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Research Article

Vitamin, Mineral, and Specialty Supplements and Risk of Hematologic Malignancies in the Prospective VITamins And Lifestyle (VITAL) Study

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Abstract

Background: Increasing evidence suggests that nutrients from fruits and vegetables have chemoprotective effects on various cancers including hematologic malignancies, but the effects of nutritional supplements are poorly examined.

Methods: Herein, we prospectively evaluated the association of vitamin, mineral, and specialty supplements with incident hematologic malignancies in 66,227 men and women aged 50 to 76 years from Washington State recruited from year 2000 to 2002 to the VITamins And Lifestyle (VITAL) cohort study. Hematologic malignancies cases (n = 588) were identified through December 2008 by linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry. HRs and 95% CIs associated with supplement use were estimated with Cox proportional hazards models.

Results: After adjustment, high use of garlic supplements [≥4 days per week for ≥3 years; HR = 0.55 (95% CI = 0.34–0.87); P_{trend} = 0.028] and ever use of grape seed supplements [HR = 0.57 (95% CI = 0.37–0.88)] were inversely associated with hematologic malignancies in our models. In addition, high use (8–10 pill-years) of multivitamins was suggestive of an inverse association [HR = 0.80 (95% CI = 0.64–1.01)]. In contrast, no associations were observed for the remaining supplements.

Conclusions: These data indicate that the use of garlic and grape seed may be associated with reduced risk of hematologic malignancies.

Impact: This is the first cohort study to suggest a possible role of these supplements in the chemoprevention of hematologic malignancies. *Cancer Epidemiol Biomarkers Prev; 20(10); 2298–308. ©2011 AACR.*

Introduction

The intake of dietary supplements has significantly increased over the last 3 decades in the United States, with nearly one-half of older adults currently estimated to use at least 1 dietary supplement on a regular basis (1, 2). Although randomized clinical trials on the safety and efficacy are generally lacking (3), dietary supplements are viewed by the general public as beneficial for a number of specific medical conditions, general well-being, and longevity (4).

Numerous epidemiologic and animal studies have suggested that fruits and vegetables might protect against various cancers, including non–Hodgkin lymphoma (NHL; refs. 5–9). On the other hand, studies of dietary intake of specific nutrients and hematologic malignancies have been less consistent (5), and only few studies have explicitly examined the preventive effect of nutrients from supplements on blood cancers (9–14). A recent report from the Iowa Women's Health Study found no associations for multivitamin use [relative risk (RR) = 1.07 (95% CI = 0.87–1.31)] or supplemental intake of vitamin C or E, although information on duration of use was not available for that cohort (9). On the other hand, multivitamin use was associated with a higher risk of NHL among women in the Nurses' Health Study [RR = 1.48 (95% CI = 1.01–2.16)] but not among men in the Health Professionals Follow-up Study [RR = 0.85 (95% CI = 0.45–1.58); ref. 10]; in both cohorts, supplements of vitamins A, C, and E were not independently associated with risk of NHL (10). In comparison, use of multivitamins for 9 years or more was associated with a reduced risk of NHL in men [OR = 0.5 (95% CI = 0.3–0.9)] but not in women in a population-based case–control study from eastern Nebraska (11). In the Alpha-Tocopherol Beta-Carotene Cancer Prevention study cohort, dietary or supplemental vitamin B_{12} was inversely associated with NHL [HR = 0.61 (95% CI = 0.37–1.00)] but not incident multiple myeloma, whereas no associations were found for folate, vitamin B_2, or vitamin

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B_6 (12). Intake of vitamin B_6, however, was associated with reduced risk of NHL in a population-based case–control study from 4 Surveillance, Epidemiology, and End Results (SEER) cancer registry centers [OR = 0.57 (95% CI = 0.34–0.95) for highest vs. lowest quartile; ref. 13]. Finally, in another case–control study conducted in 4 SEER cancer registries, vitamin D intake from diet and supplements was not associated with risk of NHL [RR = 1.10 (95% CI = 0.72–1.67) for highest quartile of vitamin D intake; ref. 14].

The VITamin And Lifestyle (VITAL) cohort study was implemented to assess whether dietary supplement use was related to cancer risk (15). Herein, we describe results from our examination of vitamin, mineral, and nonvitamin, nonmineral "specialty" supplement use and incident hematologic malignancies in the VITAL cohort.

Design and Methods

Study cohort

For study recruitment, questionnaires were mailed to 364,418 men and women aged 50 to 76 years who lived in the 13-county area in western Washington State covered by the SEER cancer registry (15). Between October 2000 and December 2002, a total of 79,300 questionnaires were returned, of which 77,719 were deemed eligible. To avoid treatment of an earlier cancer as a cause of blood cancer, we excluded 11,487 participants with prior ($n = 11,273$) or missing ($n = 214$) history of any cancer other than nonmelanoma skin cancer at baseline. For the same reason, participants were censored at the time of diagnosis of a nonhematologic cancer after baseline (i.e., at the point they met an exclusion criterion). We additionally excluded 5 cases with post–baseline blood cancer on death certificate only without a diagnosis date, leaving 66,227 men and women available for study. The VITAL study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Data collection

Participants completed a 24-page self-administered, sex-specific questionnaire on supplement and medication use, health history and risk factors, and diet. For each vitamin, mineral, and specialty supplement taken at least once a week for 1 year, we ascertained intake from single supplements and multivitamins, including the duration in years and frequency of use in days per week during the 10-year period prior to baseline. For individual vitamin and mineral supplements, we also ascertained the average dose taken per day. The nutrient content of the multivitamin each participant used was ascertained by brand name for common multivitamins using information from the Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements 2002 (16) or from the amount of each nutrient in their multivitamin reported by the participant for less common brands.

