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Multivitamin Use and Overall and Site-Specific Cancer Risks in the National Institutes of Health–AARP Diet and Health Study

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ABSTRACT

Background: Multivitamins are among the most commonly used supplements in the United States, but their effectiveness in preventing cancer remains unclear.

Objectives: We prospectively examined the association between multivitamin use and risks of overall and site-specific cancer in a large, well-characterized cohort to ascertain potential preventive or harmful relationships.

Methods: We examined 489,640 participants ages 50–71 in the NIH–American Association of Retired Persons (AARP) Diet and Health Study who were enrolled from 1995 to 1998. We linked to 11 state cancer registries in order to identify incident cancers. Multivitamin use was assessed by a baseline questionnaire. Cox proportional hazards regression models of multivitamin use were used to estimate HRs and 95% CIs for cancer risks in men and women, adjusted for potential confounders, including age, BMI, smoking, physical activity, the Healthy Eating Index 2015 score, and use of single-vitamin/-mineral supplements.

Results: A slightly higher overall cancer risk was observed in men (but not women) who consumed 1 or more multivitamins daily compared to nonusers [HRs, 1.02 (95% CI: 1.01–1.04) and 1.03 (95% CI: 1.00–1.07), respectively; *P*-trend = 0.002]. The latter reflected higher risks for prostate cancer (HR, 1.04; 95% CI: 0.98–1.10; *P*-trend = 0.005), lung cancer (HR, 1.07; 95% CI: 0.96–1.20; *P*-trend = 0.003), and leukemia (HR, 1.26; 95% CI: 1.02–1.57; *P*-trend = 0.003). Taking more than 1 multivitamin daily was also strongly positively associated with the risk of oropharyngeal cancer in women (HR, 1.53, 95% CI: 1.04–2.24; *P*-trend < 0.0001). By contrast, daily multivitamin use was inversely associated with the colon cancer risk in both sexes (HR, 0.82; 95% CI: 0.73–0.93; *P*-trend = 0.0003).

Conclusions: We found little evidence to support a cancer-preventive role for multivitamin use, with the exception of colon cancer, in both sexes in the NIH-AARP Diet and Health Study. In addition, slightly higher risks of overall, prostate, and lung cancer, as well as leukemia, were observed for greater multivitamin use in men, with a higher oropharyngeal cancer risk in women. *J Nutr* 2022;152:211–216.

Keywords: multivitamins, supplements, cancer risk, prospective cohort, AARP Study

Introduction

Half of all American adults use dietary supplements, which are taken in the belief that supplements improve overall health, although current evidence is inconsistent (1–4). Multivitamins are the most commonly used supplements in the United States (3). The substantial impact of cancer on health status and mortality in the United States has been well described (5, 6). However, the potential role and effectiveness of multivitamins in preventing cancer is unclear. An analysis of multivitamin use and risks of 4 major malignancies (i.e., lung, colorectum, prostate, and breast) in the Multi-Ethnic Cohort found no evidence of beneficial associations, including for the overall cancer risk (7). Similarly, a study in the Women's Health Initiative clinical trials and observational study cohorts showed no associations between multivitamin supplementation and risks of several cancers in postmenopausal women, including breast, colorectal, lung, endometrial, ovarian, and other cancers (8). These studies did not have data related to specific multivitamin types or cancer risks for the entire spectrum of malignancies, however.

In this study, we investigated the association between multivitamin use and risks of overall and site-specific cancer

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Abbreviations used: AARP, American Association of Retired Persons; HEI, Healthy Eating Index; PHS-2, Physicians' Health Study II; SEER, Surveillance Epidemiology and End Results.

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in an analytic cohort of 489,640 participants enrolled in the NIH–American Association of Retired Persons (AARP) Diet and Health Study. Whether the associations differed by multivitamin type (i.e., once daily, therapeutic, or stress tablets) was also evaluated, and the large size of the cohort permitted examination of associations for less common and rare cancers in both women and men.

