Women's Health Study, conducted with female health professionals, reported no effect of multivitamin use on the risk of colorectal (26) and breast cancer (27) incidence.

The National Institutes of Health (NIH)-AARP Diet and Health Study found that multivitamin use was not associated with risk of early or localized prostate cancer but was related to an increased risk of advanced and fatal prostate

**Table 5.** Hazard Ratios of Major Cancers According to Multivitamin Supplement Use in the Multiethnic Cohort Study, 1993–2004[a]

| | Prostate Cancer | | | Lung Cancer | | | Colorectal Cancer | | | Any Cancer | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI |
| Men | | | | | | | | | | | | |
| Multivitamin use | | | | | | | | | | | | |
| No use | 2,682 | 1.00 | | 875 | 1.00 | | 867 | 1.00 | | 5,830 | 1.00 | |
| Use | 2,553 | 1.05 | 0.83, 1.33 | 760 | 1.08 | 0.70, 1.68 | 627 | 1.08 | 0.66, 1.75 | 5,173 | 0.95 | 0.77, 1.16 |
| Frequency of use | | | | | | | | | | | | |
| No use | 2,682 | 1.00 | | 875 | 1.00 | | 867 | 1.00 | | 5,830 | 1.00 | |
| 1–6/week | 518 | 1.25 | 0.82, 1.91 | 121 | 1.47 | 0.68, 3.21 | 115 | 0.69 | 0.26, 1.85 | 982 | 1.20 | 0.85, 1.71 |
| 1/day | 1,451 | 0.95 | 0.73, 1.23 | 463 | 1.03 | 0.63, 1.69 | 397 | 1.09 | 0.65, 1.84 | 2,988 | 0.93 | 0.74, 1.17 |
| ≥2/day | 540 | 1.29 | 0.88, 1.88 | 163 | 1.16 | 0.56, 2.41 | 107 | 0.75 | 0.31, 1.83 | 1,112 | 0.80 | 0.57, 1.12 |
| Duration of use | | | | | | | | | | | | |
| No use | 2,682 | 1.00 | | 875 | 1.00 | | 867 | 1.00 | | 5,830 | 1.00 | |
| <5 years | 957 | 0.99 | 0.74, 1.33 | 299 | 1.46 | 0.82, 2.61 | 250 | 1.15 | 0.62, 2.14 | 1,991 | 1.00 | 0.78, 1.28 |
| ≥5 years | 1,506 | 1.11 | 0.84, 1.46 | 435 | 0.87 | 0.51, 1.48 | 363 | 1.09 | 0.61, 1.93 | 3,001 | 0.87 | 0.68, 1.11 |
| | **Breast Cancer** | | | **Lung Cancer** | | | **Colorectal Cancer** | | | **Any Cancer** | | |
| | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI | No. of Cases | HR | 95% CI |
| Women | | | | | | | | | | | | |
| Multivitamin use | | | | | | | | | | | | |
| No use | 1,589 | 1.00 | | 561 | 1.00 | | 659 | 1.00 | | 4,126 | 1.00 | |
| Use | 1,861 | 1.02 | 0.76, 1.39 | 668 | 0.73 | 0.37, 1.45 | 633 | 0.71 | 0.43, 1.18 | 4,710 | 1.03 | 0.83, 1.27 |
| Frequency of use | | | | | | | | | | | | |
| No use | 1,589 | 1.00 | | 561 | 1.00 | | 659 | 1.00 | | 4,126 | 1.00 | |
| 1–6/week | 371 | 0.72 | 0.45, 1.16 | 126 | 0.47 | 0.16, 1.44 | 117 | 0.66 | 0.27, 1.63 | 912 | 0.92 | 0.64, 1.31 |
| 1/day | 1,082 | 1.30 | 0.91, 1.84 | 400 | 0.72 | 0.33, 1.54 | 362 | 0.65 | 0.36, 1.18 | 2,752 | 1.02 | 0.80, 1.30 |
| ≥2/day | 370 | 0.76 | 0.47, 1.24 | 121 | 1.09 | 0.31, 3.78 | 145 | 1.11 | 0.50, 2.49 | 948 | 1.09 | 0.78, 1.53 |
| Duration of use | | | | | | | | | | | | |
| No use | 1,589 | 1.00 | | 561 | 1.00 | | 659 | 1.00 | | 4,126 | 1.00 | |
| <5 years | 711 | 0.95 | 0.66, 1.37 | 262 | 0.67 | 0.28, 1.63 | 240 | 0.69 | 0.36, 1.32 | 1,879 | 1.04 | 0.80, 1.35 |
| ≥5 years | 1,098 | 0.99 | 0.69, 1.44 | 374 | 0.83 | 0.36, 1.91 | 373 | 0.76 | 0.42, 1.37 | 2,676 | 0.99 | 0.76, 1.28 |