From this information, we computed a 10-year average daily dose of each supplemental nutrient by multiplying days per week/7 × years/10 × dose per day and summing over the intake from individual nutrient supplements and multivitamins. Intake of each supplemental vitamin or mineral was then categorized into 4 groups of 10-year average daily dose: none and tertiles of use. For the less commonly used vitamins and minerals (all except multivitamins, vitamin C, vitamin E, and calcium), the cutoff point for the highest category was changed to be more than the amount of that nutrient that would be obtained from 10-year daily use of the multivitamin pill Centrum Silver (Wyeth). Because the amount of iron varies considerably in different formulations of multivitamins, and the amount that would be obtained from daily use of Centrum Silver (4.0 mg/d) is relatively low, we defined the highest category of iron supplement use as greater than the amount that would be obtained from daily use of several common multivitamin pills [18.0 mg/d; e.g., Centrum (Wyeth)]. Finally, 10-year use of most specialty supplements was categorized as "no use," "low use" (<4 days per week or <3 y), or "high use" (≥4 days per week and ≥3 y). Because of small number of users, 10-year use of ginseng and of grape seed were categorized as "never use" or "ever use." Intake of specialty supplements from multivitamin sources was included in our estimates of 10-year use of garlic, *Ginkgo biloba*, ginseng, and grape seed; intake of these supplements from multivitamins alone was classified as "low" 10-year average use, because the amounts of these supplements in multivitamins are generally much lower than those in individual supplements.

Case ascertainment

Incident cases of hematologic and other malignancies were identified through December 2008 by annual linkage to the western Washington SEER cancer registry using matching algorithms described previously (15). Cases were categorized using the 2008 WHO classification system (17).

Follow-up for censoring

The end date of follow-up was the earliest date of the following events: diagnosis of hematologic malignancy (0.9%), withdrawal from study (0.03%), emigration from the SEER region (5.3%), diagnosis of cancer other than hematologic malignancy or nonmelanoma skin cancer (9.4%), death (3.1%), or last linkage to the SEER registry (December 31, 2008; 81.3%). Moves out of the SEER region were identified via linkage to the National Change of Address file, follow-up letters, and phone calls. Deaths were ascertained via linkage to the Washington State death file.

Statistical analysis

Characteristics between cases and noncases were compared with unpaired Student's t tests and Fisher's exact tests, as appropriate. Sex- and multivariable-adjusted Cox proportional hazards models using robust standard errors (18) were used to estimate HRs and 95% CIs for the associations between supplement use and

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risk of hematologic malignancies. Age was the time metric in regression models, with participants entering at the age of completing the baseline questionnaire and exiting at their age at end of follow-up. We selected *a priori* potential confounders including known and suspected risk factors for hematologic malignancies and medical conditions that may be indications for use of supplements for adjustment in multivariable regression models. Specifically, all models were adjusted for sex, race/ethnicity (white, Hispanic, other), education (high school graduate or less, some college, college or advanced degree), smoking (pack-years), self-rated health (excellent, very good, good, fair, poor), vegetable servings per day (excluding potato servings); fruit servings per day; history of coronary artery disease (defined as history of heart attack, coronary bypass surgery, angioplasty, and/or angina; yes, no), history of rheumatoid arthritis (yes, no), history of fatigue or lack of energy over the year prior to baseline (yes, no), and number of first-degree relatives with a history of leukemia or lymphoma (none, 1, ≥2). The model for iron was additionally adjusted for anemia in the year prior to baseline. The models for glucosamine and chondroitin were additionally adjusted for history of osteoarthritis or chronic joint pain. *P* values for trend were computed by using the categorized 10-year average use variable as an ordinal variable in the model. *P* values for interaction between a supplement and gender were computed by including a multiplicative term of the ordinal variable and gender in the multivariable models. Because different morphologies may have different etiologies, we examined the associations of supplement use with hematologic malignancies stratified by tumor morphology. In these analyses, cases of the other morphologies were censored at the time of cancer diagnosis. All analyses were conducted using STATA 11 (StataCorp) and all reported *P* values are 2-sided, with a *P* value <0.05 considered statistically significant.

Results

Overall, 66,227 men and women, aged 61.5±7.4 (mean ± SD) years, met inclusion criteria for this study. After a mean follow-up of 6.5 ± 1.8 years, 588 (0.89%) developed a hematologic malignancy (Table 1). Baseline characteristics of cases and noncases (demographic information, lifestyle factors, and medical history) are summarized in Table 2. Participants who developed a hematologic malignancy were older at baseline (65.6 ± 7.1 vs. 61.5 ± 7.4 years), were more likely male, and more often had 2 or more first-degree relatives with a family history of leukemia or lymphoma. Cases also more often rated their health in the lower 3 of 5 categories, more often had a history of rheumatoid arthritis or coronary artery disease, and more likely reported anemia than noncases.