Methods

Study population

The NIH-AARP Diet and Health study has been previously described (9). In brief, between 1995 and 1996, a self-administered questionnaire was mailed to 3.5 million AARP members, ages 50–71 years, who resided in 6 US states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) and 2 metropolitan areas (Atlanta, Georgia, or Detroit, Michigan). The completed questionnaire was returned by 617,119 participants. After excluding participants who did not satisfactorily complete the baseline questionnaire, 566,398 participants constituted the baseline cohort. An analytical cohort of 291,782 men and 197,822 women (total 489,604) was derived after excluding persons with the following: questionnaires completed by proxy ($n = 15{,}760$); previous diagnoses of cancer, except nonmelanoma skin cancer ($n = 51{,}334$); self-reported end-stage kidney disease ($n = 997$); only a death record for a cancer diagnosis ($n = 4254$); caloric intake of more than 2 IQRs from the median ($n = 4372$); or 0 years of follow-up ($n = 77$; **Supplemental Figure 1**). The study was approved by the National Cancer Institute Special Studies Institutional Review Board.

Multivitamin use and risk factor data

The baseline questionnaire queried about demographic characteristics, dietary intake, health-related behaviors, and medical history. In the baseline questionnaire, participants who reported taking any vitamin or mineral supplement at least once per month in the past year were asked about how frequently they used any of 3 multivitamin types—1-a-day, therapeutic or theragran, or stress-tab multivitamins—during the preceding 12 months. For each formulation type, they were asked to report the frequency of use as never, less than once weekly, 1 to 3 times per week, 4 to 6 times per week, or daily. Frequency categories for each of the 3 multivitamin types were assigned a single numerical value as follows: never was assigned 0, less than 1 time per week was assigned 0.5, 1 to 3 times per week was assigned 2, 4 to 6 times per week was assigned 5, and daily was assigned 7. Total multivitamin use was defined as the sum of the values obtained for each specific type and was categorized as never, <3 times per week, 3–6 times per week, 7 times per week, and more than once daily (10). To determine overall diet quality, as well as the quality of a range of dietary components, the Healthy Eating Index (HEI) 2015 score of 13 components that reflect the Dietary Guidelines for Americans was calculated (11).

Identification of cancer cases

The follow-up time for each participant was calculated from the date of study entry in 1995 to 1996 until the date of cancer diagnosis, death, moving out of the registry areas, or the end of follow-up (31 December 2011), whichever occurred first. Cancers were identified by the Surveillance Epidemiology and End Results (SEER) incidence site recode and the International Classification of Diseases for Oncology code (3rd ed.) as occurring in the oral cavity and pharynx (C000-C009, C019-C069, C079-C119, C129-C140, C142, and C148), esophagus (C150-C159), stomach (C160-C169), colon (C180-C189, C260), rectum (C199 and C209), liver (C220 and C221), pancreas (C250-C259), lung (C340-C349), prostate (C619), bladder (C670-C679), kidney (C649 and C659), thyroid (C739), brain (C710-C719), breast (C500-C509), ovary (C569), and endometrium (C540-C549, and C559). Non-Hodgkin lymphoma, myeloma, and leukemia were also included as defined by SEER, with the mid-level SEER cancer site groups of 35, 36, and 37–39, respectively (12).

Statistical analysis

Multivariable Cox proportional hazards models that used age as the time metric were used to estimate sex-specific HRs and 95% CIs for the cancer risk for each category of multivitamin use frequency, compared with those who never used multivitamins. The main manuscript tables reflect the total multivitamin use summed across the 3 types, whereas the supplementary tables pertain to each of the 3 specific multivitamin types as queried in the original NIH-AARP questionnaire. To investigate the potential influence of latent disease on the associations, we also conducted analyses that excluded the first 5 years of follow-up. Linear trend tests were based on ordered categorical variables in the model. All analyses were conducted by sex. The final multivariable models included age (continuous), BMI (<25, 25–30, or >30 kg/m^2), education (<8 years, 8–11 years, 12 years or completed high school, more than high school, some college, or college and postgraduate), self-reported health (excellent, very good, good, fair, or poor), physical activity (never, rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, or 5 or more times per week), marital status (married or living as married, widowed, divorced, separated, or never married), smoking status (never, former with ≤20 cigarettes/day, former with >20 cigarettes/day, current with ≤20 cigarettes/day, or current with >20 cigarettes/day), race (non-Hispanic White, non-Hispanic Black, Hispanic, or Asian, Pacific Islander, or American Indian/Alaskan Native), alcohol use (yes/no), history of diabetes (yes/no), calcium supplement use (yes/no), and HEI-2015 score (continuous). An additional adjustment for use of other single-vitamin and -mineral supplements (i.e., folic acid; vitamins A, C, and E; selenium; and zinc) was conducted to see whether there was a difference in results. Secondary exploratory subgroup analyses of those above or equal to/below the median values of age (62.7 years), BMI (26.6 kg/m^2), and follow-up time (15.5 years) were conducted for all cancers combined, as well as for specific sites showing primary associations (i.e., colon cancer in both sexes and prostate and lung cancer in men).