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Individuals with a history of corresponding cancer (based on the questionnaire or tumor registries) were excluded in the analyses. The following variables were included to rigorously control for the effects of smoking: ethnicity, smoking status, average number of cigarettes, squared average number of cigarettes, number of years smoked (time dependent), number of years since quitting (time dependent), and interactions between ethnicity and smoking status, average number of cigarettes, squared average number of cigarettes, and number of years smoked. The models were further adjusted for age at cohort entry, body mass index, alcohol consumption, education, physical activity, preexisting illness, single supplement use, vegetable intake, fruit intake, energy from fat, family history of corresponding cancer, hormone replacement therapy use, and menopausal status (for women only).

cancer (28). Two Swedish cohorts examined multivitamin use related to risk of cancer incidence and overall mortality. No association was observed with mortality among men (29), while an increased risk for breast cancer incidence was found among women (30). In the Vitamin and Lifestyle Study, multivitamin use was not related to total and cancer mortality but was associated with a decreased risk of cardiovascular disease mortality (31). No association was found for lung cancer incidence (32).

We observed an increased risk of mortality from all causes other than cardiovascular diseases and cancer among men who were frequent users (twice or more per day) or short-term users (<5 years). Causes of death other than cardiovascular diseases and cancer included respiratory, endocrine, nutritional, and metabolic diseases. To investigate the possibility that men who had early symptoms of these diseases might begin using multivitamins frequently, we repeated the analyses after excluding deaths from these causes during the first 3 years of follow-up. However, the results were similar. Because there was no increase in risk among women, the finding among men might simply be due to chance.

Two large clinical trials found that the use of high-dose β-carotene (20–30 mg/day) increased lung cancer risk among smokers (33, 34). The Cancer Prevention Study II also reported an increased risk of mortality from cancer among male multivitamin users who currently smoked at cohort entry (17). However, the authors speculated that β-carotene did not explain the findings because this nutrient was not a common component of multivitamins during the time of the study. In the current study, we found no increase in risk of cancer mortality among current smokers who took multivitamins, perhaps reflecting low levels of carotenoids in multivitamin formulations. In a survey of national brand multivitamins in the United States (24 brands and 47 products) in 2008, the majority (70%) contained β-carotene, but the median dosage was only 0.3 mg daily, which was substantially lower than those used in the clinical trials (35).

Although our study has numerous strengths, including a prospective design, a large number of subjects, and a capability to control for several confounding factors for mortality, there are also several limitations to consider. Multivitamin users are generally more health conscious than are nonusers (1, 36), which could confound the relation of multivitamin use with morbidity or mortality. Although we adjusted for well-known potential confounders including health-related behaviors such as smoking status, alcohol consumption, and physical activity (37), there may still be uncontrolled bias. In particular, we were unable to adjust for changes in potential confounders over time. The longest duration category for multivitamin use in our baseline questionnaire was 5 years and longer, although the effects of multivitamins on longevity and disease might take a longer period. When we examined longer-term use by combining data from both the baseline and the follow-up surveys, administered about 5 years apart, we did not find that long-term use (approximately $\geq$10 years) of multivitamins was related to mortality. However, the average follow-up period after the second questionnaire was relatively short (5.8 years). Furthermore, there are many multivitamin products available in the marketplace, and their composition can vary widely (38). Because we did not have information on specific types or brands of supplements for this analysis, misclassification of supplements is possible. However, our questionnaire appears to fairly accurately capture data on multivitamin use in comparison with three 24-hour recalls (13). We are currently collecting information on the types of multivitamins (e.g., one-a-day, stress-tab, or antioxidant types) from cohort participants and thus will be able to examine the multivitamin-disease/mortality relation in terms of specific types of supplements, as well as a longer duration of use, in the future.

In conclusion, in the current study, there was no clear decrease or increase in mortality from all causes, cardiovascular diseases, or cancer among multivitamin supplement users. Moreover, the risk of morbidity from overall or major cancers did not differ between multivitamin users and nonusers.

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