As shown in Tables 3 and 4, the use of none of the vitamin or mineral supplements in the 10 years prior to baseline was statistically significantly associated with risk of hematologic cancers. High use of multivitamins (equivalent to ≥8 years of daily use in the 10 years before baseline) was associated with a 20% statistically nonsignificantly reduced risk [HR = 0.80 [95% CI = 0.64–1.01)]. Table 5 summarizes the associations between specialty supplement use and hematologic malignancies. Ever use of grape seed supplements was associated with a reduced risk [HR = 0.57 (95% CI = 0.37–0.88)]. In addition, high 10-year use of garlic supplements was inversely associated with a reduced risk [HR = 0.55 (95% CI = 0.34–0.87); $P_{trend} = 0.028$]. There were no associations for the remaining supplements with hematologic malignancies.

To address the possibility that these supplements were used to treat symptoms of an occult hematologic malignancy, we repeated these analyses after exclusion of cases that were diagnosed within 2 years after baseline ($n = 149$). The associations between incident hematologic malignancies and supplement use were very similar to the analyses that included all cases [HR for ever use of grape seeds = 0.53 (95% CI = 0.32–0.89); HR for high use of garlic = 0.48 (95% CI = 0.27–0.86); and HR for high use of multivitamins = 0.80 (95% CI = 0.62–1.04)].

When the analysis was stratified by gender, we found that the associations between ever use of grape seed or high use of garlic or high use of multivitamins and incident hematologic malignancies were very similar for males and females [for males: HR for ever use of grape seed = 0.57 (95% CI = 0.33–0.99); HR for high use of garlic = 0.52 (95% CI = 0.28–0.95); and HR for high use

Table 1. Classification of incident hematologic malignancies

Disease	Cases *n* (%)
Myeloid neoplasms	138 (23.5)
Myelodysplastic syndromes	55 (9.4)
Acute myeloid leukemia	36 (6.1)
Myeloproliferative neoplasms[a]	47 (8.0)
Mature B-cell neoplasms	396 (67.3)
CLL/SLL	91 (15.5)
Plasma cell disorders	67 (11.4)
Other mature B-cell neoplasm entities	238 (40.5)
Hodgkin lymphoma	23 (3.9)
Mature T-cell and natural killer cell neoplasms	17 (2.9)
Others[b]	14 (2.4)
Total	588 (100)

[a]Includes the diagnostic category of myelodysplastic/myeloproliferative neoplasms.

[b]Includes cases of malignant lymphoma, not otherwise specified (NOS); leukemia, NOS; acute biphenotypic leukemia; and precursor B-cell lymphoblastic leukemia.

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Table 2. Associations between baseline characteristics and risk of hematologic malignancies

Characteristic	Cases ($n = 588$), *n* (%)	Noncases ($n = 65{,}639$), *n* (%)	Age- and sex-adjusted HR (95% CI)
Demographic factors			
Age at baseline, y, *n* (%)			N/A
<55	47 (8.0)	16,459 (25.1)	
55 to <60	111 (18.9)	15,531 (23.7)	
60 to <65	97 (16.5)	11,945 (18.2)	
65 to <70	123 (20.9)	10,339 (15.8)	
≥70	210 (35.7)	11,365 (17.3)	
Gender, *n* (%)			
Female	232 (39.5)	33,408 (50.9)	1.00 (reference)
Male	356 (60.5)	32,231 (49.1)	1.67 (1.42–1.98)
Race/ethnicity, *n* (%)			
White	544 (94.0)	60,047 (93.0)	1.00 (reference)
Hispanic	8 (1.4)	577 (0.9)	1.81 (0.90–3.65)
Other	27 (4.7)	3,916 (6.1)	0.80 (0.54–1.18)
Education, *n* (%)			
High school graduate or less	127 (21.9)	12,532 (19.4)	1.00 (reference)
Some college	200 (34.5)	24,711 (38.3)	0.96 (0.77–1.20)
College or advanced degree	252 (43.5)	27,316 (42.3)	1.08 (0.86–1.34)
Lifestyle			
Smoking status			
Never smoker, *n* (%)	259 (44.1)	31,381 (47.8)	
Pack-years,[a] mean (SD)	28.1 (24.0)	25.6 (23.2)	1.00 (0.99–1.00)
Medical history			
Self-reported health, *n* (%)			
Excellent	66 (11.5)	10,234 (15.8)	1.00 (reference)
Very good	218 (37.9)	25,507 (39.5)	1.24 (0.94–1.63)
Good	209 (36.3)	21,608 (33.4)	1.34 (1.02–1.77)
Fair	67 (11.7)	6,254 (9.7)	1.50 (1.07–2.10)
Poor	15 (2.6)	1,029 (1.6)	2.34 (1.34–4.09)
History of coronary artery disease, *n* (%)			
No	499 (84.9)	59,913 (91.3)	1.00 (reference)
Yes	89 (15.1)	5,712 (8.7)	1.25 (0.98–1.59)
History of rheumatoid arthritis, *n* (%)			
No	551 (93.7)	63,200 (96.3)	1.00 (reference)
Yes	37 (6.3)	2,425 (3.7)	1.60 (1.14–2.24)
History of fatigue/lack of energy, *n* (%)			
No	480 (81.6)	53,911 (82.2)	1.00 (reference)
Yes	108 (18.4)	11,714 (17.8)	1.16 (0.94–1.43)
History of anemia, *n* (%)			
No	565 (96.1)	64,181 (97.8)	1.00 (reference)
Yes	23 (3.9)	1,444 (2.2)	2.17 (1.42–3.30)
Family history of leukemia/lymphoma, *n* (%)			
None	533 (93.0)	61,335 (94.6)	1.00 (reference)
1 first-degree relative	34 (5.9)	3,346 (5.2)	1.15 (0.81–1.62)
≥2 first-degree relatives	6 (1.0)	147 (0.2)	4.13 (1.84–9.25)