All the analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc). All reported *P* values are 2-sided, with 0.05 as the significance level.

Results

In our study, 219,512 participants (44.8%) reported not using any multivitamin and 5.1% ($n = 24{,}878$) used such supplements more than once daily. Of multivitamin users ($n = 270{,}128$), 212,257 (43%), 63,190 (13%), and 31,749 (6%) reported use of 1-a-day, therapeutic or theragran, or stress-tab types, respectively, and some participants reported using more than 1 kind of multivitamin. Compared with persons who reported not taking multivitamin supplements, those who did were more likely to have a higher level of education, use additional vitamin/mineral supplements, and have a higher total HEI-2015 score, and they were less likely to be obese or have a history of diabetes (**Table 1**).

Examining the associations between the frequency of multivitamin use and overall and organ site–specific cancer risks, we found a slightly higher overall cancer risk in men who consumed 1 or more multivitamin daily compared to nonusers [HRs, 1.02 (95% CI: 1.01–1.04) and 1.03 (95% CI: 1.00–1.07), respectively; *P*-trend = 0.002]. This was not the case in women, however [HRs, 1.00 (95% CI: 0.98–1.03) and 0.98 (95% CI: 0.94–1.03), respectively; *P*-trend = 0.5; **Table 2**]. There was no material difference in the multivitamin-cancer association overall across subgroups with high and low ages (medians), BMIs, or follow-up times, and excluding the first 5 years of follow-up yielded similar results (data not shown). Greater multivitamin use in men showed stronger positive associations with prostate and lung cancers [more than 1 daily, HRs, 1.07 (*P*-trend = 0.003) and 1.04 (*P*-trend = 0.005),

TABLE 1 Distribution and characteristics of study participants according to frequency of multivitamin use in the National Institutes of Health–AARP Diet and Health Study

	Frequency of multivitamin use, number of times per week				
Characteristic	Never	<3	3–6	7[1]	>7[2]
Participants, *n*	219,512	33,621	25,638	185,955	24,878
Male, %	64.2	54.2	55.8	56.3	55.0
Age at entry, mean (SD), years	62.1 (5.4)	61.1 (5.4)	61.1 (5.4)	62.3 (5.3)	61.7 (5.4)
BMI 25 to <30 kg/m^2, %	42.4	40.9	41.6	40.8	41.0
Current smoker, %	12.6	13.8	12.1	10.8	10.8
Current use of alcohol, %	74.5	78.4	79.9	75.8	76.0
Non-Hispanic White, %	90.8	88.6	90.2	92.5	90.3
Vigorous physical activity ≥5 times/week,[3] %	18.1	13.7	15.4	21.7	21.9
Educational level of college or postgraduate, %	36.3	40.6	42.3	40.0	42.2
Self-reported health condition of excellent, very good, or good, %	85.6	87.0	88.8	87.4	86.1
Marital status of married or living as married, %	71.5	65.8	66.4	66.7	63.0
Multivitamin type[4]					
One-a-day, %	0	77.2	79.4	77.4	88.9
Therapeutic or Theragran, %	0	18.3	19.8	17.8	75.8
Stress-tab, %	0	11.8	11.6	5.2	61.2
Single supplement use[5]					
Vitamin E, %	21.0	45.3	50.9	52.6	76.6
Vitamin A, %	6.2	18.5	19.5	17.2	40.6
β-carotene, %	7.9	18.9	21.9	21.1	2.3
Vitamin C, %	22.1	54.0	56.9	55.8	79.4
Calcium, %	18.2	45.8	48.1	46.7	64.6
Zinc, %	6.6	14.9	18.1	17.9	35.9
Iron, %	4.2	14.2	14.5	13.9	26.7
Selenium, %	3.8	6.5	9.3	10.5	23.4
Folic acid, %	4.4	8.7	10.6	11.6	24.9
History of diabetes, %	10.1	6.9	6.0	8.5	8.3
Family history of any cancer, yes,[6] %	48.1	49.0	48.5	49.2	48.3
Energy intake, mean (SD), kcal/day	1,849 (825.0)	1,822 (810.0)	1,812 (777.6)	1,815 (777.7)	1,898 (853.6)
Total HEI-2015 score, mean (SD)	66.5 (9.8)	67.1 (9.4)	68.2 (9.1)	68.9 (9.3)	69.0 (9.1)