[a]Among smokers and former smokers.

of multivitamins = 0.87 (95% CI = 0.66–1.15); for females: HR for ever use of grape seed = 0.58 (95% CI = 0.30–1.13); HR for high use of garlic = 0.59 (95% CI = 0.28–1.26); and HR for high use of multivitamins = 0.73 (95% CI = 0.50–1.07)]. All tests for interaction were not statistically significant ($P > 0.80$). The smaller number of female cases in the study likely explains the wider CIs for estimates in females.

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Table 3. Associations between 10-year supplemental vitamin intake and risk of hematologic malignancies

10-y average daily use prior to baseline[a]	Cases, *n* (%)	Noncases, *n* (%)	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
Multivitamins				
None	219 (37.2)	22,882 (34.9)	1.00 (reference)	1.00 (reference)
>0–2.5 pill-years[c]	98 (16.7)	11,407 (17.4)	1.01 (0.80–1.29)	1.03 (0.80–1.33)
>2.5–8.0 pill-years	133 (22.6)	14,804 (22.6)	0.99 (0.80–1.23)	1.01 (0.81–1.27)
>8–10 pill-years	138 (23.5)	16,538 (25.2)	0.80 (0.64–0.99)	0.80 (0.64- -1.01)
P_{trend}			0.057	0.085
Retinol				
None	206 (35.2)	21,556 (33.4)	1.00 (reference)	1.00 (reference)
19.3–510.0 μg/d	129 (22.0)	14,741 (22.8)	1.02 (0.82–1.28)	1.06 (0.84–1.33)
510.1–1,200.0 μg/d	201 (34.3)	21,931 (34.0)	0.92 (0.76–1.12)	0.93 (0.76–1.15)
1,200.1–8,790.0 μg/d[d]	50 (8.5)	6,365 (9.9)	0.79 (0.58–1.08)	0.80 (0.58–1.12)
P_{trend}			0.137	0.188
β-Carotene				
None	212 (36.3)	22,750 (35.1)	1.00 (reference)	1.00 (reference)
6.4–377.0 μg/d	111 (19.0)	13,992 (21.6)	0.93 (0.74–1.17)	0.94 (0.74–1.20)
377.1–600.0 μg/d	93 (15.9)	9,254 (14.3)	1.05 (0.82–1.34)	1.10 (0.85–1.42)
600.1–13,554.0 μg/d[d]	168 (28.8)	18,880 (29.1)	0.93 (0.76–1.14)	0.94 (0.76–1.17)
P_{trend}			0.626	0.774
Folic acid				
None	206 (35.0)	21,147 (32.4)	1.00 (reference)	1.00 (reference)
8.6–200.0 μg/d	155 (26.4)	18,526 (28.4)	0.94 (0.76–1.16)	0.94 (0.75–1.17)
200.1–400.0 μg/d	178 (30.3)	20,778 (31.9)	0.84 (0.68–1.03)	0.84 (0.68–1.04)
400.1–1,400.0 μg/d[d]	49 (8.3)	4,742 (7.3)	1.05 (0.77–1.43)	0.99 (0.71–1.38)
P_{trend}			0.340	0.278
Thiamine (vitamin B_1)				
None	210 (35.8)	21,786 (33.4)	1.00 (reference)	1.00 (reference)
0.032–0.750 mg/d	131 (22.3)	15,549 (23.9)	0.95 (0.77–1.19)	0.98 (0.78–1.24)
0.751–1.50 mg/d	141 (24.0)	16,260 (25.0)	0.86 (0.69–1.06)	0.86 (0.69–1.09)
1.51–104.65 mg/d[d]	105 (17.9)	11,571 (17.8)	0.98 (0.77–1.23)	0.97 (0.76–1.25)
P_{trend}			0.466	0.493
Niacin (vitamin B_3)				
None	205 (35.0)	21,556 (33.1)	1.00 (reference)	1.00 (reference)
0.4–10.0 mg/d	148 (25.3)	17,668 (27.1)	0.97 (0.78-1.19)	1.00 (0.80–1.25)
10.1–20.0 mg/d	184 (31.5)	20,017 (30.7)	0.93 (0.76-1.13)	0.93 (0.75–1.15)
20.1–1,024.0 mg/d[d]	48 (8.2)	5,914 (9.1)	0.82 (0.60-1.13)	0.82 (0.59–1.14)
P_{trend}			0.224	0.241
Vitamin B_6				
None	203 (34.6)	21,153 (32.5)	1.00 (reference)	1.00 (reference)
0.04–1.40 mg/d	123 (21.0)	14,871 (22.8)	0.95 (0.76-1.19)	0.99 (0.78–1.25)
1.41–3.00 mg/d	152 (25.9)	16,858 (25.9)	0.88 (0.71-1.08)	0.89 (0.71–1.11)
3.01–270.0 mg/d[d]	109 (18.6)	12,310 (18.9)	0.98 (0.78-1.24)	1.01 (0.79–1.30)
P_{trend}			0.544	0.732
Vitamin B_{12}				
None	202 (34.4)	21,134 (32.5)	1.00 (reference)	1.00 (reference)
0.1–5.0 μg/d	128 (21.8)	15,542 (23.9)	0.96 (0.77–1.20)	0.98 (0.77–1.24)
5.1–25.0 μg/d	194 (33.1)	21,511 (33.1)	0.90 (0.74–1.10)	0.92 (0.74–1.14)
25.1–300.0 μg/d[d]	63 (10.7)	6,887 (10.6)	0.96 (0.72–1.28)	0.94 (0.69–1.27)
P_{trend}			0.457	0.466

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Table 3. Associations between 10-year supplemental vitamin intake and risk of hematologic malignancies (Cont'd)

10-y average daily use prior to baseline[a]	Cases, *n* (%)	Noncases, *n* (%)	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
Vitamin C				
None	168 (28.7)	17,755 (27.3)	1.00 (reference)	1.00 (reference)
1–60.05 mg/d	136 (23.3)	16,336 (25.1)	0.90 (0.71–1.12)	0.93 (0.74–1.19)
60.06–322.05 mg/d[d]	133 (22.7)	15,383 (23.6)	0.92 (0.73–1.16)	0.95 (0.75–1.22)
322.06–1,600.0 mg/d[d]	148 (25.3)	15,654 (24.0)	0.94 (0.76–1.18)	0.96 (0.76–1.22)
P_{trend}			0.663	0.799
Vitamin D[e]				
None	200 (34.3)	21,077 (32.5)	1.00 (reference)	1.00 (reference)
0.2–5.0 μg/d	153 (26.2)	18,729 (28.8)	0.94 (0.76–1.17)	0.97 (0.78–1.22)
5.1–10.0 μg/d	196 (33.6)	20,987 (32.3)	0.94 (0.77–1.15)	0.95 (0.77–1.18)
10.1–30.0 μg/d[d]	34 (5.8)	4,149 (6.4)	0.86 (0.60–1.24)	0.86 (0.58–1.27)
P_{trend}			0.415	0.463
Vitamin E[f]				
None	162 (27.7)	17,409 (26.7)	1.00 (reference)	1.00 (reference)
1.3–42.0 mg/d	130 (22.2)	16,252 (25.0)	0.90 (0.72–1.14)	0.92 (0.72–1.18)
42.1–215.0 mg/d[d]	147 (25.1)	16,042 (24.6)	0.98 (0.78–1.23)	0.95 (0.75–1.21)
215.1–1,000.0 mg/d[d]	146 (25.0)	15,456 (23.7)	0.91 (0.72–1.14)	0.89 (0.70–1.13)
P_{trend}			0.544	0.419

[a]From single supplements (and mixtures other than multivitamins) plus multivitamins. See Design and Methods for how 10-year average dose was computed and categorized.
[b]All models adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, consumption of fruits and vegetables (without potatoes), history of coronary artery disease, history of rheumatoid arthritis, history of fatigue/lack of energy, and family history of leukemia/lymphoma.
[c]Pill-years = days per week/7 × years of use in 10 years before baseline.
[d]Greater than amount of that nutrient that could be obtained from 10-year daily use of the multivitamin Centrum Silver.
[e]Denotes μg/d of cholecalciferol.
[f]Denotes mg/d of α-tocopherol.

Finally, we examined the associations of 10-year average use of multivitamin, garlic, and grape seed supplements with hematologic malignancies characterized by morphology. Long-term use of multivitamins seemed to be associated with reduced risk of myeloid neoplasms [HR = 0.71 (95% CI = 0.44–1.15) for 8–10 pill years vs. none in last 10 years], mature B-cell neoplasm other than chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or plasma cell disorders [HR = 0.87 (95% CI = 0.60–1.25)], and plasma cell disorders [HR = 0.53 (95% CI = 0.26–1.07)], but not CLL/SLL [HR = 0.99 (95% CI = 0.60–1.82)]. The use of grape seed supplements seemed to be associated with reduced risk of all 4 of these groups of hematologic malignancies (HR range 0.11–0.78 for ever vs. never use), as was high use of garlic (HR range 0.29–0.77 for high use vs. none). However, all of the CIs were wide (most likely due to the small number of cases in these disease categories) and most included 1, so no clear conclusions can be drawn.