Abbreviations: AARP, American Association of Retired Persons; HEI, Healthy Eating Index.
[1] One per day.
[2] More than 1 per day.
[3] Physical activity was defined as at least 20 minutes of activity that caused an increase in breathing or heart rate or working up a sweat.
[4] Some participants reported using more than 1 type.
[5] Use was defined as taking a single supplement at least once per month over the last 12 months.
[6] Participants reported any first-degree relatives ever diagnosed with cancer.

respectively], as well as an increased risk of leukemia (HR, 1.26; *P*-trend = 0.003; Table 3). By contrast, more frequent multivitamin use appeared inversely associated with the risk of colon cancer in both men and women (Tables 2 and 3). Among participants taking more than 1 multivitamin daily compared with those who never used multivitamins, we observed HRs of 0.82 (95% CI: 0.70–0.96) in men and 0.81 (95% CI: 0.67–0.98) in women (both sexes combined, HR, 0.82; 95% CI: 0.73–0.93; *P*-trend = 0.0003). In women, use of at least 1 multivitamin daily was associated with an approximately 50% increased risk of oropharyngeal cancer (*P*-trend < 0.0001; Table 2). Adjustment for use of other single-vitamin and -mineral supplements (i.e., folic acid; vitamins A, C, and E; selenium; and zinc) did not alter any of the above findings. Excluding the first 5 years of follow-up for the site-specific cancers also did not change the results (data not shown). After adjusting for multiple cancer site comparisons by applying the false discovery rate threshold of 0.1, all cancers, lung cancer, leukemia, prostate cancer, and colon cancer remained significant in men. In women, the results of oropharyngeal cancer and colon cancer remained significant. Restricting our analysis to nonsmokers indicated the association with oropharyngeal cancer in women was significant (*P*-trend = 0.006) but the associations for other sites were attenuated, in part based on the smaller sample size.

Results for use of the 3 specific multivitamin types were generally consistent with the findings for overall multivitamin use, albeit with variations by supplement type and some weaker associations that were not statistically significant (**Supplemental Tables 1** and **2**). For example, daily use of the 1-a-day and therapeutic vitamin types in men appeared to be associated with increased risks of overall, lung, and prostate cancer and with a lower risk of colon cancer (Supplemental Table 1). In women, daily use of 1-a-day multivitamins was associated with increased pancreatic and bladder cancer risks, daily use of therapeutic vitamins was associated with a lower risk of colon cancer and an elevated risk of oropharyngeal cancer, and daily use of stress-tab multivitamins was associated with a decreased risk of leukemia (Supplemental Table 2).

Discussion

In this study, we observed slightly higher overall cancer risks in men (but not women) with higher frequencies of multivitamin use. The association in men was primarily due to the increased

TABLE 2 HRs and 95% CIs for total and site-specific cancers according to the frequency of multivitamin use in men[1]