Discussion

In this large prospective study, high use of garlic and ever use of grape seeds were associated with a lower risk of hematologic malignancies. In contrast, we found no association between risk of total hematologic malignancies and use of any of the individual vitamins, minerals, or other specialty supplements assessed.

Over-the-counter multivitamins are the most widely used dietary supplements in the United States (19). Although experimental studies suggested favorable effects of individual vitamins on various biological processes involved in tumorigenesis (20–23), a systematic review and a recent analysis from the Women's Health Initiative cohorts found no evidence that multivitamin supplements could prevent common cancers, but hematologic malignancies have not been examined in these reports (24, 25). The few previous studies on dietary supplement use and risk of hematologic malignancies have been mostly focused on NHL and on only the most commonly

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Table 4. Associations between 10-year supplemental mineral intake and risk of hematologic malignancies

10-y average daily use prior to baseline[a]	Cases, *n* (%)	Noncases, *n* (%)	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
Calcium				
None	162 (27.7)	17,607 (27.0)	1.00 (reference)	1.00 (reference)
1.7–127.3 mg/d	161 (27.5)	16,287 (25.0)	1.11 (0.89–1.39)	1.15 (0.91–1.45)
127.3–318.6 mg/d	130 (22.2)	15,797 (24.2)	0.88 (0.70–1.12)	0.88 (0.69–1.13)
318.7–1,950.0 mg/d[c]	132 (22.6)	15,509 (23.8)	0.96 (0.75–1.22)	0.98 (0.76–1.27)
P_{trend}			0.359	0.438
Iron				
None	220 (37.9)	23,571 (36.4)	1.00 (reference)	1.00 (reference)
0.1–4.0 mg/d	130 (22.4)	13,777 (21.3)	1.02 (0.82–1.27)	1.04 (0.83–1.32)
4.1–18.0 mg/d	208 (35.9)	24,799 (38.3)	0.93 (0.76–1.12)	0.93 (0.76–1.14)
18.1–68.0 mg/d[c]	22 (3.8)	2,563 (4.0)	1.09 (0.70–1.70)	1.12 (0.71–1.76)
P_{trend}			0.585	0.668
Magnesium				
None	208 (35.5)	22,023 (33.8)	1.00 (reference)	1.00 (reference)
1.1–50.0 mg/d	151 (25.8)	17,881 (27.4)	0.98 (0.79–1.21)	1.00 (0.80–1.25)
50.1–100.0 mg/d	180 (30.7)	19,620 (30.1)	0.93 (0.76–1.14)	0.94 (0.76–1.16)
100.1–500.0 mg/d[c]	47 (8.0)	5,639 (8.7)	0.90 (0.66–1.24)	0.93 (0.66–1.30)
P_{trend}			0.410	0.495
Zinc				
None	207 (35.2)	21,834 (33.5)	1.00 (reference)	1.00 (reference)
0.32–7.50 mg/d	141 (24.0)	17,214 (26.4)	0.95 (0.77–1.18)	0.97 (0.77–1.21)
7.51–15.0 mg/d	154 (26.2)	17,650 (27.1)	0.89 (0.72–1.10)	0.90 (0.72–1.13)
15.1–130.0 mg/d[c]	86 (14.6)	8,475 (13.0)	1.01 (0.78–1.30)	0.99 (0.75–1.29)
P_{trend}			0.660	0.625
Selenium				
None	208 (35.6)	22,932 (35.1)	1.00 (reference)	1.00 (reference)
0.21–10.10 μg/d	123 (21.1)	14,228 (21.8)	1.05 (0.84–1.31)	1.07 (0.84–1.35)
10.11–20.0 μg/d	113 (19.4)	12,697 (19.5)	0.96 (0.76–1.20)	0.96 (0.75–1.22)
20.1–400.0 μg/d[c]	140 (24.0)	15,407 (23.6)	0.97 (0.78–1.20)	0.95 (0.75–1.20)
P_{trend}			0.650	0.556
Chromium				
None	220 (37.5)	23,427 (35.9)	1.00 (reference)	1.00 (reference)
0.2–34.0 μg/d	119 (20.3)	14,173 (21.7)	1.00 (0.80–1.25)	1.02 (0.80–1.29)
34.1–130.0 μg/d	228 (38.8)	25,566 (39.2)	0.93 (0.77–1.11)	0.94 (0.77–1.14)
130.1–393.0 μg/d[c]	20 (3.4)	2,094 (3.2)	0.94 (0.60–1.49)	0.86 (0.52–1.44)
P_{trend}			0.422	0.437

[a]From single supplements (and mixtures other than multivitamins) plus multivitamins. See Design and Methods for how 10-year average dose was computed and categorized.

[b]All models adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, consumption of fruits and vegetables (without potatoes), history of coronary artery disease, history of rheumatoid arthritis, history of fatigue/lack of energy, and family history of leukemia/lymphoma. The model for iron was additionally adjusted for anemia within the last year prior to baseline.

[c]Greater than amount of that nutrient that could be obtained from 10-year daily use of the multivitamin Centrum Silver.

used supplements (9–14). Together, results for multivitamin use across studies, including ours, are inconsistent for multivitamin use but generally show no associations of use of supplemental vitamin A (primarily retinol), vitamin C, or vitamin E with hematologic malignancies.

A number of experimental studies have suggested that garlic or specific garlic compounds, most prominently organic sulfur compounds (such as allicin, *S*-allylmercaptocysteine, *S*-allylcysteine, diallyl sulfide, diallyl disulfide, and diallyl trisulfide), could prevent cancer through mechanisms that may include the modulation of carcinogen metabolism, inhibition of DNA adduct formation, upregulation of antioxidant defenses and DNA repair systems, and the promotion of mitotic arrest and apoptotic cell death of cancer cells (26–33). In contrast to these *in vitro* and *in vivo* experimental investigations,

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Table 5. Associations between 10-year specialty supplement use and risk of hematologic malignancies

10-y average daily use prior to baseline[a]	Cases, *n* (%)	Noncases, *n* (%)	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
Glucosamine				
None	458 (77.9)	52,245 (79.9)	1.00 (reference)	1.00 (reference)
Low use	85 (14.5)	8,470 (13.0)	1.16 (0.92–1.47)	1.12 (0.87–1.43)
High use	45 (7.7)	4,700 (7.2)	1.00 (0.74–1.36)	0.96 (0.69–1.33)
P_{trend}			0.546	0.871
Chondroitin				
None	493 (83.8)	56,662 (86.6)	1.00 (reference)	1.00 (reference)
Low use	65 (11.1)	5,716 (8.7)	1.30 (1.00–1.68)	1.21 (0.92–1.60)
High use	30 (5.1)	3,082 (4.7)	1.01 (0.70–1.47)	0.99 (0.67–1.46)
P_{trend}			0.286	0.540
Ginseng[c]				
None	549 (93.7)	59,922 (91.6)	1.00 (reference)	1.00 (reference)
Ever use	37 (6.3)	5,507 (8.4)	0.83 (0.60–1.16)	0.79 (0.55–1.12)
$P_{difference}$			0.280	0.186
Grape seed[c]				
None	560 (95.2)	60,511 (92.4)	1.00 (reference)	1.00 (reference)
Ever use	28 (4.8)	4,991 (7.6)	0.68 (0.47–1.00)	0.57 (0.37–0.88)
$P_{difference}$			0.047	0.010
Ginko biloba[c]				
None	514 (87.9)	56,342 (86.2)	1.00 (reference)	1.00 (reference)
Low use	40 (6.8)	5,914 (9.0)	0.82 (0.59–1.13)	0.77 (0.55–1.09)
High use	31 (5.3)	3,134 (4.8)	1.05 (0.73–1.51)	0.94 (0.63–1.41)
P_{trend}			0.717	0.342
Garlic[c]				
None	523 (89.4)	57,738 (88.3)	1.00 (reference)	1.00 (reference)
Low use	38 (6.5)	4,156 (6.4)	1.06 (0.76–1.47)	1.07 (0.76–1.51)
High use	24 (4.1)	3,501 (5.4)	0.65 (0.43–0.98)	0.55 (0.34–0.87)
P_{trend}			0.084	0.028
Fish oil				
None	538 (91.7)	59,063 (90.3)	1.00 (reference)	1.00 (reference)
Low use	30 (5.1)	3,608 (5.5)	1.00 (0.69–1.44)	0.92 (0.62–1.36)
High use	19 (3.2)	2,763 (4.2)	0.71 (0.45–1.12)	0.66 (0.40–1.08)
P_{trend}			0.178	0.098

[a]Specialty supplement use was categorized as never use ("none"), low use (use for <4 days per week or <3 years), high use (use for at least 4 days per week and at least 3 years), or ever use.

[b]All models adjusted for age, sex, race/ethnicity, education, smoking, self-reported health, consumption of fruits and vegetables (without potatoes), history of coronary artery disease, history of rheumatoid arthritis, history of fatigue/lack of energy, and family history of leukemia/lymphoma. The models for glucosamine and chondroitin were additionally adjusted for history of nonrheumatoid arthritis or chronic neck/back/joint pain.

[c]From single supplements (and mixtures other than multivitamins) plus multivitamins; those with only multivitamin source coded as "low" 10-year average use.

epidemiologic studies have yielded mixed results (34). Specifically, some case–control studies have suggested reduced risk of cancers of the stomach, larynx, breast, and prostate with the use of *Allium* vegetables, including garlic (35–39). In contrast, a prospective study found a higher risk of lung cancer for subjects who exclusively used garlic supplements [HR = 1.78 (95% CI = 1.08–2.92); ref. 40] and no association with breast (41) or colorectal (42) cancer. Our study is the first to investigate garlic supplements in relation to hematologic malignances and suggests a protective association in both men and women of similar magnitude.