Cancer site	Frequency of multivitamin use, number of times per week					*P*-trend
	Never	<3	3–6	7[2]	>7[3]	
Participants, *n*	140,928	18,220	14,313	104,644	13,677	
All cancers, *n* = 79,759	1.00 (ref.)	0.97 (0.94–1.00)	0.99 (0.95–1.02)	1.02 (1.01–1.04)	1.03 (1.00–1.07)	0.002
Oropharynx, *n* = 1400	1.00 (ref.)	0.95 (0.76–1.20)	0.80 (0.60–1.06)	1.07 (0.95–1.21)	1.13 (0.88–1.45)	0.21
Esophagus, *n* = 1012	1.00 (ref.)	0.74 (0.55–0.99)	0.67 (0.47–0.95)	0.95 (0.82–1.10)	0.81 (0.59–1.12)	0.37
Stomach, *n* = 1041	1.00 (ref.)	0.86 (0.65–1.14)	1.13 (0.85–1.51)	1.01 (0.87–1.16)	0.78 (0.55–1.09)	0.79
Colon, *n* = 4953	1.00 (ref.)	0.90 (0.79–1.02)	0.92 (0.79–1.05)	0.93 (0.87–1.00)	0.82 (0.70–0.96)	0.009
Rectum, *n* = 1852	1.00 (ref.)	1.28 (1.06–1.53)	1.05 (0.84–1.31)	0.88 (0.79–0.98)	1.06 (0.85–1.33)	0.04
Liver, *n* = 743	1.00 (ref.)	1.06 (0.78–1.45)	1.02 (0.70–1.47)	1.12 (0.95–1.33)	0.94 (0.64–1.38)	0.34
Pancreas, *n* = 1725	1.00 (ref.)	0.86 (0.69–1.06)	0.85 (0.66–1.09)	0.96 (0.86–1.07)	1.16 (0.93–1.45)	0.999
Lung, *n* = 8771	1.00 (ref.)	1.02 (0.93–1.12)	0.99 (0.89–1.10)	1.08 (1.03–1.13)	1.07 (0.96–1.20)	0.003
Prostate, *n* = 31,784	1.00 (ref.)	0.96 (0.92–1.01)	1.05 (1.00–1.11)	1.03 (1.01–1.06)	1.04 (0.98–1.10)	0.005
Bladder, *n* = 5531	1.00 (ref.)	0.96 (0.85–1.08)	1.00 (0.87–1.14)	1.01 (0.95–1.08)	1.02 (0.89–1.17)	0.59
Kidney, *n* = 2251	1.00 (ref.)	0.85 (0.71–1.03)	0.81 (0.65–1.00)	0.92 (0.83–1.02)	0.91 (0.73–1.13)	0.10
Thyroid, *n* = 393	1.00 (ref.)	0.86 (0.54–1.38)	0.82 (0.48–1.39)	1.07 (0.85–1.36)	1.16 (0.72–1.87)	0.45
Brain, *n* = 741	1.00 (ref.)	1.23 (0.91–1.66)	0.92 (0.63–1.33)	1.09 (0.91–1.29)	1.12 (0.78–1.60)	0.41
Non-Hodgkin lymphoma, *n* = 2819	1.00 (ref.)	0.95 (0.81–1.12)	0.95 (0.79–1.14)	0.93 (0.85–1.02)	1.00 (0.83–1.20)	0.20
Leukemia, *n* = 1892	1.00 (ref.)	1.15 (0.94–1.40)	1.12 (0.90–1.39)	1.16 (1.04–1.29)	1.26 (1.02–1.57)	0.003
Multiple myeloma, *n* = 949	1.00 (ref.)	1.22 (0.95–1.57)	0.78 (0.55–1.10)	0.96 (0.82–1.11)	0.81 (0.57–1.16)	0.23

[1]HRs and 95% CIs were calculated using Cox regression models adjusted for the following factors: age, BMI, education, self-reported health, physical activity, marital status, smoking status, race, alcohol use, diabetes, calcium supplement use, and Healthy Eating Index–2015 score.
[2]One per day.
[3]More than 1 multivitamin daily.

risks of prostate and lung cancer, as well as leukemia. By contrast, taking more than 1 multivitamin daily was related to a lower risk of colon cancer in both sexes.

Findings from prospective studies, including controlled trials that have examined multivitamin use in relation to cancer risks, are limited. In the Physicians' Health Study II (PHS-2), a large prevention trial of male physicians, those randomly assigned to the daily multivitamin arm had a statistically significant reduction in the cancer incidence compared with those assigned a placebo (HR, 0.92; $P = 0.04$) (13). The present cohort study found slightly increased cancer risks in men who took multivitamins at least once daily, although it differs from the

TABLE 3 HRs and 95% CIs for total and site-specific cancers according to the frequency of multivitamin use in women[1]