Grape seeds are a rich source of proanthocyanidins, which possess potent antioxidant properties and, like many phytochemicals, have shown promising chemopreventive effects *in vitro* and in animal models (43–45). Although the exact mechanism underlying chemopreventive effects of grape seed proanthocyanidins

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remains unclear, several molecular targets have been identified, including nuclear factor-kappa B, mitogen-activated protein kinases, and phosphoinositide 3-kinase/AKT (45). A recent randomized controlled trial in subjects with type 2 diabetes found that grape seed extracts, but not placebo, significantly improved markers of inflammation (C-reactive protein, reduced glutathione), suggesting that grape seeds have clinically relevant anti-inflammatory properties (46). Although, to our knowledge, no study has so far assessed the association of grape seed supplements with incident hematologic malignancies, a recent report from the Iowa Women's Health Study showed that dietary proanthocyanidins were associated with a significantly reduced risk of NHL [RR = 0.70 (95% CI = 0.52–0.94); ref. 9], that is, an effect of similar magnitude as that observed in our study. Two recent studies have similarly found associations between the use of grape seed supplements and reduced risk of cancer. Specifically, we previously reported strong inverse associations between the use of grape seed supplements and the risk of prostate cancer [HR 0.59 (95% CI = 0.40–0.86)] in the VITAL cohort (47). In addition, use of grape seeds was associated with reduced risks of cutaneous squamous cell skin cancer [OR = 0.26 (95% CI = 0.08–0.89)] in a recent case–control study (48), lending further support to the hypothesis that grape seed supplements may have chemopreventive properties in humans.

Strengths of this study include its prospective design, the large cohort size, and case ascertainment through the SEER cancer registry. In addition, supplement users were targeted for recruitment and detailed information was collected on current and long-term supplement exposure (15). Because multivitamins contain multiple nutrients, we also attempted to separate associations with specific supplemental nutrients from those using multivitamin only by restricting the highest category of users to participants with a 10-year average dose that was greater than what could be obtained from 10 years of daily use of a common multivitamin formulation. Thus, our results for the highest exposure category reflect high use of the individual nutrient supplement or use of a multivitamin with a high dose of the nutrient. Only 5% of the cohort moved out of the SEER catchment area over the 7 years of follow-up, and bias due to differential loss to follow-up is therefore unlikely to explain our findings. Furthermore, the availability of baseline information on personal lifestyle and medical history allowed adjustment for major potential confounding factors, including adjustment for confounding by suspected indication for supplement use, although residual confounding cannot be excluded.

On the other hand, limitations in our measurement of supplements need to be recognized. First, our 10-year dose variable for each nutrient combines information on years, frequency, and dose per day of use of each of multivitamin and individual supplements into a summary dose variable. In so doing, the individual associations with dose per day, years of use, or some other combination of these would have been missed. Second, we only ascertained the daily dose for vitamins and minerals but not specialty supplements, in part because there is evidence that the advertised dose of specialty supplements can vary substantially from the actual dose (49). Third, supplement use was ascertained by participant self-report. However, a previous study showed high reproducibility and validity for the self-reported information on supplement use in the VITAL cohort (50). Fourth, our result for grape seed was based on a crude variable of ever/never use over the 10 years before baseline. However, among users, 84% took the supplements at least 4 days per week, 46% had taken it for at least 3 years before baseline, and 62% were still taking the supplement at baseline and would, therefore, have accumulated additional use after baseline. Measurement errors from these sources are likely to be nondifferential and would therefore attenuate our risk estimates, possibly masking small associations.

In addition, our study may be limited by the fact that some hematologic malignancies may require a prolonged period of time to develop and become clinically manifest. Although we were able to follow our study cohort for an average of 6.5 years, we cannot exclude the possibility that this follow-up is insufficient to observe a true association between supplement intake and some incident hematologic malignancies. Furthermore, stratified analyses of the associations between use of supplements and risk of hematologic malignancies were limited in power, in part due to the diversity of hematologic malignancies and low incidence of these cancers; as a result, we were unable to conduct statistically meaningful subgroup analyses exploring whether the associations of 10-year average use of garlic, grape seed, and multivitamin supplements differed by specific tumor morphology. Finally, because we investigated 24 types of supplements, the possibility of chance finding due to multiple testing needs to be acknowledged.

Of some concern is the possibility of reverse causation, that is, disease symptoms could lead to exposures (e.g., supplement use) rather than the reverse. However, for most supplements, the highest use category required many years of use, and we accounted for self-reported health in multivariable adjusted models. Nonetheless, we additionally excluded cases arising in the first 2 years of follow-up in additional analyses. In these analyses, the HRs for high use of garlic, ever use of grape seeds, and high use of multivitamin pills were very similar to those obtained when all cases were included.

In conclusion, we observed that the use of garlic and grape seeds supplements is associated with lower incidence of hematologic malignancies. Our findings suggest a possible role of these supplements in the chemoprevention of hematologic malignancies, but further, controlled studies will need to confirm these findings. The other supplements assessed in our study are unlikely to be useful for the prevention of hematologic malignancies.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

Authors' Contributions

R.B. Walter and E. White designed and carried out research, analyzed and interpreted data, and drafted the manuscript; T.M. Brasky and F. Milano analyzed and interpreted data and revised the manuscript.

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