Cancer site	Frequency of multivitamin use, number of times per week					*P*-trend
	Never	<3	3–6	7[2]	>7[3]	
Participants, *n*	78,584	15,401	11,325	81,311	11,201	
All cancers, *n* = 38,335	1.00 (ref.)	0.91 (0.88–0.95)	0.95 (0.91–1.00)	1.00 (0.98–1.03)	0.98 (0.94–1.03)	0.55
Oropharynx, *n* = 495	1.00 (ref.)	0.68 (0.43–1.06)	1.35 (0.91–2.01)	1.46 (1.18–1.81)	1.53 (1.04–2.24)	<0.0001
Esophagus, *n* = 152	1.00 (ref.)	0.63 (0.28–1.39)	0.99 (0.47–2.10)	1.12 (0.77–1.63)	1.00 (0.47–2.13)	0.49
Stomach, *n* = 308	1.00 (ref.)	0.56 (0.32–0.97)	0.92 (0.55–1.57)	0.89 (0.68–1.15)	0.93 (0.55–1.56)	0.57
Colon, *n* = 2701	1.00 (ref.)	0.99 (0.85–1.15)	0.94 (0.79–1.12)	0.91 (0.83–1.00)	0.81 (0.67–0.98)	0.0098
Rectum, *n* = 844	1.00 (ref.)	1.21 (0.94–1.56)	0.94 (0.68–1.31)	1.02 (0.86–1.19)	0.92 (0.65–1.30)	0.80
Liver, *n* = 220	1.00 (ref.)	0.69 (0.37–1.30)	0.76 (0.36–1.57)	1.02 (0.74–1.39)	1.15 (0.62–2.13)	0.71
Pancreas, *n* = 1016	1.00 (ref.)	0.96 (0.75–1.24)	0.83 (0.61–1.13)	1.02 (0.88–1.18)	1.04 (0.78–1.38)	0.78
Lung, *n* = 5487	1.00 (ref.)	0.93 (0.83–1.04)	0.92 (0.81–1.05)	1.05 (0.98–1.12)	1.02 (0.90–1.16)	0.13
Breast, *n* = 13,180	1.00 (ref.)	0.86 (0.80–0.93)	0.96 (0.89–1.04)	0.99 (0.95–1.03)	0.99 (0.91–1.07)	0.86
Ovary, *n* = 1153	1.00 (ref.)	1.03 (0.81–1.30)	0.81 (0.60–1.09)	1.09 (0.95–1.26)	1.01 (0.77–1.33)	0.30
Endometrium, *n* = 2253	1.00 (ref.)	0.91 (0.77–1.09)	1.12 (0.93–1.34)	1.01 (0.92–1.12)	1.01 (0.83–1.22)	0.63
Bladder, *n* = 1025	1.00 (ref.)	1.15 (0.91–1.47)	0.89 (0.65–1.21)	1.11 (0.96–1.28)	0.93 (0.68–1.26)	0.46
Kidney, *n* = 833	1.00 (ref.)	1.12 (0.86–1.46)	1.18 (0.87–1.59)	0.97 (0.82–1.14)	1.12 (0.81–1.53)	0.86
Thyroid, *n* = 510	1.00 (ref.)	0.92 (0.64–1.32)	0.97 (0.64–1.45)	1.09 (0.88–1.34)	0.76 (0.48–1.21)	0.77
Brain, *n* = 336	1.00 (ref.)	1.01 (0.65–1.59)	1.44 (0.92–2.23)	1.12 (0.86–1.45)	1.21 (0.75–1.98)	0.30
Non-Hodgkin lymphoma, *n* = 1508	1.00 (ref.)	0.91 (0.74–1.13)	0.88 (0.69–1.12)	0.93 (0.83–1.05)	1.06 (0.84–1.33)	0.51
Leukemia, *n* = 710	1.00 (ref.)	0.76 (0.55–1.05)	0.75 (0.52–1.08)	0.94 (0.79–1.12)	0.65 (0.44–0.96)	0.24
Multiple myeloma, *n* = 438	1.00 (ref.)	0.94 (0.65–1.38)	0.98 (0.64–1.50)	0.94 (0.75–1.17)	1.16 (0.77–1.74)	0.89

[1]HRs and 95% CIs were calculated using Cox regression models adjusted for the following factors: age, BMI, education, self-reported health, physical activity, marital status, smoking status, race, alcohol use, diabetes, calcium supplement use, and Healthy Eating Index–2015 score.
[2]One per day.
[3]More than 1 per day.

PHS-2 by having an observational design, having information regarding several multivitamin types and a range of frequency of use (including more than once daily), and having prostate cancers comprising 40% of all confirmed malignancies (as opposed to 51.4% in the PHS-2). (Excluding prostate from our overall cancer analysis in men did attenuate the positive association slightly.) A meta-analysis showed no convincing evidence that supplemental multivitamin use was related to the occurrence or severity of prostate cancer (14), whereas a previous analysis of the present cohort found an increased risk of advanced and fatal prostate cancers among men using multivitamins more than 7 times per week when compared with those that never used multivitamins (10). Our study having longer follow-up also indicates that more frequent multivitamin use is positively associated with the prostate cancer risk, consistent with a previous study that showed multivitamin use for at least 10 years was associated with an increased risk of prostate cancer compared with little or no use (OR, 1.3; 95% CI: 1.0–1.6) (15).

We found little evidence to support a cancer-preventive role for multivitamin use in organ site–specific cancers, with the exception of colon cancer in both sexes. The Nurses' Health Study, Health Professionals Follow-Up Study, and Women's Health Study showed weak associations for multivitamin use and site-specific cancers, including modest inverse associations for colon and breast cancer (16, 17). A beneficial role for multivitamins in colon cancer risk was also reported in a meta-analysis of observational studies, and a pooled analysis of prospective studies found that ever-using multivitamin supplements was associated with a 12% lower risk of colon cancer compared with never-using them (RR, 0.88; 95% CI: 0.81–0.96) (18). Multivitamins contain several specific vitamins and minerals that have biologically plausible roles for colon cancer risk reduction (19–21), including calcium, folic acid, vitamin C, vitamin E (α-tocopherol), and vitamin D, which have been examined in relation to the development of colon cancer (18, 22–25). For example, calcium is a key mineral in multivitamin-multimineral supplements that impacts many cellular functions, including direct growth–inhibiting and differentiation-apoptosis-inducing action on normal and tumor colorectal cells (22). Suppression of hyperproliferative activity by supplemental folic acid has been observed in animal experiments relevant to colorectal neoplasia (24). It is possible that the vitamin C and E in multivitamins act synergistically to reduce the colon cancer risk. Using iron as an electron donor, vitamin C (ascorbic acid) reduces reactive oxygen radicals and vitamin E (tocopherols and tocotrienols) interferes with free radical chain reactions by transferring chroman phenolic hydrogen to free radicals. For example, less reactive α-tocopheroxy radicals can in turn regain electrons from ascorbate to regenerate α-tocopherol (26). Antiproliferative, anti-inflammatory, and prodifferentiation effects of vitamin D have also been reported from experimental data (27), which are supported by a recent, large, pooled cohort analysis of serum 25-hydroxyvitamin D concentrations and risks of colorectal cancer (25).

We investigated the 3 major classes of multivitamins in our study and used the Dietary Supplement Label Database (28) to examine their formulations, which varied across the myriad retail products. In general, stress-tab and therapeutic types contained higher dosages of single vitamins, including vitamins E and C and each of the B vitamins, compared to 1-a-day types, and the therapeutic types contained more diverse combinations of vitamins and minerals compared to the other 2. Nevertheless, results for use of the 3 specific multivitamin types were generally consistent.

Our investigation has some limitations. First, we did not have information on the duration of supplement use, which might be a factor influencing the multivitamin–cancer risk associations. Second, although we adjusted for the HEI-2015 score in order to control for nutritional intake in all analyses, we could not rule out the possibility that other dietary nutrients also contributed to the observed association. In addition, we were not able determine whether supplement users were more likely to seek medical care or to have cancer screening tests during this study, as that information was not queried. Third, the self-reported multivitamin use information was subject to measurement error. Fourth, most of the study participants were of European ancestry and of higher socioeconomic status than the general US population, which impacts the generalizability of our findings. Important strengths of our study include its prospective design and that its large sample size and long follow-up provided substantial statistical power to test the multivitamin associations with not only overall cancer but a wide range of cancer sites in men and women. We had data for and were able to examine 3 specific classes of multivitamins. The long follow-up also permitted sensitivity analyses that excluded early cancers (i.e., within 5 years of the baseline questionnaire) and reduced the likelihood of reverse causality.

In conclusion, we found little evidence to support a beneficial role for multivitamin use in lowering cancer risks, with the exception of colon cancer in both sexes. In addition, slightly higher risks of overall, prostate, and lung cancer, as well as leukemia, were observed for greater multivitamin use in men, with a higher oropharyngeal cancer risk associated with greater use in women. Similar large, prospective studies of the associations for overall and site-specific cancers will be informative, along with further investigation of whether our colon cancer finding was derived from the combination of the vitamins and minerals in the multivitamins or from specific constituents of those supplements (e.g., calcium or vitamin E).

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Data Availability

The data sets analyzed for this study were obtained from the National Cancer Institute. Researchers can request access to the data from the NIH-AARP Diet and Health Study online at https://dietandhealth.cancer.gov/.

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